Conferences and Reviews

Wake Up and Smell the Coffee
Caffeine, Coffee, and the Medical Consequences

Discussant
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This discussion was selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from a transcription, it has been edited by Nathan M. Bass, MD, PhD, Associate Professor of Medicine, under the direction of Lloyd H. Smith Jr, MD, Professor of Medicine and Associate Dean in the School of Medicine.

HOMER BOUSHEY, MD*: *The recent decline in caffeine and coffee consumption reflects the widespread public awareness of the debate about possible adverse effects of caffeine on health. The enormous popularity of coffee and other caffeine-containing beverages makes this a matter of considerable importance in the field of public health. Caffeine has been implicated in diseases of a number of organ systems, and much concern, in particular, has been raised regarding its possible role as a risk factor in cardiovascular disease and pancreatic cancer. It is therefore a pleasure to introduce at this conference Tony Chou, MD, who will discuss the medical consequences of caffeine. Dr Chou is a native of West Virginia who graduated with honors from the Carnegie-Mellon University (Pittsburgh, Pa) with degrees in electrical engineering and physics. He obtained his MD degree at Case Western Reserve University (Cleveland, Ohio) and completed his residency training in internal medicine at UCSF. As a Medical Chief Resident, Dr Chou has served the numerous constituencies of our department superbly with energy, scholarship, and an enthusiasm for medicine.*

TONY CHOU, MD†: Through the ages, humanity's diligent search for stimulants has been rewarded by the discovery of the coffee bean (*Coffea arabica*) in Arabia, the tea leaf (*Thea* [or *Camellia*] *sinensis*) in China, the kola nut (*Cola nitida* and *Cola aluminata*) in West Africa, the cocoa bean (*Theobroma cacao*) in Mexico, and other plant sources of caffeine.

Caffeine is the most widely consumed stimulant drug in the world, about 75% being taken in the form of coffee. Five million tons of coffee are produced annually in 50 coffee-growing countries. It is second only to oil in international commerce, albeit a distant second. Americans consume about 45 million pounds of caffeine annually with an average daily intake of 200 mg.

More than half of Americans drink coffee daily. An even greater percentage take in caffeine in one form or another each day. The effect of this consumption on health has been the subject of much debate, and public awareness has led to a recent decrease in the amount of caffeine consumed. Caffeine and coffee consumption have been linked to diseases from myocardial infarction to schizophrenia. The studies that have examined the effects of coffee and caffeine on health often discuss the substances interchangeably. An important question is, Is it caffeine or some other substance in coffee that might cause disease?

A Brief History of Coffee

Coffee was first discovered around 850 AD by a goatherder named Khaldi in Abyssinia (Upper Egypt). Legend has it that one night his usually reliable goats did not return home. The following morning he found the animals dancing around a shiny, dark-leaved shrub with red berries. He nibbled some of the berries and, according to the legend, joined in the dance. Thus, the coffee bush was discovered. Khaldi shared his discovery with some local monks who experimented with the berries, tossing them on a fire and then soaking them in boiling water. The liquid turned out to be tasty, and drinking it allowed the monks to stay up through marathon prayer sessions. Thus, the beverage coffee was born and spread, from monastery to monastery, country to country, and continent to continent.

The coffee bean is a seed. The seeds are hulled and dried from berries of coffee tree blossoms. In general, each berry contains two oval beans. The best coffees are picked just as the berries ripen. The outer skin is immediately scraped loose, exposing the bean. There are hundreds of coffee species, but the finest are said to grow from the fragile *C arabica*, which is the principal bean of world-class coffees. Other strains, such as *C arobusta*, are frequently used for "instant" coffees. Freshly picked green beans are roasted, usually in a rotating drum, over a heat source. The end product is the beans that are ground for making coffee or are further processed for other uses.

Instant coffee was first developed at the turn of the century and became popular with the troops in the two world wars and then at home. Two basic techniques are used to produce the instant powder, "spray-drying" and freeze-drying. Instant coffee differs chemically from regular coffee. The "instantization" process conserves about 48% of the solids from the original bean. This is much higher than the 24% solid component conserved by household coffee brewing techniques. Thus, instant coffee has more "coffee."

Caffeine was first removed from coffee in the early 1900s, and decaffeinated coffee became popular in the 1930s with the introduction of Sanka. In most instances, coffee is

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TABLE 1.—*Total Soluble Solids in 225 ml (7.5 fl oz) of Coffee**

Chemical	Coffee: Roasted and Ground (1.544 grams), grams	Coffee: Soluble Spray-Dried (2.318 grams), grams
Caffeine	0.095	0.074
Chlorogenic acid	0.213	0.197
Reducing sugars—sucrose, glucose, mannose	0.168	0.197
Other carbohydrates—inositol, sorbitol, mannitol	0.230	1.008
Peptides—glutamate, glycine, aspartate	0.069	0.278
Potassium	0.115	0.085
Other minerals—calcium, magnesium, copper	0.157	0.104
Acids—quinate, acetate, citrate, maleate	0.199	0.232
Trigonellin	0.059	0.039
Volatiles—sulfur compounds, aldehydes	<0.0001	<0.0001
	1.15	1.99

*Adapted from Clinton.[3]

decaffeinated by removing the caffeine from the beans before roasting. The US Food and Drug Administration allows two organic solvents to be used in the decaffeination process: methylene chloride and ethyl acetate. Methylene chloride, the more common of the two used, has been reported to cause cancer in animals when given in high doses. This has led many companies to try to develop a pure-water process to decaffeinate coffee beans. Such a process has been patented by Nestlē along with other manufacturers. All of Nestlē's varieties of decaffeinated Taster's Choice and Nescafē are water purified.[1]

Chemistry of Coffee

Literally hundreds of chemicals have been identified in coffee (Table 1),[3] and it would be remarkable indeed if caffeine proved to be the only pharmacologically active substance. Chemical substances in coffee include chlorogenic acid, reducing sugars, other carbohydrates, peptides, and potassium. Chlorogenic acid is present in even greater quantities than caffeine.[1,2]

Of interest, there appears to be a compound in instant coffee that binds to the opiate receptor. This compound competes with tritiated naloxone for binding to opiate receptors in rat brain and has been characterized as one of several isomeric (iso)feruloylquinic lactone compounds present in coffee.[4] A cup of instant coffee contains effectively a third of an ampule of naloxone. The importance of these substances on the reinforcing properties of caffeine and coffee intake is not known.

Several mutagens have been reported in coffee. Firm evidence for mutagenicity in humans, however, has been lacking to date. One such mutagen, methylglyoxal, is also found in tomatoes and boiled potatoes. To date, no substance is found in coffee the biologic or chemical properties of which do not occur in other foods.[5]

Caffeine Consumption

In 1983, 80% of the population in the United States drank coffee. This has been on the decrease of late, with the International Coffee Organization reporting in 1991 that only 53% of Americans drank coffee, with an average intake of more than three cups per day. Higher amounts are consumed in Central and South America and Western Europe. The highest consumption occurs in the United Kingdom and Scandinavia, especially Sweden and Finland. The average consumption in these countries is about double that in the United States.

The average US daily consumption of caffeine is about 200 mg. On a milligram-per-kilogram basis, the average consumption of caffeine in the United States and Canada is about 2.4 mg per kg per day for adults and 1.1 mg per kg per day for children 5 to 18 years old. For example, a 27-kg child drinking three colas and eating three small chocolate bars in a day will ingest 7.2 mg per kg of caffeine. Heavy drinkers of caffeinated coffee (in the United States, the top 10% of coffee drinkers) can consume more than 1 gram per day or about 15 mg per kg of caffeine. A caffeine intake of 200 mg per day is equivalent to about two cups of coffee per day. Continuous use at this level over a one-year period would yield "2 cup-years" cumulative caffeine consumption, a unit sometimes used in the literature. A cup-year is equivalent to 16 lb of coffee per person per annum.

Concentrations of caffeine in coffee or tea depend on the particular bean or leaf being used (Table 2).[6] Analysis of the common coffee cup size in homes indicates that the median cup size for coffee or tea is 225 ml or 7.5 oz. In a median cup, drip coffee has the most caffeine content, with 115 to 175 mg per cup. Brewed coffee is the next most potent at 80 to 135 mg per cup. Instant coffee contains 65 to 100 mg, and decaffeinated coffee yields 3 to 4 mg per cup.

TABLE 2.—*Caffeine Content of Coffee and Tea**

Beverage	Caffeine, mg
Coffee (7.5 oz cup or 225 ml)	
Drip	115-175
Brewed	80-135
Instant	65-100
Decaffeinated	3-4
Tea (5 oz cup)	
1-min brew	20
3-min brew	35
Iced (12 oz)	70

*From Bunker and McWilliams.[6]

Tea in general is lower than coffee in caffeine per serving (Table 2). The caffeine content also depends on the brew time. Of the tea varieties, black tea is the most caffeinated, followed by oolong and green teas. A 12-fl oz glass of iced tea contains about 70 mg of caffeine.

Caffeine is added to many sodas (Table 3). Jolt, a recently released beverage, advertises that it contains "twice the sugar" and "twice the caffeine of other colas" and has the highest caffeine content per 12-oz can. Regular Coca-Cola and Diet Coke both contain 45.6 mg per 12-oz can. The average can of caffeinated soda has about half the caffeine of a cup of coffee. Soft drinks not containing cola, such as 7-Up, ginger ale, and root beer, are all caffeine-free (data from the National Soft Drink Asssociation, Institute of Food Technologists, Washington, DC, 1983).

TABLE 3.—*Caffeine Content of Soda Beverages**

Beverage	*Caffeine, mg*
Jolt	100.0
Sugar-Free Mr. Pibb	58.8
Mountain Dew	54.0
Mello Yello	52.8
Tab	46.8
Coca-Cola	45.6
Diet Coke	45.6
Shasta Cola	44.4
Shasta Cherry Cola	44.4
Shasta Diet Cola	44.4
Mr. Pibb	40.8
Dr Pepper	39.6
Pepsi Cola	38.4
Aspen	36.0
Diet Pepsi	36.0
Pepsi Light	36.0
RC Cola	36.0
Diet RC	36.0
Diet Rite	36.0
Canada Dry Cola	30.0
Canada Dry Diet Cola	1.2
7 Up, ginger ale, root beer, tonic water, seltzer	0

*Data from the National Soft Drink Association, Institute of Food Technologists, Washington, DC, 1983.

Chocolate accounts for only a fraction of the total caffeine intake. A bar of chocolate ranges from 6 to 26 mg of caffeine per oz, and chocolate milk and cocoa have only small amounts of caffeine.

Many prescription and over-the-counter drugs contain caffeine (Table 4).[6] The analgesic effect of many compounds has been reported to be improved with the addition of caffeine. Caffeine-containing prescription drugs of note include Cafergot (ergotamine tartrate and caffeine), Darvon Compound-65 (propoxyphene hydrochloride, aspirin, and caffeine), and Fiorinal (butalbital, aspirin, and caffeine). Over-the-counter stimulants include the college student staples of No Doz and Vivarin. The danger in these is not the caffeine content but the possibility of drug interactions with other ingredients in over-the-counter drugs. One of the more well-known examples is the synergistic combination of caffeine and phenylpropanolamine (ephedrine), which has been associated with severe hypertension, stroke, and myocardial infarction.

Physiologic Effects of Caffeine

The caffeine molecule, 1,3,7-trimethylxanthine, chemically closely resembles other metabolically important compounds such as the purines (adenine, guanine), adenosine, xanthine, and uric acid. Caffeine is 99% absorbed from beverages and reaches peak concentrations in the serum in 30 to 60 minutes.[2] It is lipophilic, penetrates all biologic membranes, and distributes to all body tissues.[2] It does not accumulate in any organs or tissues. Caffeine readily crosses the blood-brain barrier and the placenta. It is also present in breast milk.

Caffeine is extensively metabolized in the liver through a complex process mediated primarily by the microsomal cytochrome P-450 reductase system. From 2% to 3% is excreted unchanged in the urine. The rate of caffeine metabolism varies, with half-lives ranging from 2 to 12 hours and an average half-life of 4 to 6 hours (about 15% metabolized per

TABLE 4.—*Caffeine Content of Common Drugs**

Drug (Manufacturer)	*Generic*	*Caffeine, mg*
Prescription		
Cafergot (Sandoz Pharmaceuticals)	Ergotamine tartrate, caffeine	100.0
Darvon Compound-65 (Eli Lilly and Co)	Propoxyphene HCl, aspirin, caffeine	32.4
Fiorinal (Sandoz Pharmaceuticals)	Butalbital, aspirin, caffeine	40.0
Over the Counter		
Stimulants		
Caffedrine	Caffeine	200.0
No Doz (Bristol-Myers Products)	Caffeine	100.0 and 200.0
Vivarin (SmithKline Beecham)	Caffeine colloid	200.0
Menstrual		
Midol (Glenbrook)	Acetaminophen, caffeine, pyrilamine maleate	32.0
Analgesics		
Excedrin Extra Strength (Bristol-Myers Products), 2 capsules	Acetaminophen, aspirin, caffeine	130.0
Anacin, Maximum Strength (Whitehall), 2 tablets	Aspirin, caffeine	64.0
Cold Preparations		
Vanquish (Glenbrook)	Aspirin, acetaminophen, caffeine, magnesium hydroxide	33.0
Cope (Glenbrook)	Aspirin, caffeine	32.0
Triaminicin (Sandoz Pharmaceuticals)	Phenylpropanolanine HCl, chlorpheniramine maleate, acetaminophen	30.0

HCl = hydrochloride

*From Bunker and McWilliams.[6]

hour). Longer half-lives are seen in patients with chronic liver disease and in pregnancy.[2] Shorter half-lives are seen in smokers.[2] Smoking accelerates caffeine metabolism, and patients who stop smoking can have doubling of caffeine concentrations in the blood, which may contribute to smoking withdrawal symptoms.

It was initially thought that caffeine and other methylxanthines acted primarily as phosphodiesterase inhibitors. Although they do have this action, it is clearly not their primary effect, and the phosphodiesterase inhibition is minimal at typical serum levels. At present it appears that the most important mechanism of action of caffeine is the antagonism of adenosine receptors.

Adenosine is a locally released purine hormone that acts on two different receptors, A1 and A2. Receptors mediate either an increase or a decrease in cellular concentrations of cyclic adenosine monophosphate. High-affinity (A1) receptors inhibit adenylate cyclase; low-affinity (A2) receptors stimulate adenylate cyclase. The interplay between the two receptors is the subject of much current research. Adenosine receptors are found throughout the body, including the brain, the heart and blood vessels, the respiratory tract, kidneys, adipose tissue, and the gastrointestinal tract.

Adenosine acts locally as a vasodilator. It also reduces platelet aggregation in vitro, inhibits catecholamine and renin release, and inhibits lipolysis. Caffeine nonselectively blocks both adenosine receptors and competitively inhibits the action of adenosine.

When caffeine is consumed at regular intervals, tolerance develops within hours to days.[7] In animals, tolerance is associated with increased adenosine receptor activity and a shift of A1 receptors to the high-affinity state (an increased functional sensitivity to adenosine) and a decrease of β-adrenergic receptor activity.[8] These actions provide a mechanism for the caffeine withdrawal syndrome. Because tolerance occurs rapidly, the effect of caffeine on a person depends on how much caffeine is usually consumed. Recent data have shown that despite the tolerance that develops, the regular consumption of 6 to 11 cups of coffee per day may produce persistent small elevations in norepinephrine levels and free fatty acid release after caffeine metabolism is saturated.[9]

Caffeine and Coffee Caveats

Problems in Research

The literature on caffeine is voluminous, and recurrent flaws are evident in the research. For example, many studies in animals use doses that are hundreds to thousands of times those achieved by normal human consumption. Extrapolating the results of this work to human consumption is obviously problematic. Also, whereas most humans are caffeine tolerant, most animals are not conditioned when studied.

In humans, studies with coffee and caffeine are complicated by many extraneous factors. Coffee consumption seems to correlate with many variables: social class, race, religion, psychological state, and coronary artery disease risk factors.[1] All of these factors confuse the question of whether caffeine or coffee is the cause within an association when one is found. For example, many studies have verified that coffee consumption increases with education and income. White persons drink about 3½ times more coffee than African Americans.[10] Coffee consumption is highly correlated with membership in the Catholic Church.[11] Mormons and Seventh-Day Adventists, in keeping with church doctrine, consume much less coffee than do others in similar geographic areas.[12] In Mormons and Seventh-Day Adventists, a reduced risk of malignancy has been well documented. This is confounded, however, by the reduced smoking and alcohol intake practiced by these groups. Coffee intake is positively correlated with a diagnosis of depression and with various measures of stress and anxiety.[13]

Another general problem with caffeine and coffee research is the interchange of the two substances. Data from studies of animals and human physiologic data gathered using pure caffeine are often extrapolated and used in research questions that involve coffee, without considering the other compounds that are part of the coffee brew.

Physiologic Effects of Caffeine

Central Nervous System Effects

Caffeine acts principally as a stimulant. A dose of two cups of coffee increases vigilance and arousal. For example, generalized motor activity in young boys increases after two cups of coffee. Caffeine also reduces fatigue. Complex motor tasks, however, are disrupted. Of interest, the slowed reaction time induced by alcohol consumption is potentiated by caffeine ingestion, so coffee is not an "antidote" for intoxication.[2,14]

Caffeine also has substantial effects on sleep. Ingesting caffeine 30 to 60 minutes before sleep will increase sleep latency, decrease total sleep time, and substantially worsen subjective estimations of sleep quality. There are large variations in sensitivity to sleep disturbance, with the effects being greater in persons who do not drink caffeinated beverages regularly.[15]

Caffeine also leads to a reduction in cerebral blood flow, and several studies have now shown that blood flow is decreased by caffeine-induced cerebrovascular vasoconstriction.[16,17]

A key behavioral effect of caffeine is reinforcement. In healthy subjects, as the caffeine content per cup of coffee decreases, the number of cups consumed increases. Caffeine also may be a determinant of nicotine consumption. It has been reported that compared with regular coffee, drinking decaffeinated coffee leads to an increase in the number of cigarettes smoked by volunteers.[18] This, coupled with nicotine's ability to accelerate caffeine metabolism, leads to a reinforcing cycle between caffeine and smoking.

A caffeine withdrawal syndrome is well described. Withdrawal symptoms include headache and fatigue most prominently; anxiety, impaired psychomotor performance, nausea and vomiting, or an intense desire for coffee occur less commonly.[19] Headache is usually preceded by a feeling of fullness in the head that occurs about 18 hours after the last caffeine intake. This is followed by a diffuse, throbbing headache that worsens with exercise.

Cardiovascular Effects

There are many contradictions in the literature regarding the effect of caffeine on heart rate, blood pressure, and plasma catecholamine levels.[7,20-25] Recent data have clearly shown that the systolic blood pressure increases abruptly about 10 mm of mercury with caffeine. The heart rate slows for about an hour, then increases for two to three hours thereafter. Tolerance to caffeine develops quickly, however. Long-

term ingestion has little or no effect on the blood pressure, heart rate, or catecholamine levels.[24]

Respiratory Effects

The primary respiratory effect is an increase in the respiratory rate. Careful studies have shown that the respiratory rate correlates closely with the plasma caffeine level.[24] Caffeine has been used successfully as a stimulant in neonates to prevent recurrent apneic episodes. While the precise mechanism for caffeine's respirogenic effect is unknown, there appears to be an increased sensitivity of the medullary respiratory center to carbon dioxide.[2]

In patients with asthma, caffeine functions as a bronchodilator. Bronchodilation is only about 40% of the potency of theophylline at comparable concentrations.[26] At similar doses, caffeine has more central nervous system toxicity as well.

Endocrine and Metabolic Effects

Caffeine increases circulating catecholamine levels, and, partially through this mechanism, it increases the basal metabolic rate. Lipolysis with the release of free fatty acids occurs, and serum free fatty acid levels rise to 50% to 100% above normal. This is most likely a consequence of systemic catecholamines or may result from a local antagonism of adenosine inhibition of lipolysis.

The effect of caffeine on blood glucose has been the subject of debate. Most studies have shown that caffeine does not appreciably increase blood glucose levels in healthy people.

Debate has raged over the role of coffee and caffeine in cholesterol metabolism. Some, but not all, epidemiologic studies find an association between long-term coffee consumption and increased serum cholesterol levels. Most of the evidence in support of a coffee-cholesterol connection has come from overseas, namely Australia, Israel, Finland, Sweden, and Norway, the home of the Tromsø Heart Study.

In Tromsø more than 14,000 Norwegians were questioned, and a strong dose-response relationship between coffee consumption and serum cholesterol levels was found.[27,28] These data showed a linear relationship for both women and men, with serum cholesterol levels increasing about 30 mg per dl as coffee intake increased from zero to more than nine cups per day (Figure 1). Soon after the Tromsø reports, large epidemiologic studies from Evans County, Georgia, and Framingham, Massachusetts, failed to show this correlation in the United States.[29] Other studies that did show a correlation failed to show a dose-response relationship.

An interesting study from Stanford (California) Medical School in 1985 reported that consuming two to three cups per day of coffee seemed to correlate with higher levels of apolipoprotein B, leading some to speculate that this might be the mechanism of cholesterol elevation.[30]

Scrutiny of the coffee-cholesterol relationship by several researchers revealed that the method of brewing appeared to have a considerable effect on the cholesterol-raising ability of coffee.[27,31,32] The predominant method of brewing coffee in Norway is by boiling, in contrast to the percolated or instant methods in the United States. In several studies that have compared boiled and filtered coffee, boiled coffee had a stronger effect on cholesterol levels in almost all cases.[32] A surfactant coffee factor has been identified that is precipitated by hard water and removed by filtration, and there has been speculation that this surfactant might be responsible for the changes observed in the Tromsø study.[33] Others have proposed that the temperature difference of boiled coffee, which is kept at higher temperatures for longer periods of time, frees some "agent" that raises cholesterol levels.[33] Most recent epidemiologic data have shown no difference in total cholesterol or low-density lipoprotein levels between persons who drink boiled coffee and those who consume filtered coffee.[33]

It must be kept in mind that coffee, rather than caffeine, has been the target of many of the epidemiologic studies. In fact, in several studies showing a coffee-cholesterol connnection, the caffeine-equivalent dose of tea did not have the same effect. In addition, the same effects on cholesterol and low-density lipoprotein levels have been reported with decaffeinated coffee.

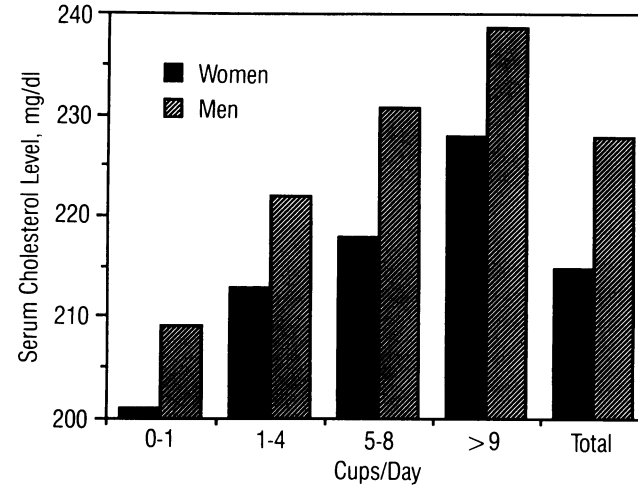

Figure 1.—Serum cholesterol levels were measured versus cups of coffee consumed per day as determined by a survey of more than 14,000 Norwegians demonstrating a strong dose-response relationship (adapted from Thelle et al[27]).

At present, the role of caffeine in causing an increase in cholesterol levels is tenuous. It is more likely that a relationship exists between a non-caffeine component of coffee and serum cholesterol and low-density lipoprotein levels. There are also confounding factors such as the brewing method and associated risks found in coffee drinkers, such as saturated fat intake, that still need to be evaluated.

Gastrointestinal Effects

In the gastrointestinal tract, caffeine stimulates the small intestine to secrete water and sodium. Of interest, coffee does not have this effect, suggesting that there is some interfering substance present. In the distal colon, coffee stimulates motility and promotes defecation. As the same effect is seen with decaffeinated coffee, it is unlikely to be mediated by caffeine.

Since the 1940s, it has been known that coffee stimulates the secretion of gastric acid and pepsin. Caffeine has a direct effect on gastric acid secretion. In a now-famous study, Cohen and Booth at the University of Pennsylvania examined the dose-response relationships between caffeine, regular and decaffeinated coffee, and gastric acid secretion and lower esophageal sphincter pressure in normal subjects.[34] Eight subjects were administered caffeinated coffee, decaffeinated coffee, pure caffeine, or distilled water by nasogastric tube after an eight-hour fast. The response in peak acid

output was higher with both regular and decaffeinated coffee than with pure caffeine (Figure 2). The difference at the higher doses between either the regular or decaffeinated coffee and caffeine was statistically significant. A similar difference was found on manometric measurement of the lower esophageal sphincter tone. In order of potency, regular coffee, then decaffeinated coffee, and then pure caffeine decreased the tone. To date, the ingredient in coffee responsible for these effects on gastric acid secretion and lower esophageal sphincter tone has not been identified. Based on these findings, decaffeinated coffee is not an alternative for patients with peptic ulcer disease or gastroesophageal reflux.

Caffeine and Coffee Consumption in Human Disease

Many diseases have been associated with caffeine and coffee consumption. Caffeine and coffee intake have often been associated with hypertension. Blood pressure, as discussed earlier, changes initially but shows little abnormality in the long term.

The use of caffeine in pregnancy has long been debated. Studies of animals have shown that caffeine can retard fetal growth and cause skeletal abnormalities at doses equivalent to 12 to 24 cups of coffee per day.[35] In humans, retrospective epidemiologic studies in the 1970s found an increased incidence of birth defects and low birth weights with coffee consumption and led the Food and Drug Administration to remove caffeine from the "Generally Regarded as Safe" list of substances in 1980.[36] Large epidemiologic studies since then have not supported this concern. Despite this, most obstetricians at present recommend that caffeine intake be limited to less than 400 mg per day during pregnancy.[36]

A dose-response relationship between coffee intake and premenstrual syndrome has been reported.[37] This has led

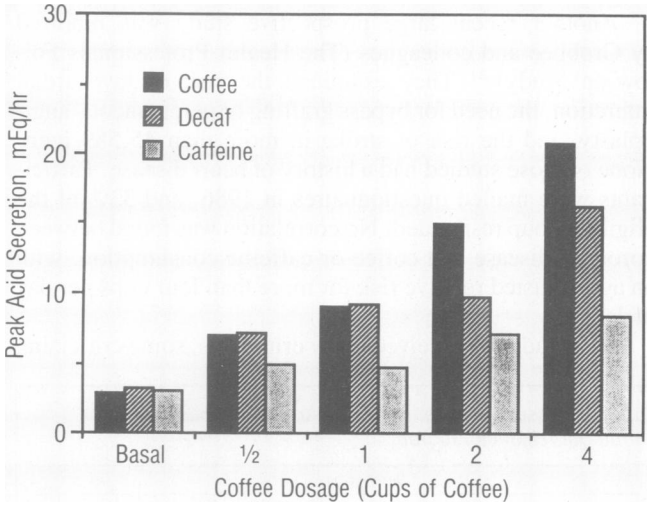

Figure 2.—The graph shows peak gastric acid response to regular coffee, decaffeinated coffee (Decaf), and equivalent doses of caffeine (adapted from Cohen and Booth[34]).

many to recommend that those who suffer from premenstrual symptoms abstain from caffeine.

As mentioned earlier, coffee decreases the lower esophageal sphincter tone and hence promotes gastroesophageal reflux. It is interesting to note that coffee also seems to have a direct irritant effect when infused into the esophagus. Peptic ulcer disease and caffeine intake were first linked in the 1950s. In 1974 in a large study of 11,000 male college students, a positive correlation was reported between coffee consumption and peptic ulcer disease later in life.[38] Other studies have failed to show a correlation. Nevertheless, it is common practice to recommend that patients who have peptic ulcer disease avoid drinking either regular or decaffeinated coffee.

Caffeine is well known to cause nervousness, restlessness, anxiety, and insomnia. It has also been reported to aggravate psychiatric disease. A disorder known as "caffeinism" was first described in 1974 and is currently listed in the *Diagnostic and Statistical Manual of Mental Disorders.*[39,40] It is defined as a state in which high doses of caffeine acutely manifest as frequent urination, jitteriness, lightheadedness, irregular heartbeat and breathing, upset stomach, diarrhea, and heartburn.

An interesting and fortunately rare occurrence is caffeine overdose. In high doses, caffeine causes hypotension from vasodilation (β-adrenergic mediated) and pronounced tachycardia with massive systemic catecholamine release. Deaths have been reported after the intravenous, oral, and rectal administration of caffeine or coffee,[2] the lethal dose being about 10 grams or 170 mg per kg, which is equivalent to 75 cups of coffee, 125 cups of tea, or 200 cans of cola.

The three principal medical diseases that have received the most notoriety are coronary heart disease, arrhythmia, and pancreatic cancer.

Coronary Heart Disease

Epidemiologic studies have associated coffee consumption with many of the accepted coronary risk factors. In general, the risk factors of greatest concern are cigarette smoking, diabetes mellitus, alcohol abuse, socioeconomic status, and oral contraceptive use.

One of the best-established correlations is between smoking and coffee consumption.[1,41,42] At age 50, only 20% of those who did not drink coffee were smokers. Of those who drank more than ten cups of coffee per day, 71% were smokers. Smoking is particularly associated with coffee intake in young and middle-aged adults. Smoking should be and usually is accounted for in most studies. On the other hand, elevated cholesterol levels and hypertension have had inconsistent associations with caffeine or coffee intake, and there is little evidence to support controlling for these in large clinical studies.

Other known risk factors probably have less of an effect. There is little evidence supporting an association between coffee and diabetes mellitus.[2,43] In many studies, alcohol use in moderation has been found to be negatively associated with the risk of coronary artery disease. Alcohol use is most often positively correlated with coffee consumption.[41] Therefore, some authors suggest that it should be controlled for in coffee-coronary heart disease studies.[1] Oral contraceptive use clearly increases the risk of coronary disease in women of reproductive age. Oral contraceptive use has been related to cigarette smoking, but its relation to coffee use is unknown. But because coffee drinking and cigarette smoking are so closely linked, many authors think that oral contraceptive use and coffee consumption are associated and should be controlled for.[1] Clearly the role of oral contraceptives in the larger picture of coronary heart disease is small in comparison to smoking and other risk factors.

Bearing the confounding associations among known risk factors in mind, the data from the studies that have reported an association between coffee consumption and coronary

heart disease can be critically examined. The first report of an association between coffee consumption and ischemic heart disease was published in 1963.[44] It was based on data from an eight-year prospective study of 2,000 male employees of the Western Electric Company in Chicago, Illinois. Those who consumed five cups or more of coffee per day were reported to have higher rates of angina and myocardial infarction than men consuming less. Initially it was suggested that the sugar in coffee was to blame. Later it was shown that the association between coffee consumption and ischemic heart disease could be accounted for by cigarette smoking alone. Nevertheless, this study sparked a controversy that has persisted.

In 1972 the Boston Collaborative Drug Surveillance Program published its results based on 276 patients with 1,104 matched controls drawn from hospitals around the world.[45] It found that drinking more than six cups of coffee a day was associated with a more than twofold increased risk of myocardial infarction that could not be accounted for by smoking. The increased risk held up when data were analyzed separately for smoking, sex, and age. No association with tea drinking was found, implying that a component of coffee other than caffeine was responsible.

A second more comprehensive study by the Boston Program, involving about 13,000 hospital inpatients, including 440 with the diagnosis of myocardial infarction, confirmed a greater than twofold increased risk among patients who consumed more than six cups of coffee a day.[46,47] Relative risks were 1.6 for those drinking one to five cups per day and 1.9 for those drinking six cups or more. Again, no association with tea was found, exonerating caffeine as the factor.

These reports from Boston were immediately followed by studies from Britain that supported the coffee-coronary disease connection.[48] In the wake of these studies, which generated considerable interest, more than a dozen studies, both retrospective and prospective, have since failed to show an association between coffee consumption and coronary heart disease (Table 5).[29,31,43,49-55]

By 1983 the preponderance of negative studies was overwhelming. Strong arguments were made by Klatsky and the group at the Oakland (California) Kaiser Foundation Medical Center, reporting on patients with myocardial infarction, who showed no difference in coffee consumption compared with matched controls in interview studies.[49] In addition, the Framingham study included more than 4,000 patients and found no evidence for an association.[29,57]

Then in 1986 LaCroix and co-workers reported the results of a 25-year study of 1,130 male Johns Hopkins University (Baltimore, Maryland) medical students with multiple, repeated measures of caffeine intake over the years.[55] They showed a strong dose-response relationship between coffee consumption and the risk of coronary heart disease. Relative risks ranged from 1.3 for one or two cups to 2.5 for more than five cups of coffee per day compared with drinking no coffee at all. The study controlled for smoking but not for other life-style factors that may be associated with coronary disease, such as diet high in total and saturated fats, high serum cholesterol levels, a sedentary life-style, and high levels of occupational stress. These data once again brought into question the long-term effects of coffee drinking.

Recently Klatsky and associates reported a vast cohort study of Kaiser Foundation patients and concluded that heavy coffee intake may increase the risk of coronary artery disease, reversing their earlier conclusions reported in the 1970s.[58] More than 100,000 patients, including 1,914 patients with coronary disease, admitted between 1978 and 1985 were examined. Patients completed questionnaires about sociodemographic traits, habits, and health as well as health measurements and laboratory test results. The median follow-up was five years. Compared with noncoffee drinkers, the following relative risks were found: 1.1 for one to three cups, 1.4 for four to six cups and 1.4 for more than six cups per day. There was no clear dose-response relationship, however, and, again, tea consumption was not related to myocardial infarction or other coronary events. The authors concluded that a weak, independent correlation of coffee use to acute myocardial infarction existed, not mediated by an effect on blood cholesterol levels.[58] They recommended that persons at risk for myocardial infarction should consider limiting their coffee intake to less than four cups per day.

Another recent large prospective study was reported by Grobbee and colleagues (The Health Professionals Follow-up Study).[31] They examined the risk of myocardial infarction, the need for bypass grafting or percutaneous angioplasty, and the risk of stroke in more than 45,589 men. None of those studied had a history of heart disease. Participants were mailed questionnaires in 1986, and 33% of the eligible group responded. No correlation was found between coronary disease and coffee or caffeine consumption, with an age-adjusted relative risk for more than four cups per day of 1.04.

This study has received many criticisms, some criticizing

TABLE 5.—*Studies Failing to Find an Effect of Coffee or Caffeine Consumption on Coronary Artery Disease Following the Boston Collaborative Drug Surveillance Program*

Reference	*Patients, No.*	*Description*
Klatsky et al, 1973[49]	464	Matched case-control study of patients with MI
Dawber et al, 1974[29]	1,992 men 2,500 women	12 years' follow-up of men and women from Framingham, Mass, data base
Hennekens et al, 1976[43]	649	Interviewed wives of patients with sudden death
Yano et al, 1977[50]	7,705	Cohort study of Japanese-Hawaiian men observed for 6 years
Heyden et al, 1978[51]	2,530	Cohort was observed for 4.5 years in Evans County, Georgia
Rosenberg et al, 1980[52]	487	Case-control study of women after an MI
Murray et al, 1981[53]	17,000	Observed Lutheran Brotherhood for 11.5 years
Welin et al, 1984[54]	834	Prospective study of 50-year-old Swedish men
LaCroix et al, 1986[55]	1,130	Prospective study examining male medical students over 25 years
Yano et al, 1987[56]	7,705	Reexamined Japanese-Hawaiian cohort and again found no association
Grobbee et al, 1990[31]	45,589	Prospectively studied risk of MI or revascularization in men

MI = myocardial infarction

TABLE 6.—*Studies That Fail to Correlate Coffee Intake and Arrhythmia*

Reference	Description of Study
Newcombe et al, 1988[63]	Caffeine (500 mg) given to 34 normal persons; no increase in ventricular arrhythmias on a 24-hour Holter recording
Myers et al, 1988[64]	A randomized, placebo-controlled, within-patient, crossover study design of postinfarction patients given 300 mg of caffeine
Myers et al, 1990[65]	35 patients after infarction received 300 mg of caffeine followed by a second 150-mg bolus after 4 hours
Graboys et al, 1989[66]	Single-blind, crossover study of patients with history of malignant ventricular arrhythmias given 200 mg of caffeine
Chelsky et al, 1990[67]	Electrophysiologic study of 22 patients with a history of symptomatic nonsustained or sustained ventricular tachycardia or ventricular fibrillation; patients were studied before and 1 hour after coffee ingestion with 275 mg of caffeine

the 33% response rate to the initial questionnaire. Also, the authors did not fully explore the more-than-five-cup threshold that was found by LaCroix and others to be associated with coronary disease.[55,59] The study was also criticized for excluding patients who had coronary disease at the initial questioning. It may well be that the excluded cohort represented those who had already suffered from and were sensitive to the effects of coffee or caffeine, as the age of the cohort started at 40 and ended at 75. Also, there was no review of past habits of coffee consumption. LaCroix's medical student study[55] suggested a long-term effect (25 years) that Grobbee and co-workers did not address.

In summary, the evidence to date that coffee or caffeine intake at normal levels is correlated with coronary heart disease is inconsistent. The long-term effects of coffee use are still not clear. The recent work of LaCroix and colleagues does raise the question of whether coffee drinking produces effects that may manifest only after several decades. Heavy caffeine use (>4 cups per day of coffee) may be associated with coronary artery disease and needs further investigation.

Arrhythmia

Although there is much anecdotal acceptance that there is an association between caffeine intake and arrhythmia, the literature contains little evidence to support this. Studies using animals have shown that caffeine in massive doses can reduce the ventricular fibrillation threshold and alter electrical excitation in cultured cardiac cells.[60] There have also been many studies in the literature that examine this question in humans.

Prineas and colleagues measured ventricular extrasystoles in 7,311 subjects who had a two-minute single-lead electrocardiogram done as part of a coronary risk factor screening program.[61] They found that persons who drank nine or more cups of coffee or the equivalent amount of tea a day were more likely to have at least one premature ventricular beat. Their data showed a poor dose-response relationship, however.

Dobmeyer and associates performed electrophysiologic studies in 7 healthy volunteers and 12 patients with heart disease.[62] Caffeine use did not affect cardiac conduction but did alter some of the electrophysiologic measurements. The authors concluded that caffeine exerted little or no effect on cardiac conduction but might aggravate an existing predilection to arrhythmia.

Many subsequent negative studies confirmed these conclusions (Table 6).[63-67] They include careful dose-response studies in patients with malignant arrhythmias and in those who had had myocardial infarction,[63,64] as well as an electrophysiologic analysis in which low doses of caffeine were given to patients with known arrhythmia.[67]

The evidence is thus mounting that the common recommendation to avoid caffeine use when patients have "arrhythmias" is not warranted. Myers in a recent review article summarizes this opinion:

> [M]oderate ingestion of caffeine does not increase the frequency or severity of ventricular arrhythmias in normal persons, patients with ischemic heart disease, or those with pre-existing serious ventricular ectopy.[68(p149)]

Pancreatic Cancer

Caffeine or coffee intake have been implicated in many solid tumors such as pancreatic cancer, urinary tract cancer (most notably bladder cancer), renal cell carcinoma, ovarian cancers, and breast cancer. Confounding risk factors, recall bias, and small numbers have usually precluded making definitive statements on these tumors.

The suggestion that pancreatic cancer may be associated with coffee consumption emerged from several "ecologic" studies (Table 7).[69-74] These typically searched for positive correlations between coffee consumption or coffee importation and national pancreatic cancer mortality rates. Remarkably, mortality rates from pancreatic cancer tracked coffee use trends consistently, with a ten-year lag in most studies (Table 7). Several of these studies showed a clear correlation, but these could only be considered at best a suggestion of a direct link.

Then in 1981 MacMahon and colleagues published a case-controlled interview study of 369 patients with pancreatic cancer, investigating how much coffee or tea they consumed before diagnosis.[75] Their answers were compared with those of a control group of 644 hospital inpatients without pancreatic cancer. A significant increase in cancer prevalence among coffee drinkers, but not among tea drinkers, was found. The overall risk ratio was 1.8 (95% confidence limits, 1.0 to 3.0). The dose-response relationship was statistically significant only in women.

The selection of controls in this study has been criticized because 40% had chronic gastrointestinal disease, which may have led to lower caffeine intake. Also, the control group was skewed by the exclusion of smoking and alcoholic patients, which may have eliminated heavy coffee drinkers as well.[2] Others emphasized that the duration of coffee consumption needs to be considered, as do other variables such as coffee additives. Also puzzling was the fact that the dose-response relationship was only present for women.

A plethora of studies have since examined the question of a link between coffee drinking and pancreatic cancer. A total of 18 case-control studies carried out between 1981 and 1990 have yielded both affirming and negating results (Table 8).[76-83] Although the case-control studies have not been conclusive, existing prospective studies have been consistent in their findings: none of the six prospective investigations performed between 1983 and 1990 that examined coffee intake and risk of pancreatic cancer (Table 9)[84-89] have shown an association.

In summary, many of the studies that have found a corre-

TABLE 7.—*Ecologic Studies Correlating Pancreatic Cancer and Coffee Intake*

Reference	*Description of Study*
Stocks, 1970[69]	Correlated death rates from cancers with several variables including coffee in 20 countries; positive correlation between pancreatic cancer and coffee drinking in men
Cuckle and Kinlen, 1981[70]	Found significant correlations between coffee consumption patterns for 16 countries and pancreatic cancer mortality rates
Spector, 1981[71]	Found trend in coffee imports tracked with pancreatic cancer death rates between 1948 and 1978 in the United Kingdom
Benarde and Weiss, 1982[72]	Found per capita coffee consumption patterns for the United States from 1950 to 1980 were tracked by pancreatic cancer incidence rates offset by 10 years
Binstock et al, 1983[73]	Found per capita coffee imports from 1957 to 1965 in 22 countries correlated with pancreatic cancer death rates in 1971 to 1974
La et al, 1987[74]	Found moderate correlation between coffee consumption and pancreatic cancer mortality in 20 Italian regions

TABLE 8.—*Case-Control Studies Examining Pancreatic Cancer and Coffee Intake*

Reference	*Patients, No.*	*Description of Study*
Jick and Dinan, 1981[76]	78	Pancreatic cancer patients, with hospital inpatients as controls, were interviewed; no association was found
Lin and Kessler, 1981[77]	109	Found that patients with pancreatic cancer drank more decaffeinated coffee than did controls
Goldstein, 1982[78]	45	Reviewed coffee history in the charts of pancreatic cancer patients and found no correlations when compared with prostate and breast cancers
Severson et al, 1982[79]	22	Case-control study addressing asbestos in drinking water found no correlation
Wynder et al, 1983[80]	275	No correlation found
Kinlen and McPherson, 1984[81]	216	Pancreatic cancer patients compared with other cancer patients; no correlation found
Gold et al, 1985[82]	274	Patients interviewed and matched to controls; no association found
Hsieh et al, 1986[83]	176	Patients compared with hospital controls; slight increase for heaviest consumption found, but no dose response

MI = myocardial infarction

lation between coffee drinking and pancreatic cancer have been limited. All are retrospective case-control studies. Although there is a correlation at a national level between coffee consumption and pancreatic cancer mortality rates, there is little evidence at this time that coffee directly contributes to pancreatic cancer.

Summary

Caffeine is a methylxanthine whose primary biologic effect is antagonism of the adenosine receptor. Its presence in coffee, tea, soda beverages, chocolate, and many prescription and over-the-counter drugs makes it the most commonly consumed stimulant drug. Initially caffeine increases blood pressure, plasma catecholamine levels, plasma renin activity, serum free fatty acid levels, urine production, and gastric acid secretion. Its long-term effects have been more difficult to substantiate.

Most of the caffeine consumed in the United States is in coffee, which contains many other chemicals that may have other biologic actions. The consumption of coffee is a self-reinforcing behavior, and caffeine dependence and addiction are common.

Coffee and caffeine intake have been linked to many illnesses, but definitive correlations have been difficult to substantiate. Initial trials showing coffee's association with coronary disease and myocardial infarction have been difficult to reproduce and have many confounding variables. Recent studies showing a larger effect over long follow-up periods and with heavy coffee consumption have again brought the question of the role of coffee in disease states to the fore. Caffeine in average dosages does not seem to increase the risk of arrhythmia. At present there is no convincing evidence that caffeine or coffee consumption increases the risk for any solid tumor.

The intake of coffee and caffeine has clearly been decreasing in this country over the past two decades, largely brought about by the increasing health consciousness of Americans. Although there have been many studies that hint that the fears of increased disease with coffee drinking may be warranted, many questions have yet to be answered about the health effects of coffee and caffeine use.

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TABLE 9.—*Prospective Studies Examining Pancreatic Cancer and Coffee Intake*

Reference	*Patients, No.*	*Description of Study*
Heuch et al, 1983[84]	16,713	Prospective study of Norwegians who received dietary questionnaires in 1967 and were followed up in 1978; relative risks for coffee intake were all < 1.0
Snowden and Phillips, 1984[85]	23,912	Observed Seventh-Day Adventists between 1960 and 1980 and found no increase in risk
Whittemore et al, 1985[86]	50,000	Male former students from University of Pennsylvania and Harvard University observed from ages 16 to 50 years; found no association between coffee drinking while in college and later pancreatic cancer
Nomura et al, 1986[87]	7,355	Prospective study of Japanese men on Oahu, Hawaii, who had 24-hour dietary surveys done in 1965 to 1968 and were observed until 1983; coffee intake not found associated with increased risk
Mills et al, 1988[88]	34,000	Observed California Seventh-Day Adventists from 1976 to 1983; no increased risk associated with coffee consumption
Hiatt et al, 1988[89]	122,894	Kaiser group with 6-year follow-up; no increase in risk found associated with coffee

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