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Does Coffee Influence the Lipid Metabolism?

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With 1 figure and 3 tables

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It is desirable to divide this topic into two sections, the first one dealing with the influence of caffeine on free fatty acids, the second one with the influence on cholesterol metabolism and alleged consequences of atherogenesis.

a) Influence of Caffeine on Free Fatty Acids

A considerable amount of literature has accumulated in the last five years pertaining to the rise of plasma free fatty acid concentrations after ingestion of coffee, intravenous and intramuscular caffeine injections and after drinking coca cola (Bellet et al. 1968) which contains caffeine. There are wide individual variations in the response of the free fatty acid levels to caffeine; however, in general a significant increase over control levels *within* four hours after administration of caffeine can be observed. The peak free fatty acid concentration in the blood of dogs after caffeine administration occurs two hours later. In human subjects the peak concentration of free fatty acids is given at three to four hours after coffee ingestion.

An interesting finding made during these experiments was that glucose apparently blocked the free fatty acid increase normally produced by coffee ingestion. The suppression of caffeine-induced free fatty acid mobilization by sucrose or glucose is probably a result of the effect of sucrose and glucose on reesterification of the released free fatty acids. When the effect of glucose administration has dissipated, the lipolytic effect of caffeine is no longer counteracted by the glucose and a significant increase in plasma free fatty acids is observed (Bellet, Kershbaum and Finck 1968).

Although the measurement of blood caffeine concentrations has been plagued by methodological difficulties, it can be assumed that maximum concentrations of caffeine in the blood are reached within one hour, after which a gradual decline occurs over a period of seven to nine hours (Bellet et al. 1968).

There is nothing specific about the free fatty acid elevation induced by and associated with the use of coffee. Physical exercise, cigarette smoking, emotional stress, prolonged starvation and alcohol consumption in excessive amounts are all known to increase free fatty acids temporarily to a significant degree. The mobilization of free fatty acids in physical exercise, cigarette smoking and emotional stress is facilitated through circulating catecholamines. To produce an effective level of circulation catecholamines in the blood, both the adrenal glands and the sympathetic nervous system must be functioning concomitantly.

"There is little doubt that norepinephrine plays a cardinal role in elevating the FFA level during exercise" (RODAHL et al. 1964). Nobody has shown an *increase* in cholesterol levels following exercise, however. In cigarette smoking, KERSHBAUM and co-workers (1962, 1963) have demonstrated that the increased release of epinephrine and norepinephrine by the sympathetic nerve endings and adrenal glands cause the mobilization of free fatty acids from adipose tissues since in patients with bilateral adrenalectomy no free fatty acid elevation in the blood was seen after cigarette smoking. It was this group of investigators in Philadelphia, KERSHBAUM and BELLET, who had repeatedly stated that the free fatty acid elevation after cigarette smoking "may be important in view of subsequent hypercholesterolemia". However, during the last ten years it has become increasingly clear, mainly from epidemiologic studies, that cigarette smokers do not differ from non-cigarette smokers in regard to their cholesterol levels. The pooled data from the Albany and Framingham Heart Studies indicated that lipid levels are not correlated with smoking habits (DOYLE 1968). BLACKBURN and co-workers (1960) did not find any association between cigarette smoking and higher cholesterol levels in a long-term study.

Table 1. Cholesterol Levels in Non-smokers and Smokers

Occupational Groups	Non-Smokers	Cigarette Smokers
Business Men	234.8 mg%	242.7 mg%
Students	173.7 mg%	179.0 mg%
Railroad Workers	224.8 mg%	232.2 mg%
Firemen	241.7 mg%	251.1 mg%

From: BLACKBURN et al., 1960.

In a cross-sectional study of 500 Swiss factory workers (males 30 to 60 years of age) cigarette smokers and their triglyceride and cholesterol levels were compared with the respective levels of "non-smokers", including ex-smokers, cigar and pipe smokers and those who did not inhale cigarette smoke (HEYDEN 1967). The differences were insignificant: 23% of the cigarette smokers and 20% of the "non-smokers" had hypertriglyceridemia ($\geq$ 135 mg%). Hypercholesterolemia ($\geq$ 250 mg%) was equally seen in 47% of cigarette smokers and 47% of "non-smokers". On the basis of these findings we cannot subscribe to a visible long-term effect of nicotine on blood lipids. EPSTEIN (1965) likewise stated "the effect is probably not mediated by cholesterol (or blood pressure) since these variables are not consistently associated with smoking".

The other frequent assumption that cholesterol levels are increased under conditions of emotional stress has been refuted in several studies. LEVI (1967) in a very careful short term experiment on 33 male volunteers has documented a significant increase of free fatty acids in the serum of men undergoing stress situations whereas the cholesterol levels in the same subjects remained unchanged. Similarly, RAAB and KRZYWANEK (1966) found mean FFA levels markedly elevated during combined sensory and mental stresses but serum

cholesterol concentrations were not influenced. Although it has become a popular opinion that cholesterol levels rise with emotional stress, more recent investigations have shown that there was really no difference in cholesterol levels of men undergoing stressful situations or being in stressful occupations (Lit. see HEYDEN 1969).

Finally, the effect of prolonged starvation on blood lipids of obese subjects is usually a fall of cholesterol and triglyceride levels, but a rise of FFA levels above baseline (JACKSON 1969).

b) Influence of Caffeine on Cholesterol Metabolism

To return to the problem of cholesterol metabolism and coffee consumption we are faced with two studies in human subjects which contradict each other but nevertheless have caused great concern to laymen and physicians alike.

1. LITTLE and co-workers (1965) tried to correlate dietary intake with serum cholesterol levels in 86 patients with coronary heart disease and 84 control persons and found none of the correlation coefficients statistically significant. Among the dietary factors considered were coffee and tea consumption, as indicated by the number of cups of coffee, the number of cups of tea and the number of cups of tea and coffee combined.

They stated: "Our coronary patients took less tea and coffee and less sugar than the control persons". However, their coronary group when examined alone showed a positive and statistically significant correlation of coffee intake with *plasma cholesterol*. In 1966 the same group (LITTLE et al.) reported that in the coronary group coffee showed a consistently positive and significant correlation with each of the serum lipid and serum lipoprotein fractions measured. The authors mentioned that "in our retrospective study of Canadians, coronary patients and controls drink equal amounts of coffee. This difference in results (in comparison to the Americans examined by Paul) cannot be explained unless after the onset of coronary symptoms patients drank less coffee". And later they also stated, "The data suggest that coffee contains a substance which elevates serum lipids in susceptible persons and that such persons may be liable to coronary heart disease. It has yet to be shown, however, that other serum lipid fractions (besides plasma unesterified fatty acids) will become elevated with long-term drinking of coffee or that increased atherosclerosis results".

2. The second investigation, an epidemiologic study by PAUL and co-workers (1963) found that there was a significant correlation between the use of coffee and the later development of coronary disease ($P < 0.025$). In 1968 this same group reported: "We did not have evidence that the serum cholesterol level was significantly higher in the group with the highest coffee consumption, although it was slightly higher in these men than in those with the lowest or no coffee consumption. It did not appear that the association of coffee drinking with an increased incidence of coronary disease could be entirely explained on this basis".

We have voiced our criticism that although there was statistical significance it was really not enough to make one confident of the biological importance. The statistical significance in this first analysis back in 1963 depended on the excessive coffee intake of 10 patients out of 54 coronary

patients. Even if taken at face value, the effect on the coronary arteries could not necessarily be attributed to the coffee intake because of the competing effect of other factors, e. g. nicotine inhalation which had not been taken into account in this particular statement by PAUL. It is a general observation that those individuals who are excessive coffee drinkers and also smoke tend to smoke cigarettes excessively. In a second study by PAUL and co-workers reported in the Lancet of November, 1968, these factors were considered together and it was now stated that the simple relation between the coffee and cigarette habit was analyzed and they are significantly associated with a $P < 0.001$. An additional, more statistically sophisticated, analysis of the 1963 data was performed. The 66 subjects with CHD histories were compared to 85 randomly selected controls using the logit transformation. This transformation allows for the comparison of the risks of high and low coffee drinkers separately from the risks attendent on cigarette smoking. The results were summarized: "It is clear that the high cigarette users are severely at risk. The heavy coffee drinkers have somewhat more myocardial infarctions and deaths from coronary disease than do those who take little, but this difference is not statistically significant". The important point about this analysis is that the transformation has eliminated the interaction between cigarette smoking and coffee drinking. The authors concluded by stating "The heavy use of coffee may be implicated as a risk factor although the importance is clearly much less (than cigarettes) and may be questioned".

It is evident, then, that the alleged statistically significant correlation between coffee consumption and coronary heart disease development may even be biologically unimportant. Neither a study by WALKER and GREGORATOS (1967) at the Walter Reed Army Hospital in Washington nor the prospective epidemiological study in Framingham, Massachusetts (KANNEL 1966) has shown a significant association between the excessive use of coffee and the development of coronary heart disease.

It is interesting to note that ZELLER and AMMON were unable to increase the cholesterol level or the level of esterified fatty acids in the serum of 52 patients with liver disease as well as 41 healthy control persons after injections of caffeine or drinking of coffee. These results were obtained in six laboratory determinations on each subject over a period of three hours after intravenous application of 250 mg of caffeine or consumption of 225 mg of caffeine. However, as expected, they saw a marked increment of free fatty acids in healthy persons with a peak serum level two hours after caffeine administration and a peak serum level one to six hours after caffeine administration in patients with liver disease.

Two British studies, one by BROWN in 1962 and the other one by NAISMITH and co-workers in 1969, could not show a positive correlation between use of coffee and coronary heart disease or coffee consumption and cholesterol levels. The study by NAISMITH and co-workers which was just reported was conducted on 20 healthy adult volunteers with an average age of 32. From records of the number of cups of tea and coffee consumed for ten consecutive days, the 'background' daily intake of caffeine for the individual and for the group was calculated. During the first two weeks of the experiment each subject drank ten cups of decaffeinated coffee per day totaling 20 gm Sanka instant coffee containing 12 mg caffeine. Subsequently, for 20 days 10 cups of coffee (20 gm

Maxwell House instant coffee = 875 mg caffeine) were consumed daily. The subjects were asked not to make any changes in their customary diets apart from avoiding other beverages containing caffeine (Fig. 1).

The mean 'background' caffeine intake for the entire group was high (560 mg per day). After two weeks on an almost *caffeine free regimen* plasma cholesterol levels were increased. The change in cholesterol levels was regarded statistically highly significant. The *P* value was not given. With the reintroduction of caffeine into the diet, the picture was reversed. The plasma cholesterol fell to near normal values and again the changes in cholesterol levels were given as statistically highly significant.

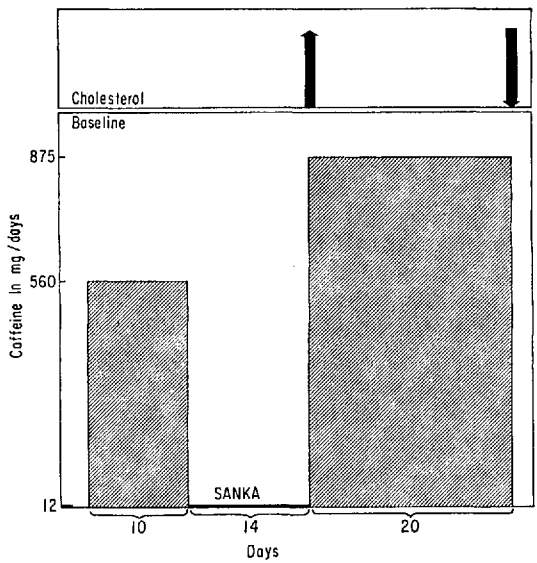

Fig. 1

Although the total impact of the previously mentioned observations in humans was that of essentially no correlation between coffee drinking and the development of hypercholesterolemia or ischemic heart disease, the suspicion had been raised and one solution seemed to be animal experimentation. Here again, the several reported results were negative, i.e. indicating a non-cholesterol elevating effect and non-atherogenic effect of caffeine. However, a few studies demonstrated the development of hypercholesterolemia, e. g. NAISMITH et al. 1969, the same group of investigators who found no cholesterol enhancing effect of caffeine in humans but rather a cholesterol lowering effect!

The hypothesis that coffee or caffeine might be harmful to the coronary arteries has been advanced most recently by a group of the Bio-Medical Division of the University of California. They contended "that the overt coffee drinking population has a higher degree of atherosclerosis than the overt tea drinking population" (YOUNG et al 1967).

They compared the degree of coronary atherosclerosis of 155 Caucasians whom they designated as 'coffee drinking population' with the degree of coronary atherosclerosis of 50 Chinese whom they designated as 'tea drinking population'. The age and sex were not mentioned (!). The mean degree of coronary atherosclerosis in Caucasians was given as "58", in the Chinese as "37". In view of the great variation with their method it is highly unlikely that these differences are significant. It is impossible to perform any statistical comparison because the authors have failed to report standard deviations (Table 2).

Table 2. Degree of Atherosclerosis in Habitual Coffee Drinkers and Habitual Tea Drinkers

	Coronary Atherosclerosis	Total Examined	Cerebral Atherosclerosis	Total Examined
Coffee drinking population (white)	58	155	33	150
Tea drinking population (Chinese)	37	50	12	40

From: YOUNG et al.: Tea and Atherosclerosis (Nature *216*, 1015 (1967).

In a total number of 150 examinations of cerebral arteries in Caucasians they found a mean degree of "33" in cerebral atherosclerosis and among 40 examinations of cerebral arteries in Chinese a mean degree of "12" in cerebral atherosclerosis.

Basically, we would agree to search for environmental factors in order to explain still existing differences in the rate and amount of atherosclerosis in the Caucasian and the Oriental race. But this particular study can not be called a search for factors, e. g. nutritional habits since the subjects were already deceased and were post mortem categorized into either white = "coffee drinking" or Chinese = "tea drinking".

It is quite an assumption to "lump" a Caucasian because of his white color into the "coffee drinking population", particularly after one has studied the coffee drinking habits of *white* people in our Evans County (Georgia) Study where we find actually more tea drinkers. However, in the absence of age- and sex-specific data and standard deviations of the grading of atherosclerosis of the coronary and cerebral arteries these numbers are useless and would lead us to become skeptical about the outcome of an animal experiment which this same group of investigators conducted. The purpose of their experiment was to explore the relationship between tea drinking and atherosclerosis (Table 3). Since tea contains a considerable amount of caffeine it is pertinent to discuss this experiment briefly.

Rabbits were maintained for 3 months on a diet consisting of rabbit chow augmented with 3% Wesson oil and 0.25% cholesterol. Data on serum lipids were available on 4 groups of animals but the frequency with which these determinations were made (or whether they represent a mean value) was not

Table 3. Relationship between Atherosclerosis and the Concentration of Serum Lipoproteins in Rabbits

Animal Group	(n)	Lipoproteins sf 0–12	12–20	20–100	Degree of Atherosclerosis
Control	(6)	50	16	0	0
Diet Alone	(5)	309	251	623	7.2
Diet and Tea	(4)	214	79	437	2.0
Diet early and Tea later	(10)	374	169	389	6.0

From: YOUNG et al.: Tea and Atherosclerosis (Nature *216*, 1015 (1967).

stated. The group of major interest was the one which was fed the diet plus tea. It consisted of 4 animals; the control group which received neither the high fat diet nor tea consisted of six animals and the group which received diet alone had 5 animals. Finally, the group which was on a diet 3 months before the tea was supplied in the drinking water had 10 animals. The table shows the results which led the investigators to the conclusion: "The data show that tea decreases concentration of lipids in the serum . . . they further suggest that if the atherosclerosis proceeds beyond a reversable stage, tea cannot reverse it. Probably tea must be supplied simultaneously with fat or immediately after a meal of fat. Theophylline and theobromine are far less effective, if at all, than tea in preventing the aorta from forming atheroma. Thus it seems that some active principle other than theophylline in the tea extract must be responsible for preventing the formation of atheroma". In view of the small number and variability of sample size, the absence of information on sex, age and weight of these animals and particularly in view of the preconceived hypothesis of this group of investigators, demonstrated in their study of coronary and cerebral atherosclerosis in man, we seriously doubt the validity of these conclusions.

We have participated in two experimental studies ourselves, both of which had a negative outcome as far as atherosclerosis of the aorta and the coronary arteries of rabbits or cholesterol metabolism were concerned (HEYDEN and RÜTTNER 1966 and HEYDEN et al. 1969). We have discussed our results with Dr. STAMLER in Chicago, who also found no hypercholesterolemia enhancing effect of coffee in chickens (personal communication, unpublished data).

Summary

For the past five years the medical literature dealing with coffee is replete with statements made by the two groups of investigators, LITTLE et al. and PAUL et al. quoted previously. From our discussion of the original articles and subsequently published papers by the same authors, it becomes clear that they do not support each other.

The statement by LITTLE and co-workers that the raised concentration of free fatty acids "may accelerate rate of synthesis and release of lipoproteins and raise serum lipid levels" is an assumption which they themselves questioned in these words: "It has yet to be shown, that other serum lipid fractions (besides free fatty acids) will become elevated with long-term drinking of coffee or that increased atherosclerosis results". PAUL and co-workers could not confirm the finding by LITTLE's group by stating: "We did not have evidence that the serum cholesterol level was significantly higher in the group with the highest coffee consumption". On the other hand LITTLE's group was unable to confirm the observation by PAUL's group that there was a significant correlation between the use of coffee and the later development of coronary disease in American patients. The Canadian coronary patients drank equal amounts of coffee as their controls and it was specifically mentioned that Toronto physicians have not prescribed modification of coffee ingestion in patients after myocardial infarction.

If therefore the two studies on which all future statements and speculations were based not only disagree but actually contradict each other we have good reasons to dismiss the issue at this time. This is an even more desirable decision as PAUL and co-workers themselves have retracted their 1963 statement when they admitted in 1968 that the importance of heavy use of coffee as a risk factor may be questioned. The fact that one of the most reliable epidemiological long-term studies, the Framingham Study, after 16 years of observation in over 5,000 adults could demonstrate "no substantial effect of heavy consumption of coffee or tea on morbidity and mortality" from coronary heart disease according to a 1967 report by KANNEL et al., favors our conclusion to dismiss the issue.

In addition we have attempted to demonstrate from several other conditions which cause an increment in free fatty acids that a subsequent rise in cholesterol levels is not observed. There is no reason to believe that the temporary elevation of free fatty acids after coffee ingestion necessarily leads to an increase in serum cholesterol concentrations. Our own observations in an animal species which is known to have a species specific susceptibility for hypercholesterolemia and atherogenesis convinced us that caffeine – regardless of the route of administration – over a three months period has no hypercholesterolemia enhancing effect at all.

In conclusion we feel the time has come to put an end to the allegations that coffee might exert a negative influence on the fat metabolism and its sequelae.

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HISTORISCHES

Zur Geschichte der Deutschen Gesellschaft für Verdauungs- und Stoffwechselkrankheiten

Von R. AMMON und U. RITTER

Am 2. Pfingstfeiertag 1912 fanden in Homburg v.d.H. die ersten Vorbesprechungen zur Gründung einer Gesellschaft statt, die sich mit Fragen auf dem Gebiete der Verdauung und des Stoffwechsels befassen sollte. Die eigentliche Gründung erfolgte 1913, und als am 24. April 1914 im Goldsaale des Kurhauses in Homburg v.d.H. der Geh. Medizinalrat Professor Dr. C. A. EWALD aus Berlin die 1. Tagung über Verdauungs- und Stoffwechselkrankheiten eröffnete, gab er eine Übersicht über den Anlaß und das Ziel der Tagung. Er sagte dabei u. a. wörtlich:

„Unsere Tagung soll diejenigen zusammenschließen, die sich so lebhaft an dem Ausbau der Verdauungs- und Stoffwechselkrankheiten interessieren, daß ihnen der Rahmen, in dem sich die Erörterung dieser Dinge bisher in Vereinen und Kongressen bewegt, zu beschränkt geworden ist. Ich möchte aber ausdrücklich betonen, daß damit nicht gesagt sein soll, daß es sich hier um eine Versammlung von Spezialisten für Spezialisten handelt.

Unter uns sind schon jetzt viele, deren wissenschaftliche und praktische Tätigkeit über das gesamte weite Feld der inneren Medizin führt, und wir möchten alle die zu uns rufen und sie bitten, sich uns anzuschließen, die nach irgendeiner Richtung hin ein ernstes Interesse an den Fragen der Verdauungs- und Stoffwechselkrankheiten nehmen, mögen sie nun Anatomen, Physiologen, Chemiker oder Ärzte im engeren Sinn sein. Das Feld ist so groß, die Probleme sind so mannigfaltig, daß sie ohne Gefährdung anderer Disziplinen oder der inneren Klinik als der alma mater und dem Brennpunkte, in dem sich alle divergierenden Strahlen wieder vereinigen, ihre Sonderbehandlung vertragen können".