the consulting room or the family home that many of those worried by AIDS can be helped. Consideration must also be given to the well being of staff, many of whom have known affected families for years and have watched the hitherto successful application of home therapy and prophylaxis.

To cope we think it imperative that the medical, nursing, social work, and laboratory support provided to every centre treating people in any group at risk, including haemophilia centres, should be assessed as a matter of urgency. Extra support is also needed by the voluntary societies concerned with the care of patients with AIDS in the community.

We thank the staffs of the Northern Regional Haemophilia Service and the Infectious Diseases Unit at Newcastle General Hospital for their help in the preparation of this paper. Dr John Craske of the regional virus laboratory, Withington Hospital, Manchester, gave us great help and advice.

Appendix: Centres for Disease Control Surveillance definitions

AIDS is (a) the presence of reliably diagnosed disease at least moderately predictive of cellular immune deficiency, and (b) the absence of an underlying cause for the immune deficiency or of any defined cause for reduced resistance to the disease. AIDS related complex is a condition in which a person must have two or more symptoms or signs of specific chronic unexplained conditions for three months or longer, together with two or more abnormal laboratory values. The symptoms and signs include non-inguinal lymphadenopathy, weight loss, fever, diarrhoea, fatigue-malaise, and night sweats and the laboratory studies include measurements of lymphocyte subsets and other blood cells, increased serum globulin concentrations, and measurements showing reduction in immune response. To fulfil the criteria of generalised lymphadenopathy at least two

extrainguinal sites must be affected for at least three months in the absence of any current illness or drug known to cause lymphadenopathy.

References

- 1 Ammann AJ, Cowan MJ, Wara DW, *et al.* Acquired immunodeficiency in an infant: possible transmission by means of blood products. *Lancet* 1983;i:956-8.
- 2 Barre-Sinoussi F, Chermann JC, Rey F, *et al.* Isolation of a T-lymphotropic retrovirus from a patient at risk for acquired immune deficiency syndrome (AIDS). *Science* 1983;220:868-71.
- 3 Gallo RC, Shearer GM, Kaplan M, *et al.* Frequent detection and isolation of cytopathic retroviruses (HTLV III) from patients with AIDS and at risk for AIDS. *Science* 1984;224:500-3.
- 4 Goedert JJ, Sarngadharan MG, Eyster ME. Antibodies reactive with human T cell leukaemia viruses in the serum of haemophiliacs receiving factor VIII concentrate. *Blood* 1985;65:492-5.
- 5 Moffat EH, Bloom AL, Mortimer PP. HTLV III antibody status and immunological abnormalities in haemophilic patients. *Lancet* 1985;i:935.
- 6 Bloom AL, Forbes CD, Rizza CR. HTLV III, haemophilia, and blood transfusion. *Br Med J* 1985;290:1901.
- 7 Evtatt BL, Ramsey RB, Lawrence DN, *et al.* Acquired immune deficiency syndrome in patients with haemophilia. *Ann Intern Med* 1984;100:499-504.
- 8 Johnson N McI. Pneumonia in the acquired immune deficiency syndrome. *Br Med J* 1985;290:1299-301.
- 9 Gottlieb MS, Young LS. Adverse reactions to pyrimethamine-sulfadoxine in context of AIDS. *Lancet* 1985;i:1389.
- 10 Eyster ME, Goedert JJ, Sarngadharan MG, *et al.* Development and early natural history of HTLV III antibodies in persons with haemophilia. *JAMA* 1985;253:2219-23.
- 11 Curran JW, Lawrence DN, Jaffe H, *et al.* Acquired immunodeficiency syndrome (AIDS) associated with transfusions. *N Engl J Med* 1984;310:69-75.
- 12 Clavel F, Klatzmann D, Montagnier L. Deficient LAV, neutralising capacity of sera from patients with AIDS or related syndromes. *Lancet* 1985;i:879-80.
- 13 Eyster ME, Goedert JJ. The potential spread of HTLV III to sexual partners of persons with haemophilia. *AIDS update: medical bulletin*. New York: National Hemophilia Foundation, 1985:23.
- 14 Redfield RR, Markham PD, Salahuddin SZ, *et al.* Frequent transmission of HTLV III among spouses of patients with AIDS-related complex and AIDS. *JAMA* 1985;253:1571-3.
- 15 Harris C, Small CB, Klein RS, *et al.* Immunodeficiency in female sexual partners of men with the acquired immunodeficiency syndrome. *N Engl J Med* 1983;308:1181-4.
- 16 Jones P. *AIDS and the blood*. London: Haemophilia Society, 1985.
- 17 Lane HC, Masur H, Gelmann EP, *et al.* Correlation between immunological function and clinical subpopulations of patients with the acquired immunodeficiency syndrome. *Am J Med* 1985;78:417-22.
- 18 Siegel FP. Normal delayed type skin reactions in early stages of acquired cellular immunodeficiency. *N Engl J Med* 1982;307:184.
- 19 Evans BA, Lawrence A, Oates JK, Samarasinghe PL. Clinical work-load of HTLV III infection. *Lancet* 1985;i:1388.

(Accepted 15 August 1985)

Coffee, tea, and plasma cholesterol: the Jerusalem Lipid Research Clinic prevalence study

J D KARK, Y FRIEDLANDER, N A KAUFMANN, Y STEIN

Abstract

The association of intake of coffee and tea, assessed by 24 hour dietary recall, with plasma cholesterol and its lipoprotein fractions was studied in a sample of 1007 men and 589 women aged 35-64 resident in Jerusalem.

Jerusalem Lipid Research Clinic, Hadassah University Hospital, Jerusalem

J D KARK, MD, PHD, epidemiologist, Department of Social Medicine, Hebrew University and Hadassah School of Public Health and Community Medicine, Faculty of Medicine, POB 1172, Jerusalem 91010

Y FRIEDLANDER, PHD, biostatistician, Department of Medicine B, Hadassah University Hospital

N A KAUFMANN, MD, professor and chairman, Department of Nutrition, Hebrew University—Hadassah Medical School, Jerusalem

Y STEIN, MD, professor and chairman, Department of Medicine B, Hadassah University Hospital

Correspondence to: Dr J D Kark, Department of Social Medicine, Hebrew University and Hadassah School of Public Health and Community Medicine, Faculty of Medicine, POB 1172, Jerusalem 91010.

These cross sectional data showed a significant linear association ($p < 0.001$) between consumption of coffee in men and plasma cholesterol and low density lipoprotein cholesterol concentrations. Men who drank five cups of coffee or more had plasma cholesterol concentrations about 0.5 mmol/l (20 mg/100 ml) higher than non-drinkers after controlling for age, ethnicity, body mass, education, season of year, smoking, tea drinking, and dietary intake of fat and carbohydrates. In women adjusted mean plasma cholesterol concentration was 0.34 mmol/l (13 mg/100 ml) higher in coffee drinkers grouped together ($p < 0.01$). The test for a linear trend was not significant. The association in both sexes was largely with the low density lipoprotein cholesterol fraction. High density lipoprotein cholesterol concentrations were somewhat increased in women who drank coffee ($p < 0.01$ for a linear trend) but not in men. Tea drinking was not associated with unadjusted plasma cholesterol concentrations in either sex. Male tea drinkers, but not female, had slightly higher adjusted plasma cholesterol concentrations than non-drinkers (0.15 mmol/l (6 mg/100 ml), $p = 0.04$). No dose response relation was evident.

In this population, characterised by a low intake of saturated fatty acids and relatively low mean plasma cholesterol concentrations, coffee drinking may be a determinant of low density lipoprotein cholesterol concentrations.

Introduction

Recently the Tromsø heart study reported a strong linear association between consumption of coffee and serum cholesterol concentrations in a large population sample of men and women. Intake of nutrients was not controlled in the analysis.¹ The same investigators subsequently supported their cross sectional findings with a small crossover trial using black boiled coffee.² We studied this relation in a sample of 1596 residents of Jerusalem for whom detailed dietary data as well as information on intake of beverages were available. The Israeli and Norwegian

ded details of additives (mainly milk and sugar) but not of methods of brewing or strength of the beverage. We coded the number of cups of coffee consumed in the 24 hour period of recall according to whether the coffee was drunk with or without added milk. Our primary question related to the association of coffee drinking with plasma cholesterol concentrations, but the issue of whether tea showed the same association as coffee was also of interest. Coffee and tea drinking were inversely correlated in our study population ($r = -0.4$). Each beverage was controlled for when the independent effects of the other were assessed. We adjusted for two nutrient variables—namely, saturated fatty acids and sugar—each of which was expressed as a percentage of 24 hour intake of energy. The main additives to beverages in Israel, milk and sugar, are reflected in these variables. Intakes of monounsaturated and polyunsaturated fatty acids, cholesterol, starch, and other carbohydrates were also controlled for in additional analyses.

Plasma lipid and lipoprotein concentrations were measured according to the protocol of the Lipid Research Clinics in blood samples drawn after a 12 hour fast.¹² Plasma cholesterol concentrations were determined with a Technicon (USA) Autoanalyzer II, which uses the

TABLE 1—Selected characteristics of study population

	Men	Women
No of subjects	1007	589
Age (years):		
Mean (SD)	48.9 (5.7)	44.9 (5.3)
Range	35-64	35-59
Country of birth (No (%)):		
Israel	311 (31)	197 (33)
Europe	261 (26)	127 (22)
Asia	256 (25)	149 (25)
North Africa	179 (18)	116 (20)
Mean (SD) plasma cholesterol (mmol/l)*:		
Israel	5.23 (0.98)	5.08 (0.94)
Europe	5.43 (1.00) [5.44]	5.15 (0.91) [5.20]
Asia	5.27 (0.88) [5.25]	5.30 (1.04) [5.21]
North Africa	5.08 (1.02) [5.09]	4.93 (0.86) [4.95]
Mean (SD) low density lipoprotein cholesterol (mmol/l)	5.00 (0.93) [4.99]	4.91 (0.92) [4.91]
Mean (SD) high density lipoprotein cholesterol (mmol/l)	3.34 (0.85)	3.13 (0.85)
Mean (SD) body mass index (kg/m ²)	1.05 (0.27)	1.32 (0.33)
Mean (SD) saturated fatty acid (% of total energy)	26.4 (3.4)	27.2 (4.7)
Mean (SD) sugar (% of total energy)	10.1 (3.9)	11.0 (4.0)
No (%) of current smokers	9.6 (6.6)	10.4 (7.6)
Coffee consumption (mean No of cups in 24 h and range)	401 (40)	138 (23)
Tea consumption (mean No of cups in 24 h and range)	2.3 (0-14)	2.5 (0-12)
	1.5 (0-10)	1.2 (0-9)

*Figures in square brackets are age adjusted plasma cholesterol concentrations for each country or continent of birth.

Conversion: SI to traditional units—Cholesterol: 1 mmol/l $\approx$ 38.6 mg/100 ml.

populations differ considerably in their blood cholesterol concentrations¹⁻⁵ and dietary characteristics, particularly their intakes of total fat and food rich in saturated fatty acids, complex carbohydrates and fibre,^{6,7} and coffee and tea.¹⁻⁶ Nevertheless, the findings reported here are remarkably similar to those of the Tromsø study.

Methods

Details of the design and methodology of the Jerusalem Lipid Research Clinic prevalence study and characteristics of the population have been reported previously.^{8,9} Briefly, from 1976 to 1979, 8646 Jewish residents of Jerusalem aged 17 attending for compulsory medical examination before military service participated in a health survey whose primary purpose was to determine the distribution of blood lipids and lipoproteins. A 56% random sample of their parents were invited in pairs to participate in a similar survey; 6952 (72%) adults responded. Subsequently a 20% random sample of mothers and a 44% random sample of fathers were invited to a more detailed examination that included a dietary interview; 614 (86%) of the women and 1095 (77%) of the men responded. Data were collected according to the standardised protocol of the Lipid Research Clinics.¹⁰ Characteristics of non-respondents are reported elsewhere.⁸ The analyses reported here are based on 1007 men aged 35-64 and 589 women aged 35-59 after exclusion of 68 older men and two older women, eight men and 10 women because of missing data, and an additional 12 men and 13 women who reported use of lipid lowering agents or gonadal hormones or whose dietary recall was judged unreliable.

The methods of dietary interview and computation of nutrient content have been reported.^{7,11} Dietary intake was assessed by means of a 24 hour recall. Information on consumption of coffee and tea inclu-

Liebermann-Burchardt method. High density lipoprotein cholesterol concentrations were measured directly from the plasma after precipitation of the apolipoprotein B containing lipoproteins with heparin and manganese chloride. Low density lipoprotein cholesterol concentrations were estimated after preparative ultracentrifugation at a density of 1.006 g/ml and subtraction of the high density lipoprotein cholesterol concentration from the cholesterol concentration in the bottom fraction.

Ethnic origin was determined by country of birth and was classified into four groups: Israel, Europe, Asia, and north Africa.

The χ^2 statistic was used for testing associations in contingency tables. Differences in means and distributions of plasma lipid concentrations between categories of coffee consumption were tested by one way analysis of variance and the non-parametric Kruskal-Wallis method. Both methods gave similar results. Multiple linear regression was subsequently used to control for covariates, which were selected because of their univariate association with coffee intake and with total plasma cholesterol or its lipoprotein fractions, or both.^{5,13-15} Intakes of coffee and tea were grouped as 0, 1-2, 3-4, and 5+ cups in each 24 hours and introduced into the regression as categorical (dummy) variables with non-drinkers as the reference group.

Regressions were repeated with the beverages coded as the actual (ungrouped) number of cups to test for a linear trend. Age was introduced as linear and quadratic terms, ethnic origin as three dummy variables, and body mass index as kg/m²; education was classified as elementary school, partial high school, high school, or higher education; smoking was classified as 0, 1-10 cigarettes a day = 1, 11-20 cigarettes = 2, 21-30 cigarettes = 3, or 31+ cigarettes = 4; intake of saturated fatty acids and sugar was expressed as a percentage of total energy; and season was modelled by sine and cosine functions of the time that had elapsed between 1 January and the day of examination transformed to a scale of 0-2 π .¹⁴ Significance tests were two sided.

TABLE II—Distribution of intake of coffee and tea reported in 24 hour period of recall according to sex and country of birth. (Figures are numbers (%) of subjects)

No of cups	Coffee					Tea				
	Israel	Europe	Asia	North Africa	Total	Israel	Europe	Asia	North Africa	Total
Men										
0	21 (7)	31 (12)	85 (33)	33 (18)	170 (17)	163 (52)	129 (49)	42 (16)	43 (24)	377 (37)
1	44 (14)	54 (21)	63 (25)	45 (25)	206 (20)	60 (19)	57 (22)	59 (23)	48 (27)	224 (22)
2	81 (26)	72 (28)	44 (17)	45 (25)	242 (24)	38 (12)	38 (15)	54 (21)	37 (21)	167 (17)
3	71 (23)	41 (16)	34 (13)	25 (14)	171 (17)	22 (7)	18 (7)	38 (15)	20 (11)	98 (10)
4	37 (12)	28 (11)	16 (6)	18 (10)	99 (10)	18 (6)	12 (5)	28 (11)	21 (12)	79 (8)
5+	57 (18)	35 (13)	14 (5)	13 (7)	119 (12)	10 (3)	7 (3)	35 (14)	10 (6)	62 (6)
Total No of men	311	261	256	179	1007	311	261	256	179	1007
Women										
0	5 (3)	16 (13)	36 (24)	15 (13)	72 (12)	119 (60)	68 (54)	46 (31)	34 (29)	267 (45)
1	25 (13)	24 (19)	38 (26)	36 (31)	123 (21)	47 (24)	31 (24)	26 (17)	33 (28)	137 (23)
2	42 (21)	20 (16)	33 (22)	33 (28)	128 (22)	16 (8)	11 (9)	33 (22)	27 (23)	87 (15)
3	46 (23)	29 (23)	20 (13)	16 (14)	111 (19)	8 (4)	4 (3)	19 (13)	12 (10)	43 (7)
4	35 (18)	18 (14)	13 (9)	14 (12)	80 (14)	3 (2)	6 (5)	11 (7)	7 (6)	27 (5)
5+	44 (22)	20 (16)	9 (6)	2 (2)	75 (13)	4 (2)	7 (6)	14 (9)	3 (3)	28 (5)
Total No of women	197	127	149	116	589	197	127	149	116	589

Test for homogeneity of coffee drinking between place of origin: in men $\chi^2_{15} = 118.6$, $p < 0.0001$; in women $\chi^2_{15} = 94.8$, $p < 0.0001$. Test for tea drinking: in men $\chi^2_{15} = 136.1$, $p < 0.0001$; in women $\chi^2_{15} = 80.7$, $p < 0.0001$.

TABLE III—Plasma cholesterol and low and high density lipoprotein cholesterol concentrations by number of cups of coffee and tea reported in 24 hour period of recall expressed as unadjusted and adjusted mean (SE) difference (in mmol/l) between each category of drinkers and non-drinkers

No of cups	No of subjects	Cholesterol		Low density lipoprotein cholesterol		High density lipoprotein cholesterol	
		Unadjusted	Adjusted	Unadjusted	Adjusted	Unadjusted	Adjusted
Coffee							
Men							
0+	170	(4.94)		(3.13)		(1.07)	
1-2	448	0.26** (0.09)	0.21* (0.09)	0.19* (0.08)	0.17* (0.08)	-0.03 (0.02)	-0.03 (0.03)
3-4	270	0.36** (0.1)	0.3** (0.1)	0.27** (0.08)	0.24** (0.09)	-0.02 (0.03)	-0.02 (0.03)
5+	119	0.63** (0.12)	0.56** (0.13)	0.05** (0.1)	0.47** (0.11)	-0.05 (0.03)	-0.05 (0.04)
p Linear trend§		<0.0001	0.0005	<0.0001	0.0004	(-) 0.42	(-) 0.42
Women							
0+	72	(4.79)		(2.86)		(1.31)	
1-2	251	0.28* (0.12)	0.33* (0.13)	0.27* (0.11)	0.29* (0.12)	-0.02 (0.04)	-0.01 (0.04)
3-4	191	0.37** (0.13)	0.38** (0.14)	0.34** (0.12)	0.32* (0.13)	0.03 (0.05)	0.06 (0.05)
5+	75	0.34* (0.15)	0.31 (0.17)	0.35* (0.14)	0.31* (0.16)	0.08 (0.06)	0.08 (0.06)
p Linear trend§		0.031	0.14	0.026	0.18	0.018	0.007
Tea							
Men							
0+	377	(5.24)		(3.35)		(1.04)	
1-2	391	0.02 (0.07)	0.15* (0.08)	0.02 (0.06)	0.12 (0.06)	0.02 (0.02)	0.01 (0.02)
3-4	177	-0.09 (0.09)	0.13 (0.10)	-0.06 (0.08)	0.01 (0.09)	0.05 (0.02)	0.03 (0.03)
5+	62	-0.07 (0.13)	0.19 (0.14)	-0.02 (0.12)	0.17 (0.13)	-0.03 (0.04)	-0.03 (0.04)
p Linear trend§		(-) 0.26	0.18	(-) 0.39	0.26	0.59	(-) 0.89
Women							
0+	267	(5.10)		(3.16)		(1.31)	
1-2	224	-0.03 (0.09)	0.03 (0.09)	-0.04 (0.08)	0.02 (0.08)	0.01 (0.03)	0.02 (0.03)
3-4	70	0.02 (0.13)	0.2 (0.13)	0.01 (0.12)	0.2 (0.13)	0.03 (0.04)	0.04 (0.05)
5+	28	-0.15 (0.19)	-0.04 (0.2)	-0.3 (0.17)	-0.15 (0.18)	0.12 (0.07)	0.11 (0.07)
p Linear trend§		(-) 0.56	0.3	(-) 0.17	0.59	0.056	0.039

†Unadjusted mean absolute values for non-drinkers given in parentheses.

‡Adjusted by linear regression for age, age squared, ethnic origin, Quetelet's index, level of education, smoking, saturated fatty acids, sugar, season, and tea or coffee (beverages introduced as dummy variables). Test for difference between each level of coffee (or tea) intake and non-drinkers: * $p < 0.05$; ** $p < 0.01$.

§Obtained from linear regression with same variables except that coffee and tea were introduced as linear terms retaining their initial (ungrouped) values. Beverage not being tested was controlled as dummy variable. (-) Denotes inverse association—that is, negative regression coefficient.

||For low and high density lipoprotein cholesterol concentrations two women had missing values, leaving 587 for analyses.

Conversion: SI to traditional units—Cholesterol: 1 mmol/l $\approx$ 38.6 mg/100 ml.

Results

Table I shows selected characteristics of the population studied. Salient features were the ethnic differences in plasma cholesterol concentrations and the relatively low mean plasma cholesterol concentrations and the low intake of saturated fatty acids as compared with Scandinavian and North American populations, for example.^{3 4 16-18}

Consumption of coffee during the 24 hour period of recall was reported by 83% of the men and 88% of the women (table II). Only 12% of men and 13% of women drank five cups or more. Tea drinking was less common: 63% of men and 55% of women reported having drunk tea in the 24 hour period. Coffee drinking was more common among people born in Israel or Europe than people born in Asia or north Africa (and was also more common in the educated and was inversely associated with age). The reverse was true for tea drinking. Intake of both beverages, but particularly tea, was increased in the winter months.

Tables III and IV show the association of intake of coffee and tea with plasma cholesterol and its major lipoprotein constituents, low density and high density lipoprotein cholesterol. The crude and multi-variable adjusted mean values of plasma cholesterol concentrations in men showed a stepwise increment with increasing intake of coffee ($p = 0.008$ for a linear trend) and was 13% lower in heavy coffee had adjusted plasma cholesterol and low density lipoprotein cholesterol concentrations that were 0.56 mmol/l (22 mg/100 ml) and 0.47 mmol/l (18 mg/100 ml) higher, respectively, than non-drinkers of coffee (11% and 15% higher than in non-drinkers). High density lipoprotein cholesterol concentrations were slightly lower in coffee drinkers (not significant). Almost the entire association with plasma cholesterol concentrations could be attributed to low density lipoprotein cholesterol. The ratio of high density lipoprotein cholesterol concentrations to total cholesterol concentrations adjusted for covariates was inversely associated with consumption of coffee ($p = 0.008$ for a linear trend) and was 13% lower in heavy coffee drinkers than non-drinkers. Among women adjusted mean

TABLE IV—Mean plasma cholesterol and low density lipoprotein cholesterol concentrations in men and women by intake of coffee over 24 hours adjusted by analysis of covariance for age, ethnic origin, body mass, season, and consumption of tea (yes, no), saturated fatty acids, and sugar

No of cups	Total plasma cholesterol (mmol/l)		Low density lipoprotein cholesterol (mmol/l)	
	Men	Women	Men	Women
0	4.98	4.78	3.14	2.85
1-2	5.19	5.11	3.31	3.15
3-4	5.29	5.16	3.40	3.20
5+	5.55	5.08	3.62	3.19

Conversion: SI to traditional units—Cholesterol: 1 mmol/l ≈ 38.6 mg/100 ml.

plasma cholesterol concentrations were higher by 0.31-0.38 mmol/l (12-15 mg/100 ml) in coffee drinkers (at the three levels of intake) than in non-drinkers. In female coffee drinkers grouped together adjusted cholesterol concentrations were 0.34 mmol/l (13 mg/100 ml) higher than those in non-drinkers (p=0.007) and mean low density lipoprotein cholesterol concentrations were 0.30 mmol/l (12 mg/100 ml) higher (p=0.008). There was no clear dose response relation. The test for a linear trend for unadjusted cholesterol and low density lipoprotein cholesterol concentrations (p<0.05 for both) became non-significant on controlling for covariates. Addition of a quadratic term for coffee did not significantly improve the fit of the regression. High density lipoprotein cholesterol concentrations were mildly but significantly higher in women who drank coffee (p<0.01 for a linear trend). The ratio of high density lipoprotein cholesterol to total cholesterol concentrations showed no consistent association with coffee drinking.

Intake of tea was weakly inversely associated with plasma cholesterol concentrations on univariate analysis (not significant). After multivariate adjustment plasma cholesterol concentration in the men was higher by 0.15 mmol/l (6 mg/100 ml) in tea drinkers than non-drinkers (p=0.04), mostly in the low density lipoprotein cholesterol fraction. A test for a linear trend was not significant. Confounding by intake of coffee may have obscured a weak association of tea with plasma cholesterol concentrations in men in the univariate analysis. There was no association of tea drinking with high density lipoprotein cholesterol concentration. In women there was no significant association of tea with total cholesterol or low density lipoprotein cholesterol concentration. High density lipoprotein cholesterol concentrations were slightly increased in women tea drinkers (p=0.04 for a linear trend).

The analyses for both beverages were repeated adjusting for additional dietary fat and carbohydrate nutrient variables. Findings remained essentially unchanged.

The association of intake of coffee with plasma cholesterol concentrations was examined according to country of birth. In seven of the eight groups defined by sex and country of origin people who drank no coffee had the lowest unadjusted mean plasma cholesterol and low density lipoprotein cholesterol concentrations and those who drank five or more cups the highest (data not shown). Women born in Israel, of whom only five did not drink coffee, showed weak and non-significant inverse associations between intake of coffee and cholesterol and low density lipoprotein cholesterol concentrations. Reanalysis of the data for women in table III after exclusion of those born in Israel showed a strong and significant linear association of both plasma cholesterol and low density lipoprotein cholesterol concentra-

tions with intake of coffee (p=0.004 and p=0.009, respectively) in multiple linear regression. The regression coefficients for men and women did not differ much within each ethnic group except for those born in Israel, in whom the coefficients for men were positive and for women negative. Owing to the relatively small numbers in some of the groups defined by sex and area of origin data for men and women were pooled for each area of origin and a term for sex was added to the multiple regression (table V). Sex pooled data for those born in Israel should be viewed cautiously. In three of the four groups defined by area of origin total cholesterol and low density lipoprotein cholesterol concentrations were considerably higher in consumers of five or more cups of coffee than in non-drinkers. A test for a linear trend for low density lipoprotein cholesterol concentrations was significant at the 0.05 level for all areas of origin except Israel. Findings were similar when interaction terms of sex with each control variable were included in the regression models. The regression slope coefficients for plasma cholesterol and low density lipoprotein cholesterol concentrations were largest in men and women born in north Africa. An overall test for an interaction between ethnic group and coffee consumption was significant for total plasma cholesterol concentrations (p<0.05) but not for low density lipoprotein cholesterol concentrations.

Discussion

In our multiethnic population there appeared to be a substantial association of plasma cholesterol concentration with the reported intake of coffee over 24 hours. The evidence was stronger in men than in women. The findings were generally positive in the ethnic groups in both sexes. Apparent ethnic differences in the strength of the association require confirmation. The ethnic groups in Israel differ in their dietary intake and probably in their coffee brewing habits. A linear association was maintained in men after control for several covariates, including nutrients that reflect additives to the beverages as well as dietary patterns. In the smaller sample of women, coffee drinkers had higher adjusted mean plasma cholesterol concentrations than non-drinkers, although a test for a linear trend was not significant except when those born in Israel were excluded. The association in both sexes was mostly with the low density lipoprotein fraction of plasma cholesterol. Adjustment for potential confounders had a moderate overall effect on the magnitude and standard error of the regression coefficients for cholesterol and low density lipoprotein cholesterol. Adjustment for several variables (season, intake of fat, and particularly ethnicity) tended to weaken the association; this was partly offset by other variables (age, intake of tea, body mass). The relation with high density lipoprotein cholesterol concentrations was weakly inverse in men and moderately positive in women (limited mainly to women born in Asia and north Africa). The ratio of high density lipoprotein cholesterol to total cholesterol was lower in male coffee drinkers but not in female. In the larger Tromsø study a linear association with cholesterol concentrations was evident in both sexes, whereas findings for high density lipoprotein cholesterol concentrations on adjustment were inconsistent.¹

TABLE V—Plasma cholesterol and low density lipoprotein cholesterol concentrations by intake of coffee expressed as adjusted mean (SE) difference (in mmol/l) between each category of drinkers and non-drinkers, and adjusted regression coefficients, for subjects born in Israel, Europe, Asia, and north Africa (men and women grouped together)

No of cups of coffee	Israel			Europe			Asia			North Africa		
	No of subjects	Cholesterol	Low density lipoprotein cholesterol	No of subjects	Cholesterol	Low density lipoprotein cholesterol	No of subjects	Cholesterol	Low density lipoprotein cholesterol	No of subjects	Cholesterol	Low density lipoprotein cholesterol
0	26			47			121			48		
1-2	192	0.23 (0.20)	0.12 (0.18)	170	0.4* (0.16)	0.29* (0.14)	178	0.15 (0.11)	0.17 (0.10)	159	0.23 (0.15)	0.25* (0.13)
3-4	189	0.15 (0.21)	0.15 (0.18)	116	0.41* (0.17)	0.31* (0.15)	83	0.31* (0.15)	0.25 (0.13)	73	0.57* (0.17)	0.46** (0.15)
5+	101	0.22 (0.23)	0.17 (0.02)	55	0.54** (0.19)	0.50** (0.17)	23	0.42 (0.23)	0.37 (0.20)	15	0.87** (0.27)	0.49* (0.24)
Regression slope coefficient (SE)*		0.003 (0.025)	0.012 (0.022)		0.051 (0.026)	0.051 (0.024)		0.084 (0.033)	0.066 (0.030)		0.135 (0.036)	0.096 (0.032)
p linear trend†		0.90	0.57		0.051	0.031		0.012	0.029		<0.001	0.003

Adjusted by linear regression for sex, age, age squared, Quetelet's index, level of education, smoking, saturated fatty acids, sugar, season, and tea (yes = 1, no = 0) with coffee introduced as dummy variable. Significance of difference between each level of intake of coffee and non-drinkers: *p<0.05, **p<0.01.
*Expressed as mmol cholesterol/l per cup of coffee.
†Obtained from linear regression with same variables except that coffee was introduced as linear term (ungrouped number of cups).
Conversion: SI to traditional units—Cholesterol: 1 mmol/l ≈ 38.6 mg/100 ml.

In the Evans county study an association of low density lipoprotein cholesterol concentrations with intake of coffee was apparent only in cigarette smokers.¹⁹ In our study there was no evidence for an interaction between smoking and coffee (data not shown).

Our data are lacking in that we did not collect information about the methods of brewing coffee or about the strength of the coffee. Our impression is that consumption of decaffeinated coffee was rare and use of percolators was unusual in Israel during the period of the study. Most coffee was probably prepared as instant coffee, ground coffee to which boiling water was added, or boiled ground coffee. According to national food balance sheets, coffee extract was processed from over 40% of imports of coffee beans.⁶ A standard serving of instant coffee in Israel comprises 1.8 g, but we have no estimate of the proportion of people who drink instant coffee who use this quantity for each cup. In this sample from Jerusalem men drank about 60% of their coffee with milk and women over 80%. Subjects born in north Africa and Asia drank a smaller proportion of their coffee with milk than those born in Israel and Europe (41% and 43% v 64% and 75% in men and 56% and 77% v 89% and 88% in women, respectively). We repeated the analyses including separate terms for coffee with and without added milk. Associations with cholesterol concentrations did not differ significantly in the two categories.

Support for an association between coffee and cholesterol in the Israeli population comes from a small study in Jerusalem.²⁰ Among 247 men and women aged 25-44 relations of total cholesterol, low density lipoprotein cholesterol and high density lipoprotein cholesterol concentrations with intake of coffee on the previous day were similar to those reported here. In the current study we controlled for the main known correlates of blood cholesterol concentrations in our population. Nevertheless, it is possible that confounding (possibly related to unmeasured psychobehavioural characteristics or to inadequate control of dietary determinants deriving from use of a 24 hour recall) or some other source of bias might underlie the relation. The overall consistency of our data with the Norwegian study¹ and trial² indicate, however, that these associations apparently prevail in populations that differ considerably in lifestyle, dietary intake, blood cholesterol concentrations, and genetic characteristics. Blood cholesterol concentrations are substantially higher in Tromsø^{1,3} and elsewhere in Norway⁴ than in the Jewish population of Jerusalem. National food balance sheets show that the intake of dietary fat in Norway was 41.4% compared with 32.2% in Israel. Israelis use more foods that contribute complex carbohydrates and fibre, such as cereals, pulses, fruit, and vegetables.⁶

Several studies have reported an association between coffee and cholesterol while others have shown no relation. Cross sectional studies among men and women in Tecumseh and men in Minnesota showed positive unadjusted correlations.^{21,22} In the very large Kaiser-Permanente study of over 40 000 people an association was evident in both sexes.²³ Among American-Japanese men in Hawaii intake of caffeine was related to low density lipoprotein cholesterol concentrations but not to high density lipoprotein cholesterol concentrations.²⁴ In a study in Australia serum cholesterol concentrations were associated with estimated intake of caffeine in women and with caffeinated coffee in men.²⁵ Findings for coffee were positive in smaller studies: in Norway,²⁶ among vegetarians in the United States,²⁷ in a sample of 77 men in California (where the association was shown to be with low density lipoprotein cholesterol concentrations and apolipoprotein B),²⁸ in smokers though not in non-smokers among 361 men and women in Evans county,¹⁹ among male survivors of an acute myocardial infarction in Canada though not among a small group of controls,²⁹ and among young adults but not elderly people in Germany.³⁰ No association was evident, however, in the Framingham study,³¹ the Western Electric study,³² the second United States national health and nutrition examination survey,³³ or a study in the Netherlands.³⁴ The conflicting findings (mainly in the different study populations in the United States),

other than reflecting methodological differences, suggest that differences in types of coffee or brewing methods could be important, or that coffee may interact with dietary intake or other population characteristics, or alternatively may argue against a causal relation. The trial recently reported from Tromsø supports a causal interpretation at least for black boiled coffee.³

To what extent does 24 hour dietary recall reflect usual coffee consumption? This question would be particularly relevant if the effect of coffee on the increase in cholesterol concentrations (if causal) were non-acute. Misclassification of intake of coffee would then probably tend to underestimate the true association. The Tromsø trial suggests that the response is incremental over at least four weeks.³ A small study in Jerusalem, however, showed a stronger association with intake of coffee reported for the previous day than with usual coffee consumption.²⁰ A subsample (numbering 606) of our population analysed in the present report was re-examined after a median of 27 months. The correlation of intake of coffee in the two 24 hour periods of recall was over 0.6 in both men and women, while the corresponding correlations for tea were 0.5 and 0.6. The correlations for saturated fatty acids and sugar were much lower. Thus coffee drinking in our population as ascertained by 24 hour recall was moderately consistent over long periods and almost certainly more so over several weeks.

Evidence in our study for an association of tea drinking with total plasma cholesterol concentrations was equivocal in men and absent in women. After adjustment for coffee drinking and other covariates a weak relation emerged in men. This could be a chance finding. There was no evidence for a dose response. The lack of a positive relation was noted in several studies.^{20-23,29,30} One report, however, showed a linear association (with caffeine estimated from intake of tea) in women, though not in men.²⁵ Few of the studies controlled for the potential confounding effect of coffee.^{20,25}

The role of caffeine, present in both coffee and tea, in raising cholesterol concentrations has been questioned. On the basis of a trial that showed an increase in serum cholesterol concentrations after subjects used decaffeinated coffee for 14 days,³⁵ and the apparent lack of a positive association with intake of tea in several studies, it was suggested that constituents in coffee other than caffeine may play a part in raising cholesterol concentrations.^{1,2} Others argue that caffeine is the component responsible.²⁶

The magnitude of the association of coffee and cholesterol was similar in our study and in Tromsø, where about 80% of the coffee consumed was boiled ground coffee taken strong and black and where 60% of men and 50% of women drank five or more cups a day. The amounts consumed in Jerusalem were much smaller. Information from the national food balance sheets of Norway and Israel is consistent with these data on coffee consumption.⁶ The supply of ground coffee was much larger in Norway than in Israel (19.0 v 4.3 g/day) and supply of coffee extract about equal (0.7 v 0.8 g/day), while that of tea was larger in Israel (0.6 v 2.7 g/day). Thus the potential effect of coffee drinking on serum or plasma cholesterol concentrations in the population, assuming causality, is lower in Israel than in Scandinavia, although still quite substantial (about 0.13-0.26 mmol/l (5-10 mg/100 ml) as estimated from our study).

Further trials are needed to establish whether the relation is causal and to determine the responsible constituent(s). Studies of coffee consumption and the risk of myocardial infarction, which could be mediated through an increase in plasma cholesterol concentrations, have yielded contradictory findings.^{1,36} Clearly, additional investigation of this issue is indicated.

This study was supported by the United States National Heart, Lung, and Blood Institute.

References

- 1 Thelle DS, Arnesen E, Forde OH. The Tromsø heart study. Does coffee raise serum cholesterol? *N Engl J Med* 1983;306:1454-7.
- 2 Arnesen E, Forde OH, Thelle DS. Coffee and serum cholesterol. *Br Med J* 1984; 288:1960.

- 3 Thelle DS, Forde OH, Try K, Lehmann EH. The Tromsø heart study. Methods and main results of the cross-sectional study. *Acta Med Scand* 1976;200:107-18.
- 4 Bjartveit K, Foss OP, Gjervig T. The cardiovascular disease study in Norwegian counties. Results from the first screening. *Acta Med Scand* [Suppl] 1983;675:1-184.
- 5 Halfon S-T, Rifkind BM, Harlap S, et al. Plasma lipids and lipoproteins in adult Jews of different origins: the Jerusalem lipid research prevalence study. *Isr J Med Sci* 1982;18:1113-20.
- 6 United Nations Food and Agriculture Organisation. *Food balance sheets (1975-77 average) and per caput food supplies (1961-65 average, 1967-1977)*. Rome: Food and Agriculture Organisation of the United Nations, 1980.
- 7 Kaufmann NA, Friedlander Y, Halfon S-T, et al. Nutrient intake in Jerusalem—consumption in adults. *Isr J Med Sci* 1982;18:1183-97.
- 8 Slater PE, Friedlander Y, Baras M, et al. The Jerusalem lipid research clinic: sampling, response and selected methodological issues. *Isr J Med Sci* 1982;18:1106-12.
- 9 Kark JD, Slater PE, Stein Y, eds. Cardiovascular risk factors in Jerusalem. The lipid research clinic prevalence study. *Isr J Med Sci* 1982;18:1075-252.
- 10 Central Patient Registry and Coordinating Center of the Lipid Research Clinics. *Reference manual for the lipid research clinics program prevalence study*. Vols 1 and 2. North Carolina: Department of Biostatistics, University of North Carolina at Chapel Hill, 1974.
- 11 Kaufmann NA, Friedlander Y, Halfon S-T, et al. Nutrient intake in Jerusalem—consumption in 17-year-olds. *Isr J Med Sci* 1982;18:1167-82.
- 12 National Heart Lung and Blood Institute. *Manual of laboratory operations. Lipid research clinics program*. Vol 1. *Lipid and lipoprotein analysis*. Bethesda, Maryland: National Institutes of Health, 1974. (DHEW publication No (NIH) 75-628.)
- 13 Harlap S, Baras M, Friedlander Y, et al. Contribution of different lipoprotein fractions to variations in total cholesterol between Israeli origin groups and social classes. *Isr J Med Sci* 1982;18:1131-6.
- 14 Harlap S, Kark JD, Baras M, Eisenberg S, Stein Y. Seasonal changes in plasma lipid and lipoprotein levels in Jerusalem. *Isr J Med Sci* 1982;18:1158-65.
- 15 Halfon S-T, Green M, Heiss G. Smoking status and lipid levels in adults of different ethnic origin in the Jerusalem LRC program. *Int J Epidemiol* 1984;13:177-83.
- 16 Ehnholm C, Huttunen JK, Pietinen P, et al. Effect of diet on serum lipoproteins in a population with a high risk of coronary heart disease. *N Engl J Med* 1982;307:850-5.
- 17 Lipid Research Clinics. *The lipid research clinics population studies data book*. Vol 1. *The prevalence study*. Washington, DC: National Institutes of Health, 1980. (NIH publication No (PHS) 80-1527.)
- 18 Lipid Research Clinics. *The lipid research clinics population studies data book*. Vol 2. *The prevalence study in nutrient intake*. Washington, DC: National Institutes of Health, 1982. (NIH publication No (PHS) 80-2014.)
- 19 Heyden S, Heiss G, Manegold C, et al. The combined effect of smoking and coffee drinking on LDL and HDL cholesterol. *Circulation* 1979;60:22-5.
- 20 Kark JD, Friedlander Y, Donchin M, Kaufmann NA, Stein Y. Coffee and tea drinking and plasma lipids in Kiryat Hayovel (Jerusalem). [Abstract]. *Public Health Rev* 1984;12:115-6.
- 21 Nichols AB, Ravenscroft C, Lamphiear DE, Ostrander LD. Independence of serum lipid levels and dietary habits. The Tecumseh study. *JAMA* 1976;236:1948-53.
- 22 Prineas RJ, Jacobs DR, Crow RS, Blackburn H. Coffee, tea and VLB. *J Chronic Dis* 1980;33:67-72.
- 23 Klatsky AL, Petitti DB, Armstrong MA, Friedman GD. Coffee, tea and cholesterol. *Am J Cardiol* 1985;55:577-8.
- 24 Rhoads GG, Kagan A, Yano K. Associations between dietary factors and plasma lipoproteins [Abstract]. *Circulation* 1976;54:II-53.
- 25 Shirlow MJ, Mathers CD. Caffeine consumption and cholesterol levels. *Int J Epidemiol* 1984;13:422-7.
- 26 Bjelke E. Colon cancer and blood cholesterol. *Lancet* 1974;i:1116-7.
- 27 Sacks FM, Castelli WP, Donner A, Kass EH. Plasma lipids and lipoproteins in vegetarians and controls. *N Engl J Med* 1975;292:1148-51.
- 28 Williams P, Wood P, Vranizan K, Albers J, Garay S, Taylor C. Association of coffee intake with apolipoprotein B, low density lipoprotein cholesterol, and total cholesterol [Abstract]. *Arteriosclerosis* 1984;4:549.
- 29 Little JA, Shanoff HM, Csina A, Yano R. Coffee and serum-lipids in coronary heart-disease. *Lancet* 1966;ii:732-4.
- 30 Arab L, Kohlmeier M, Schlierf G, Schettler G. Coffee and cholesterol. *N Engl J Med* 1983;309:1249-50.
- 31 Dawber TR, Kannel WB, Gordon T. Coffee and cardiovascular disease. Observations from the Framingham study. *N Engl J Med* 1974;291:871-4.
- 32 Shekelle RB, Gale M, Paul O, Stamler J. Coffee and cholesterol. *N Engl J Med* 1983;309:1249-50.
- 33 Kovar MG, Fulwood R, Feinleib M. Coffee and cholesterol. *N Engl J Med* 1983;309:1249.
- 34 Hofman A, Van Laar A, Klein F, Valkenberg HA. Coffee and cholesterol. *N Engl J Med* 1983;309:1248-9.
- 35 Naismith DJ, Akinyanju PA, Szanto P, Yudkin J. The effect in volunteers of coffee and decaffeinated coffee on blood glucose, insulin, plasma lipids and some factors involved in blood clotting. *Nutrition and Metabolism* 1970;12:144-51.
- 36 Parsells J, Rosenberg L, Kaufman D, Helmrich S, Shapiro S. Coffee consumption and myocardial infarction [Abstract]. *Am J Epidemiol* 1984;120:487.

(Accepted 20 May 1985)

SHORT REPORTS

Topical treatment of recurrent cutaneous leishmaniasis with ointment containing paromomycin and methylbenzethonium chloride

Cutaneous leishmaniasis, a protozoal disease, continues to present important therapeutic problems and, though usually self limiting, can cause considerable morbidity. It may result in severe disfigurement. Recurrent cutaneous leishmaniasis, or leishmaniasis recidivans, is a rare form of the disease caused by *Leishmania tropica* (formerly *L. tropica minor*), and occurs on or near healed leishmaniasis scars months to years after total or partial resolution of the acute lesion.

Currently, no satisfactory treatment exists for either condition. The available drugs—the pentavalent antimonials, the diamidines, amphotericin B, and emetine hydrochloride—are all unpredictable and unsatisfactory and occasionally cause severe toxicity.¹ Few studies have dealt with topical treatment. Recently, local treatment with chlorpromazine ointment was successfully used against diffuse cutaneous leishmaniasis.² Topical treatment with imidazole derivatives, however, was ineffective in cutaneous leishmaniasis in both experimental animals and man.³

During the past few years an effective topical treatment of cutaneous leishmaniasis has been developed. BALB/c mice with early and advanced infection with *L. major* LRC-L137 were treated with an ointment containing 15% paromomycin sulphate and 12% methylbenzethonium chloride in white soft paraffin (UK patent number GB 2117237A). All the mice were completely cured of cutaneous disease after application of the ointment twice daily for six to 10 days.⁴ Treatment of lesions in the base of the tail eliminated only the parasites in those lesions; the internal organs and other, untreated lesions remained heavily infected.

Case reports

In a preliminary clinical study two patients with recurrent cutaneous leishmaniasis were treated with an ointment comprising 15% paromomycin sulphate and 1% methylbenzethonium chloride (supplied by Teva Pharmaceutical Industries Ltd, Jerusalem) twice daily for 80 days.

Effect of treatment on recurrent cutaneous leishmaniasis. Case 1: (a) before treatment; (b) four months after end of treatment; Case 2: (c) before treatment; (d) one month after end of treatment.

Case 1—The patient was a 54 year old woman with a 50 year history of leishmaniasis who had immigrated from Iraq in 1951. She had three crusted, ulcerated lesions 1-3 cm in diameter, one on the nose and two on her left cheek (figure (a)). Before attending our clinic she had been treated unsuccessfully with emetine hydrochloride, with severe toxic side effects.

Case 2—The patient was a 58 year old man with recurrent cutaneous leishmaniasis, which had first developed 47 years previously, also in Iraq. He had been unsuccessfully treated with various drugs including emetine