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EPIDEMIOLOGY

Wine, alcohol, platelets, and the French paradox for coronary heart disease

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In most countries, high intake of saturated fat is positively related to high mortality from coronary heart disease (CHD). However, the situation in France is paradoxical in that there is high intake of saturated fat but low mortality from CHD. This paradox may be attributable in part to high wine consumption. Epidemiological studies indicate that consumption of alcohol at the level of intake in France (20–30 g per day) can reduce risk of CHD by at least 40%. Alcohol is believed to protect from CHD by preventing atherosclerosis through the action of high-density-lipoprotein cholesterol, but serum concentrations of this factor are no higher in France than in other countries. Re-examination of previous results suggests that, in the main, moderate alcohol intake does not prevent CHD through an effect on atherosclerosis, but rather through a haemostatic mechanism. Data from Caerphilly, Wales, show that platelet aggregation, which is related to CHD, is inhibited significantly by alcohol at levels of intake associated with reduced risk of CHD. Inhibition of platelet reactivity by wine (alcohol) may be one explanation for protection from CHD in France, since pilot studies have shown that platelet reactivity is lower in France than in Scotland.

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Description of the French paradox

The findings of the MONICA project,[1] a worldwide monitoring system for cardiovascular diseases organised by the World Health Organisation (WHO), confirm that the mortality rate from coronary heart disease (CHD) is much lower in France than in other industrialised countries such as the USA and UK. The MONICA results (table I) show that the mortality rate from ischaemic (coronary) heart disease in France is closer to rates in Japan or China than to rates in the USA or UK, particularly for women, despite intakes of saturated fat (14–15% of energy[2]) and concentrations of serum cholesterol that are similar to those of the USA and UK. This finding constitutes the French paradox for CHD. Other risk factors for CHD, such as blood pressure, body-mass index, and cigarette smoking (at least in men), are no lower in France than in other industrialised countries (table I).[1] We know of no adequate explanation for these paradoxes.

Dietary habits consistent with protection from CHD have been considered too restrictive (high in polyunsaturated fats and/or vegetarian); however, the diet in Toulouse, France, is varied and characterised by low consumption of butter and high consumption of bread, vegetables, fruit, cheese, vegetable fat, and wine (table II)—ie, a Mediterranean-type diet. In addition, foie gras and other foods associated with a gourmet diet are eaten. The high wine intake and low mortality from CHD in Toulouse may be considered surprising. Nevertheless, this observation accords with previous reports[4,5] of an inverse association between consumption of alcohol and cardiac mortality in developed countries, the potentially beneficial effect of alcohol being reported as essentially due to consumption of wine.[4]

TABLE I—AGE-STANDARDISED ANNUAL MORTALITY FROM CHD, AND RELATED RISK FACTORS IN MONICA POPULATIONS (35–64 YEARS)

MONICA centre	Annual CHD mortality/ 100 000 population		Mean serum cholesterol (mg/dl)*		Mean systolic blood pressure (mm Hg)		Proportion of regular cigarette smokers (%)	
	Men	Women	Men	Women	Men	Women	Men	Women
Japan	33	9	..	..	..	..	..	..
Beijing, China	49	27	163	166	130	129	50	16
Toulouse, France	78	11	230	224	133	128	37	17
Strasbourg, France	102	21	218	216	145	137	34	15
Lille, France	105	20	252	248	139	135	39	11
Switzerland	103	17	248	232	132	126	32	21
Stanford, USA	182	48	209	205	128	124	40	37
Belfast, UK	348	88	232	236	135	132	34	33
Glasgow, UK	380	132	244	248	138	134	52	50

Data from ref 1. *mmol/l serum cholesterol = mg/dl ÷ 38·7.

We have used data from the WHO and the Organisation for Economic Cooperation and Development (OECD) to show that of many different foodstuffs only dairy fat is significantly positively associated with the mortality rate from CHD.[6] Statistics from 17 countries that report consumption of wine show that the correlation between mortality from CHD (in 1987)[1] and intake of dairy fat

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TABLE II—CHD MORTALITY, HIGH-DENSITY-LIPOPROTEIN (HDL) CHOLESTEROL, AND DIET IN MEN IN THREE FRENCH MONICA CENTRES

	Strasbourg	Toulouse	Lille
CHD mortality/100 000 men	102	78	105
Mean serum HDL cholesterol (mg/dl)	45	52	60
Diet (g/day)			
Bread	164	225	152
Vegetables	217	306	212
Fruit	149	238	160
Butter	22	13	20
Cheese	34	51	42
Vegetable fat	16	20	15
Wine	286	383	267

Data from refs 1–3. About 600 subjects aged 35–64 measured for HDL cholesterol.

(OECD, 1980–85) is highly significant ($r = 0.73$, $p < 0.001$) for pooled data from men and women (fig 1) and for men and women separately (data not shown). It can be seen in fig 1 that the data point for France lies some distance from the regression line—ie, despite an intake of dairy fat in France similar to that in the UK, Australia, and Germany, mortality from CHD is low. This is a clear demonstration of the French paradox, and the Swiss present a similar paradox. The UK offers the opposite paradox in that the mortality rate from CHD is higher than that in countries with a similar intake of dairy fat. Stepwise multivariate analysis (STAT-80 statistical software, Salt Lake City, Utah, USA) shows that in the 17 countries that report wine consumption, wine is the only foodstuff in addition to dairy fat that correlates significantly with mortality (fig 2). By this type of analysis wine intake has a negative sign indicating a protective effect that accords with previous reports.[4] The data point for France is now located close to the regression line and no longer offers a paradox compared with other countries. This finding suggests that in France the untoward effects of saturated fats are counteracted by intake of wine. In addition, the greater significance found in fig 2 than in fig 1 indicates that the protection afforded by wine also applies to Switzerland and other industrialised countries. The opposite paradox of the UK, no longer seen in fig 2, can be explained by the low consumption of wine in that country.

The French paradox for CHD may be due to high consumption of wine. Support for this hypothesis comes

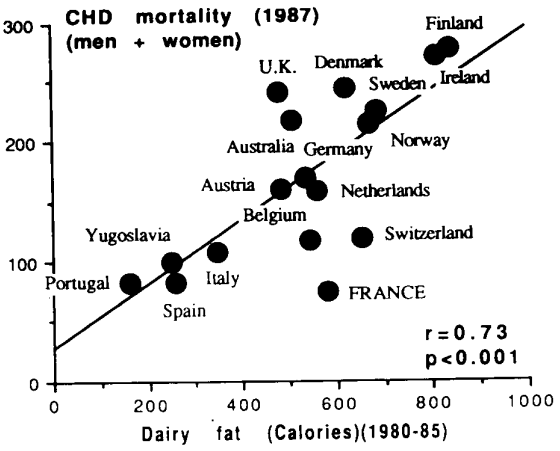

Fig 1—Relation between age-standardised death rate from CHD (mean for men and women)[1] and consumption of dairy fat in countries reporting wine consumption.

Regression equation: $y = 26.3 + 0.27$ dairy fat.

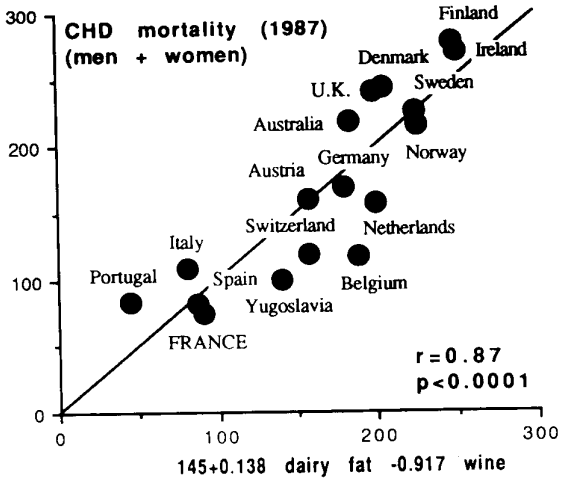

Fig 2—Relation between age-standardised death rate from CHD (mean for men and women)[1] and consumption of dairy fat and of wine in countries reporting wine consumption.

Regression equation: $y = 145 + 0.138$ dairy fat $- 0.917$ wine.

from the two populations in the world with the greatest life expectancy—the Cretans[7] and the Japanese[1]—both of whom consume moderate amounts of alcohol: the Cretans 20 g per day mostly in the form of wine,[8] and the Japanese 28 g per day, primarily in the form of beer.[9]

Wine or alcohol in the prevention of CHD

An inverse association between moderate alcohol consumption and CHD has been demonstrated in several epidemiological studies. A study of more than 51 000 men[10] supported the view that moderate alcohol consumption (30–50 g per day) reduces the risk of CHD (95% CI for relative risk 0·35–0·79). This protective effect of alcohol is seen in men and women,[11] in the elderly,[12] in smokers and non-smokers,[10,13] and also applies to total mortality.[11] However, the risk increases at high levels of alcohol consumption,[13] especially when in the form of binge or heavy weekend drinking.[14] It must be emphasised that alcohol is a drug that, studies suggest, should be used regularly but only at moderate doses of about 20–30 g per day. At this level of consumption the risk of CHD can be decreased by as much as 40%.[10-12] Thus, alcohol taken in moderation may be one of the most efficient drugs for protection from CHD.

As to whether wine is more protective than beer or spirits, most studies done in USA indicate that beer, wine, and spirits are equally inversely related to CHD.[10] However, in one study,[13] beer and wine were associated with a greater reduction in CHD than spirits in non-smokers. When CHD mortality in Toulouse, France, is compared with that in Stanford, USA (table I), there is a 57% reduction in men (78 *vs* 182/100 000). The average consumption of alcohol in Toulouse is about 38 g per day, 34 g in the form of wine, whereas that in Stanford is not known but can be expected to be much lower. Compared with Belfast and Glasgow, the reduction in CHD mortality in Toulouse is even more striking at 78–79%. If this degree of prevention is due largely to alcohol drinking, it can be speculated that wine should have a greater protective effect than other kinds of alcoholic beverages because the consumption of wine but not of other alcoholic drinks, although not yet reported, is expected to be small in Belfast and Glasgow compared with

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Toulouse. An alternative explanation is that because wine is mostly consumed during meals it is absorbed slowly, and thus has a prolonged protective effect on, for example, blood platelets at a time when they are under the influence of alimentary lipids that are known to increase their reactivity.[15] This explanation of the protective effect of wine and its superiority over other alcoholic beverages awaits confirmation by experimental studies.

Mechanism of the protective effect of alcohol

Because studies have shown that alcohol consumption is positively associated with high-density-lipoprotein (HDL) cholesterol and that HDL cholesterol is predictive of CHD in men and women,[16] the mechanism responsible for the protective effect of alcohol was thought to act through HDL cholesterol. The main role of HDL may be the transport of cholesterol from arteries to liver for subsequent excretion, thus preventing accumulation of cholesterol and hence atherosclerosis. However, it is now known that the effect of alcohol on HDL can explain only half the protection against CHD afforded by alcohol.[17] In addition, it does not seem that alcohol protects exclusively, or, perhaps, even primarily, through its action on atherosclerosis. When cirrhosis is used as a marker of excessive alcohol consumption, patients with this condition usually show less atherosclerosis than controls,[16] but this is not necessarily the case when possible bias is eliminated. Moore and Pearson[16] reviewed seven necropsy studies in which, instead of relying on cirrhosis as a marker, alcohol consumption was estimated; five studies found no association between alcohol consumption and severity of atherosclerosis. These observations are consistent with animal studies that showed that inhibition of arterial lesions could be obtained at high (36% of energy),[19] but not low (10% of energy),[20] alcohol intake.

It has been shown in prospective[21] and case-control studies[22] that moderate intake of alcohol can prevent myocardial infarction, and by inference coronary thrombosis, but not stable angina pectoris,[21] which is primarily the result of atherosclerotic lesions. In addition, the rapid loss of protection from CHD experienced by ex-drinkers[21] is unlikely to be due to increased atherosclerosis because such lesions do not progress quickly. Finally, alcohol drinking seems to increase the risk of subarachnoid haemorrhage,[23] an observation consistent with a possible effect of alcohol on haemostasis. Among the haemostatic factors, platelets play a crucial part in coronary thrombosis. Drugs such as aspirin that inhibit platelet aggregability protect against myocardial infarction. An increase in platelet aggregation has been significantly associated with increased prevalence[24] and incidence[25] of CHD. Alcohol ingestion or infusion inhibits platelet aggregability in man, and it has been shown in rats that addition of 4–6% ethanol to drinking fluid reduces platelet aggregation, an effect that occurs rapidly but is also lost rapidly with rebound effects.[26] A study in Wales of 1600 subjects[27] found that aggregation of platelets to ADP was inhibited to the same degree, and by the same level of alcohol consumption, as reported previously[10] to protect from CHD (table III). Of course, the dose-related effect of alcohol on platelets does not exclude additional beneficial effects on other haemostatic factors such as fibrinogen and fibrinolytic activity.

In conclusion, it seems that consumption of alcohol is associated with inhibitory effects on atherosclerotic lesions in man and animals, but only at levels of alcohol consumption incompatible with a healthy life. At the moderate intake associated with the prevention of CHD, the mechanism of protection seems to be, at least partly, a haemostatic effect, possibly a decrease in platelet reactivity. The rebound effect on platelets after alcohol withdrawal[26] could explain the increased risk, especially for sudden death,[14] associated with binge and excessive drinking.

TABLE III—EFFECT OF ALCOHOL ON RESPONSE OF PLATELETS TO ADP AND ON RISK OF CHD

	Alcohol intake (g/day)				p for trend*
	0	0·1–5·0	5·1–30·0	>30·0	
95% CI for odds ratio for high ADP-S†	1·0	0·40–1·13	0·19–0·80	0·08–0·54	<0·001
95% CI for relative risk of CHD‡	1·0	0·74–1·33	0·56–0·97	0·35–0·79	<0·0001

ADP-S = secondary aggregation to ADP.
*Mantel test; †data from ref 27; ‡data from ref 10.

Platelets and the French paradox

Compared with Belfast, protection from CHD in Toulouse is not associated with a low serum cholesterol[1] or a high HDL cholesterol. Research on HDL subfractions and subclasses may shed further light on their role in the French paradox; however, it appears that the concentration of the antiatherogenic fraction apoAI is decreased rather than increased by alcohol drinking.[28] Although platelet reactivity has not yet been evaluated in the MONICA centres, we have compared farmers from Var, southern France (low in CHD mortality), with farmers from south-west Scotland for this variable in pilot studies.[29,30] Platelet aggregation was strikingly lower in Var. Secondary aggregation to ADP, the test that undergoes the greatest decrease with alcohol,[27] was 55% lower in Var than in Scotland, whereas mean HDL cholesterol was 69 mg/dl in Girvan, Scotland, 66 mg/dl in Stranraer, Scotland, and 63 mg/dl in Var. Consumption of alcohol was greatest in Var (45 g per day *vs* 20 g per day in Scotland), mostly in the form of wine.

Ulbricht and Southgate[31] have stated that there are seven dietary factors, not including alcohol, implicated in CHD. We believe that alcohol is an important dietary factor in the regulation of the CHD process.

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BOOKSHELF

Atrial Natriuretic Hormones

David L. Vesely. New Jersey: Prentice Hall. 1992. Pp 240. $64. ISBN 0-130505846.

The discovery that the heart synthesises a peptide (atrial natriuretic peptide or ANP) with natriuretic-diuretic properties had an effect akin to passing a catheter in a patient with urinary retention; it relieved a block (to salt and water research), produced a tremendous flow (of papers), and gave a general feeling of relief (amongst those who had predicted its existence). As the paper diuresis diminishes to a comparative trickle, a steady stream of books have begun to appear with the aim of summarising the literature and placing the observations in context. Or, in this case, highlighting the authors' own papers.

Unravelling the physiology of ANP has been a multidisciplined effort and the task of presenting a comprehensive and unbiased account is quite a challenge for a single author. One disappointment with this book is the lack of space given to brain natriuretic peptide, C-natriuretic peptide, and urodilatin. These peptides are structurally related to ANP, creating a "family of natriuretic peptides", but their synthesis and secretion may be differentially regulated. The author gives preference to his own experiments with the N-terminal fragment of the prohormone of ANP, which he believes subdivides into three biologically active peptides. This idea has not been widely studied by other groups, which may explain the high percentage of self-citation in some chapters. Another disappointment is the limited reference to endopeptidase-24.11. This cell-surface enzyme has an important role in metabolising and clearing ANP and presents the most promising target for pharmacological enhancement of endogenous ANP as a treatment for disorders of sodium and water balance, such as heart failure.

The book is well laid out and may appeal to those interested in the measurement of the plasma concentration of ANP (and its prohormone) in health and disease. However, it cannot be said to serve as an adequate testimony to the current state of our knowledge of ANP (and related peptides) or to the efforts of the many who have contributed to it.

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Infections of the Central Nervous System

Edited by Harold P. Lambert. London: Edward Arnold. 1991. Pp 402. £60. ISBN 0-34054922X.

Infections of the Nervous System

Edited by David Schlossberg. Berlin: Springer-Verlag. 1990. Pp 396. DM 328. ISBN 0-38797332X.

To the neurologist, infections of the nervous system pose the greatest challenge because they require quick, accurate diagnoses and correct therapy. Two books on infections of the nervous system have been on my desk for almost a year and both now have been read, re-read, searched for specific information, and compared and contrasted with perhaps the best standard textbook of neurology—*Principles of Neurology* by Raymond Adams and Maurice Victor.

Both books are multi-authored, of a similar size, and are written for the same audience; but there the similarity ends. In my view, they illustrate a phenomenon that is hard to define—namely, why one text should be so successful and attractive whilst the other, though adequate, is so much less appealing. A successful text usually has a single author or a dedicated editor, who is often an enthusiastic teacher eager to impart knowledge. These people commonly stamp the

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