The French Paradox: Fact or Fiction?

Invited Editorial

L. H. Opie

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Invited Editorial

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THE FRENCH PARADOX:
ARE “THEY” REALLY SO DIFFERENT?

Brian Bronte-Stuart, then a physician at Groote Schuur Hospital at the University of Cape Town, first proposed in 1958 (a mere 50 years ago) that “ischemic heart disease is no problem among the fish-eating Japanese, the maize-eating Bantu, and the olive-oil-eating peoples along the Mediterranean,”¹ thus paving the way for the view that the Mediterranean diet protected those French living in the Mediterranean littoral. The catchy term, the “French paradox,” was invented by the wine-loving French, much as the concept of “extra virgin” olive oil was invented by the Italians. Note the closely related term, “l’exception française” as used by Michelle Holdsworth in her article, and still used politically (as I recently heard on French television channel TV5), seemingly to justify the apparently different and possibly thought-provoking approach that the French might claim to have in attempting to solve insoluble problems.

But back to 1992, when Renaud and de Lorgeril wrote in The Lancet and eternalized the unforgettable phrase, the “French paradox”: “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.”² Thus by adding wine (French of course—and note that in France wine is regarded as food and strongly linked to food) to the protection of olive oil,¹ the combination constitutes strong evidence for the role of food in CHD in France. Who can

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dispute that the French are masters of food, relentlessly extolling and castigating restaurants in their own country as well as throughout the world, by bestowing or removing the highly coveted Michelin stars? A famous chef committed suicide several years ago after losing a “star” in the new edition of the Michelin…

In this issue of *Dialogues*, the lead article by Hugh Tunstall-Pedoe analyzes the slow but sure evolution of the French and Western dietary habits and the increasing depth of our understanding of cardiovascular prevention. First he outlines the defects in the mortality statistics, but even after correction, the French might be living longer than expected. Then the major emphasis is on diet and the heart. Starting with Ancel Keys, the evolution has been from saturated fat to cholesterol, then to low-density cholesterol (LDL), then to oxidized LDL, then to antioxidants and micronutrients, and then on to the current concept of endothelial damage as an inflammatory process. On this background the Mediterranean diet, olive oil, fish, alcohol and wine, onions and garlic, nuts, and dark chocolate all enter into the thorough analysis that could explain the French paradox (if it exists), not to mention genetics and social patterns of eating. Will we ever get the answer? Indeed in 20 years time, cardiovascular disease might nearly have vanished from France and even from less blessed parts of Europe.

In the popular mind, the French paradox is often interpreted as the inexplicable, but unestablished, capacity of the French to eat all the foie gras and cheese they want, provided that fatty items are swished down with much red wine. As attractive as this concept might seem, the hypothesis that drinking wine can undo the sins of gluttony and excess fat consumption remains to be proven. That alcohol consumption can be related to an overall J-shaped mortality curve is no longer in doubt, thus proving the benefits of moderate alcohol consumption. Of note, this relates to total alcohol intake and suggests that teetotalers, taking no alcohol at all, are actually harming themselves. The definitive study shows a genetic variation in hepatic alcohol dehydrogenase, which slows the rate of ethanol metabolism and is associated with higher levels of protective plasma high density cholesterol (HDL) and lower rates of myocardial infarction. The latest development also mentioned by Joël de Leiris and François Boucher, is the concept that wine, but not specifically red wine, has a “fish-like” effect on blood omega-3 fatty acid levels. This can be achieved by ethanol alone.

**IS IT REALLY (RED) WINE, RATHER THAN ALCOHOL?**

Now we have to move on to the red wine hypothesis. Most large-scale epidemiological data come from North America, where data seem most accurate, suggesting that there are no cardiovascular protective differences between white and red wine. The hard data suggesting that red wine has protective qualities result from a few experiments on dealcoholized red wine, which has cardiovascular protective effects in short-term studies on humans with coronary disease. Thus, 250 mL of dealcoholized Greek red wine
decreased arterial stiffness and improved the augmentation index, which reflects aortic stiffness. Additional data come from dogs with stenosed coronary arteries, in whom administration of French blended red wine, apparently almost vintage, eliminated cyclic flow reductions caused by periodic acute platelet mediated thrombus formation, thus supporting the original suggestion of the inhibitory effects of wine on platelets.

IS THERE REALLY A FRENCH PARADOX?

While there are major differences in the national eating habits in France and within France, compared with other countries (see Michelle Holdsworth’s paper), that does not provide solid evidence for the French paradox. Perhaps procyanidin-rich French wines are much more protective than others, as proposed by Joël de Leiris and François Boucher, which could be linked to the apparent longevity in the Gers area of France. The extra longevity claimed for this small part of France seems based on hearsay evidence, at least in the original article in Nature, and one wonders why there has been no reported intense scientific investigation into strict epidemiological data with mortality data, and lifestyle assessment, while taking into account classic risk factors including blood pressure, blood lipid profiles, and blood glucose values. Thus this component of the story is only hypothesis-generating in the absence of good data. Furthermore, this small geographic area could not account for any paradox involving the whole of France, if indeed the French paradox exists.

THE MORE MEDITERRANEAN, THE BETTER?

Although the definitions of the Mediterranean diet differ, there is now consensus that the Mediterranean-style diet is cardioprotective. Furthermore, the more Mediterranean it is, the more protective it is against overall mortality, postinfarct mortality, and diabetes. As far as postinfarct protection is concerned, the Mediterranean diet outperforms the American Heart Association low-fat diet as shown in a classic paper, appropriately from France. However, Michelle Holdsworth doubts that the average French diet is really Mediterranean. Rather, she stresses differences in French social behavior — eating for pleasure and conviviality. “Food is bought, cooked, and celebrated,” all of which is true.

A stringent French look at the data by Pierre Ducimetière (in this publication) shows that the geographic position of living on the north-south latitude might be more important than belonging to any country such as France. Thus if Pierre Ducimetière is correct, then only the southern part of France enjoys low cardiovascular mortality. Indeed the protective effect of living in Toulouse is as strong as living in Barcelona. This view emphasizes that France is a country divided by diet, with different cardiovascular event rates from the top to the bottom, with specific sites no different from those in other countries at similar latitudes. The clear conclusion, driven by the facts as summarized by Pierre Ducimetière, is that the rates of CHD are not so low in France, animal fat...
intake is not so high, and the diet-heart concept is not so unique that the existence of a “French paradox” can be sustained, except for satisfying cultural fantasy or for wine enthusiasm and marketing. Thus, the real paradox is why the French paradox continues to exist as a concept, when it should be replaced by the less mystifying view, namely, “the more Mediterranean, the better.”

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Mediterranean alpha-linolenic acid-rich diet in secondary prevention of coronary heart disease.  
The French paradox

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The coronary heart disease prevention message in the 1970s, coming from the USA, was negative and discouraging. “Avoid cigarettes, alcohol, fatty and rich foods.” A diet containing saturated fat would lead to high blood cholesterol levels and high coronary risk. The French did not fit into this picture. Paradoxically, they appeared to enjoy rich food with wine, a high fat intake, similar cholesterol levels to Americans, and a very low coronary heart disease mortality. The review demonstrates the international statistics that underlie the “French paradox,” and then uses data from the WHO MONICA Project (World Health Organization—MONItoring of trends and determinants in Cardiovascular disease) to examine French mortality statistics. It traces the origins of the “diet-heart hypothesis” through the Framingham study, the Seven Countries Study, and metabolic ward feeding experiments, to the time in the 1970s when what foods did to blood cholesterol levels was all that seemed to matter. It then follows the way in which the diet-heart hypothesis was later modified to take account of antioxidants and micronutrients and became multidimensional. Possible key contributors to the French/Mediterranean/“healthy” diet are considered, including olive oil, wine, garlic and onions, vegetables and fruit, and fish. It concludes by speculating on the future fate of the French paradox.

Keywords: mortality rate; coronary heart disease; French paradox; diet-heart hypothesis; risk factor; protective factor; lipid, micronutrient; Mediterranean diet

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self-denial. Transgressors must, (how unjust if they did not!) inevitably suffer. From the 1950s, it became clear that the penalty for being top nation was premature death from coronary heart disease. To avoid it, the enlightened should follow precepts, mostly based, like the biblical Ten Commandments, on “Thou shalt not…” As interpreted by its acolytes in health promotion, the doctrines of the high priests of coronary disease prevention in the 1960s and early 1970s, based in Framingham, Massachusetts,9 Chicago, Illinois,10 and Minneapolis, Minnesota, USA,11 were essentially negative—following the Framingham concept of “risk factors” all of which then made things worse. A generation after prohibition, avoidance meant alcohol alongside cigarettes, fat, and rich foods.

Such doctrines were promoted in countries sharing American-style prosperity and its coronary epidemic. English-speaking countries dominated the World Health Organization (WHO) league table for coronary heart disease mortality from the 1950s to 1980s (a notable interloper was Finland).12 A feature of the Anglo-Saxon/American lifestyle was that meals became rapid refueling stops involving large portions of high-energy, often industrialized, convenience foods; indeed they might be taken without stopping other activities, like in-flight refueling, or involve browsing between meals (Figure 2). There was a parallel subculture for alcohol, shared by northern countries, of telescoping alcohol consumption, often beer and spirits, into “binges” remote from food. By contrast, the French, cocooned by their language, were preoccupied with good living, and if anything, by the health of their livers, rather than their hearts. Food was enjoyed in a leisurely manner, in modest quantities, as a social activity or en famille, with conversation, and wine imbibed slowly, although often in large quantities. France was the first geographical contact for Anglo-Saxons in Europe, and to “rich” continental cuisine containing butter, cream, cheese, and pâté. Yet those WHO statistics placing English-speaking countries at the top of the league table for coronary heart disease mortality put France virtually at the bottom. Hence the French paradox.12

Unlike a religious sermon, a medical postgraduate lecture on cardiovascular epidemiology, otherwise very similar, has time for awkward questioners. Challenges to the orthodoxy of “avoid fatty foods to avoid coronary heart disease” in the 1970s were “What about the ---?” The ---? at first were the Masai; later the Eskimos (Inuit). These remote minorities had lifestyles few would emulate. The Japanese were distant and exotic, and although industrialized, not great fat eaters. Arrival of the French as the ---? in the 1980s posed a greater challenge. They existed nearby in a modern industrialized state, whose lifestyle was not freakish, but similar to others.

The French paradox put the assumed superiority of Anglo-Saxon civilization under threat. Could the high priests of prevention be wrong? Could the French, once considered in national stereotyping to be effeminate and foppish (based on eighteenth-century courtly mannerisms) or even degenerate, but who saw themselves as the custodians and leaders of Western civilization, have secrets unknown to Anglo-Saxons? Could
their civilization be superior in some way, so they got away with self-indulgence—eating, drinking, and being merry—but not dying tomorrow (Figure 3, page 162)? Did Framingham risk factors operate in France? Were there protective factors unrecognized by the soothsayers, additional to the postulated effects of physical exercise and high-density lipoprotein (HDL) cholesterol? Was alcohol truly bad? Alternatively, could the French deficit of coronary deaths be simple misdiagnosis? Finally—a throwback to earlier discredited racial theories, and a counterblast to “degeneracy”—could the French have some genetic advantage that protected them?

These questions impinge on national pride and susceptibilities, but are relevant to disease causation, prediction, and prevention—and therefore public health policy. Despite my teasing introduction (apologies for any hurt feelings), nation states, their susceptibilities, and stereotypes are becoming blurred. Vested interests are now multinational. Explanations for the French paradox are of commercial interest—whether or not they are valid.

New hypotheses may echo older medical, apothecary, and alchemical theories. A magic bullet, an elixir of life, distilled from the French paradox, a quintessence of French coronary disease resistance, might be marketed as an extra, without relinquishing other lifestyles or diets. Such a panacea would be acceptable even to puritans provided it was “medicine” and could be made to taste sufficiently nasty. Commercial interest behind such work should not be underestimated. Nor should “spin” put on alleged research findings by public relations and medical consultancies, feeding media demand for “health news.” Reader, beware of publication bias, in media hype, Internet posting, or peer-reviewed publications.

Let us start with standard international statistics, inevitably subject to error and bias, but free from partisan opportunism.

**THE FRENCH PARADOX IN BASIC STATISTICS**

**Mortality rates**

National mortality statistics have been disseminated by WHO since soon after the Second World War. Formerly in printed Annual Reports they now download from the Internet. Experience of different countries can be compared through age- and sex-specific, or age-standardized mortality rates. The validity of these depends not solely on comparability of cause of death diagnoses, but also on the accuracy of the demographic data on population denominators, and completeness of death registration. WHO disseminates standard model death certificates, coding rules for establishing underlying cause of death, and the International Statistical Classification of Diseases and Health Related Problems, now in its Tenth Edition (ICD-10), and produces standardized tables for comparison. It cannot control what is written on individual death certificates, who is legally responsible, whether a doctor, other health worker or lawyer, and whether the diag-
nosis is evidence based, for example by postmortem or other medical documentation, or merely an expression of one person’s opinion. Such things are controlled state by state, or even by county, depending which is the responsible medicolegal authority. While these cannot determine all individual judgments, it is the systematic, not the random variations, that matter in making national comparisons.

National mortality statistics are fundamental to the French paradox. Table I shows mortality rates for one age group (55 to 64), one year (2000) and seven selected countries: from coronary heart disease, from all causes, from cardiovascular disease, and from cerebrovascular disease. At all ages, death rates from coronary heart disease in France in both men and women are a fraction of those in most other industrialized countries, especially northern (and now eastern) Europe and the English-speaking New World. This applies to a lesser extent to cardiovascular disease as a whole. Despite popular mythology it does not extend to mortality from all causes in both sexes. French men pay back their deficit in coronary heart disease with an excess of other diseases: for example liver and gastrointestinal diseases, accidents, and violence (see WHO). While differing in different age groups, death rates overall in French men are similar to those in the United Kingdom. French women, by contrast, seem to have the secret of success, with low death rates overall, as well as in those attributed to coronary heart disease.

Since WHO began publishing, and more so since the French paradox was recognized, there have been big changes in overall death rates, and in those attributed to coronary heart disease. In many countries the latter are a half to one third of what they were a generation ago. French death rates have also declined, maybe less dramatically than some. Those for coronary heart disease

<table>
<thead>
<tr>
<th>Cause</th>
<th>CHD M</th>
<th>CHD F</th>
<th>ALL M</th>
<th>ALL F</th>
<th>CVD M</th>
<th>CVD F</th>
<th>CBV M</th>
<th>CBV F</th>
</tr>
</thead>
<tbody>
<tr>
<td>France</td>
<td>99</td>
<td>16</td>
<td>1156</td>
<td>472</td>
<td>230</td>
<td>67</td>
<td>39</td>
<td>18</td>
</tr>
<tr>
<td>Finland</td>
<td>350</td>
<td>59</td>
<td>1190</td>
<td>521</td>
<td>481</td>
<td>129</td>
<td>60</td>
<td>40</td>
</tr>
<tr>
<td>Germany</td>
<td>213</td>
<td>56</td>
<td>1208</td>
<td>571</td>
<td>385</td>
<td>131</td>
<td>52</td>
<td>25</td>
</tr>
<tr>
<td>Greece</td>
<td>216</td>
<td>49</td>
<td>1014</td>
<td>432</td>
<td>385</td>
<td>131</td>
<td>84</td>
<td>42</td>
</tr>
<tr>
<td>Japan</td>
<td>70</td>
<td>18</td>
<td>924</td>
<td>388</td>
<td>215</td>
<td>82</td>
<td>85</td>
<td>40</td>
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<tr>
<td>UK</td>
<td>292</td>
<td>84</td>
<td>1076</td>
<td>659</td>
<td>409</td>
<td>161</td>
<td>49</td>
<td>38</td>
</tr>
<tr>
<td>USA</td>
<td>291</td>
<td>111</td>
<td>1231</td>
<td>772</td>
<td>444</td>
<td>208</td>
<td>47</td>
<td>35</td>
</tr>
</tbody>
</table>

Table 1. Annual mortality rates per 100,000 in selected countries for the year 2000 at age 55–64 from coronary heart disease (CHD), all causes, cardiovascular disease (CVD), and cerebrovascular disease (CBV).

Source: World Health Organization Statistical Database.
disease obstinately continue to crawl along the bottom of the graph, where they rank just above those for Japan. Theorists anticipating the schadenfreude of seeing them increasing (as also for Japanese rates) must be disappointed. Rates for five calendar years at five-yearly intervals from 1980 to 2000 are shown in \textit{Table II}. Despite major reductions in coronary heart disease mortality in countries with higher event rates, France and Japan retain significantly lower rates in relative terms, if not absolutely.

<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td></td>
<td>M</td>
<td>F</td>
<td>M</td>
<td>F</td>
</tr>
<tr>
<td>France</td>
<td>189</td>
<td>37</td>
<td>190</td>
<td>38</td>
</tr>
<tr>
<td>Finland</td>
<td>878</td>
<td>167</td>
<td>806</td>
<td>158</td>
</tr>
<tr>
<td>Germany*</td>
<td>448</td>
<td>99</td>
<td>424</td>
<td>106</td>
</tr>
<tr>
<td>Greece</td>
<td>258</td>
<td>58</td>
<td>268</td>
<td>62</td>
</tr>
<tr>
<td>Japan</td>
<td>92</td>
<td>31</td>
<td>71</td>
<td>24</td>
</tr>
<tr>
<td>UK</td>
<td>733</td>
<td>215</td>
<td>686</td>
<td>213</td>
</tr>
<tr>
<td>USA</td>
<td>580</td>
<td>188</td>
<td>475</td>
<td>164</td>
</tr>
</tbody>
</table>

*Federal Republic until 1990.

Britons and 0.3 years compared with Germans, whereas French women had 2.8 years more than Britons and 1.9 years more than Germans. If there is a French elixir of life it favors the ladies over the men, or is being vitiated by something French men are doing wrong.

Food

Another United Nations body, FAO (Food and Agricultural Organization), publishes national profiles, extracted here for comparison (\textit{Table IV, page 164}). The table shows numbers of calories per capita per day overall, and for selected food items. These are not inclusive and do not cumulate to the total calories shown. Calories shown are not age- and sex-specific. They are of food “disappearance,” not allowing for food wasted, thrown out, fed to pets, or nonfood uses—biofuels will be a problem. Alcohol in its different forms,

\begin{table}
\centering
\begin{tabular}{|c|c|c|c|c|c|c|c|}
\hline
          | 1987/8 | 2000 | 2005 |
\hline
France    | 72.6   | 75.4 | 76.8 |
          | 81.1   | 82.8 | 83.9 |
Finland   | 70.7   | 74.2 | 75.7 |
          | 78.9   | 81.0 | 82.4 |
Germany   | 72.3   | 74.9 | 76.5 |
          | 79.1   | 80.9 | 82.0 |
Greece    | 74.1   | 75.4 | 76.9 |
          | 78.9   | 80.7 | 82.1 |
Japan     | 75.8   | 77.7 | 78.7 |
          | 81.9   | 84.6 | 85.5 |
UK        | 72.5   | 74.6 | 76.6 |
          | 78.2   | 79.4 | 81.1 |
USA       | 71.6   | 74.1 | 75.3 |
          | 78.6   | 79.4 | 80.4 |
\hline
\end{tabular}
\caption{Table III. Calculated life expectancy at birth for selected countries based on life tables constructed from mortality rates at three time periods. \textit{Source: World Health Organization Statistical Database.}}
\end{table}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure4}
\caption{French women, here idealized by Marianne busts, the symbol of the French Republic, have little coronary heart disease compared with their sisters elsewhere, and also live significantly longer. In the last forty years, Marianne has been modeled on Brigitte Bardot (1968), Mireille Mathieu (1978), Catherine Deneuve (1985), Inès de la Fressange (1989), Laetitia Casta (2000), and Evelyne Thomas (2003). Can you identify any of these? What other nation pays such homage to women? All rights reserved.}
\end{figure}
olive oil, total vegetable oils, other root vegetables, green vegetables, and fruit do not appear in these tables. They are of interest in showing what FAO chooses to show and what not, although other items are available in larger, less accessible databases. If food tables were produced for WHO they might emphasize the consumer health interest—what are currently naively labeled as “healthy” and “unhealthy” foods—although one can imagine debates on what these are, and lobbying round the fringes for nostrums such as red wine and chocolate.

These tables are about major contributors to calorie intake. France does not stand out in its pattern of consumption from more coronary-prone countries such as the United States, United Kingdom, Finland, and Germany. In its consumption of animal fats, and bovine meat, France exceeds that of the British, whom the French once labeled as “les rosbifs” = the roastbeefs. French food consumption shows little similarity to that of Japan or Greece, although its coronary mortality is more akin to theirs.

**Risk factors**

WHO does not yet publish standard profiles of cardiovascular risk factors for different countries. Such information, however, was obtained in random population surveys in specific localities, although not nationally, through the multinational collaboration called the WHO MONICA Project (MONItoring trends and determinants in Cardiovascular disease). MONICA collected data from 38 populations (for some things 37) over a decade, beginning in the 1980s and ending in the 1990s. Table V shows mean values for classic risk factors, and coronary event rates from the early 1990s for three participating French populations, Lille, Strasbourg, and Toulouse, compared with North Karelia in Finland, Glasgow UK (which both then had high coronary event rates), the German industrial city of Bremen, Californian communities near Stanford University, and the overall mean for 38 participating populations.

French risk factor values are unremarkable, some above and some below the 38-population mean, but coronary event rates are low—well below the 38-population mean. French total cholesterol levels are similar to those in many other MONICA populations. (HDL cholesterol measurements were insufficiently standardized for international comparisons—a problem now resolved by improved technology). Food and alcohol data were not collected in the “core” study, already considered costly and difficult enough to standardize. However, these were often attempted locally or in small collaborations, as was true for fibrinogen and other candidate risk factors.

**Table IV. Per capita daily calorie intake from selected food items by country 2001-2003.**


<table>
<thead>
<tr>
<th>Country</th>
<th>France</th>
<th>Finland</th>
<th>Germany</th>
<th>Greece</th>
<th>Japan</th>
<th>UK</th>
<th>USA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calories/day</td>
<td>3640</td>
<td>3150</td>
<td>3490</td>
<td>3680</td>
<td>2770</td>
<td>3440</td>
<td>3770</td>
</tr>
<tr>
<td>Rice</td>
<td>56</td>
<td>46</td>
<td>42</td>
<td>79</td>
<td>619</td>
<td>52</td>
<td>95</td>
</tr>
<tr>
<td>Wheat</td>
<td>735</td>
<td>628</td>
<td>647</td>
<td>958</td>
<td>359</td>
<td>746</td>
<td>607</td>
</tr>
<tr>
<td>Maize</td>
<td>88</td>
<td>0</td>
<td>70</td>
<td>11</td>
<td>72</td>
<td>29</td>
<td>100</td>
</tr>
<tr>
<td>Potatoes</td>
<td>119</td>
<td>135</td>
<td>134</td>
<td>125</td>
<td>43</td>
<td>221</td>
<td>101</td>
</tr>
<tr>
<td>Sugar</td>
<td>357</td>
<td>313</td>
<td>370</td>
<td>308</td>
<td>188</td>
<td>386</td>
<td>325</td>
</tr>
<tr>
<td>Soybean oil</td>
<td>45</td>
<td>37</td>
<td>107</td>
<td>13</td>
<td>132</td>
<td>90</td>
<td>499</td>
</tr>
<tr>
<td>Palm oil</td>
<td>12</td>
<td>1</td>
<td>10</td>
<td>0</td>
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<tr>
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<td>68</td>
<td>1</td>
<td>39</td>
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<tr>
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<td>33%</td>
<td>39%</td>
<td>35%</td>
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*Raw & Butter
Summing up the statistics

The basic statistics show that, despite low reported mortality from coronary heart disease, the French consume large quantities of animal fat. Their classic risk factor levels including cholesterol are unremarkable compared with those in populations reporting higher mortality from coronary heart disease.

“Paradox” challenges “Orthodox.” The French paradox was so named because this combination challenged the accepted 1970s orthodoxies on what caused coronary heart disease. The paradox is valid insofar as the statistics are correct, and the orthodoxy unchanged.

VALIDITY OF FRENCH MORTALITY STATISTICS

Clinicians often discount analyses of death certificate data by epidemiologists as unreliable, despite—perhaps because—most diagnoses originate with clinicians themselves. It is not always so: death is a legal problem also. Clinicians pride themselves competitively against others in getting diagnoses right.4 This created problems when your reviewer made a short presentation on the French paradox to a plenary session of the American Heart Association in November 1993, posing the three alternative explanations (reiterated here): did the French have a superior lifestyle; did they miss the diagnosis, or did they have a genetic advantage? Unfortunately the second question produced a ripple of laughter and applause from the largely North American audience. A journalist improved my talk by converting my teasing into an insult and my question into a conclusion. Distorted accounts of what I said led to the need for a fulsome apology to French cardiologists, which was accepted. This was necessary because the people most hurt by what happened were French collaborators in MONICA. They themselves and their predecessors had done pioneering work on French coronary disease and in elucidating the French medicolegal process in their mortality statistics.1,2,4,13

This question is being dealt with in a Respondent Article in this issue of Dialogues by Pierre Ducimetière. Here I will confine discussion to the WHO MONICA Project in which we both participated, along with investigators from 19 other countries.

### Table V

<table>
<thead>
<tr>
<th>Population</th>
<th>Cigarette smokers %</th>
<th>Systolic blood pressure mm Hg</th>
<th>Total cholesterol mmol/L</th>
<th>Body mass index kg/m²</th>
<th>Risk score</th>
<th>Annual coronary event rate (per 100,000)</th>
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</thead>
<tbody>
<tr>
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<td></td>
<td></td>
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<td>Toulouse</td>
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<td>6.2</td>
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Table V. Risk factor means and coronary event rates age standardized 35-64 years for selected WHO MONICA Project populations 1990-95

Source: WHO MONICA Project.

* Exact years vary by population.
The aim of the WHO MONICA Project was to study trends over 10 years in coronary heart disease (and stroke), and in their determinants, in defined populations in different countries, in men and women below age 65. Data on coronary deaths was complemented by that on nonfatal myocardial infarction through establishing registers in each population. In these registers information on suspected coronary events was subjected to standardized data extraction, and diagnostic algorithms. Information on these procedures and results is available in MONICA publications.20-22

What MONICA investigators could not standardize was the amount of information collected before a coronary diagnosis was attempted, whether that information was accessible to register staff (most problematic in relation to deaths and the confidentiality of medicolegal information), and how closely local clinicians or medicolegal authorities paralleled MONICA in their diagnostic reasoning. Quality control exercises were carried out within and between different coronary register teams, coordinated by my quality control center in Dundee, Scotland20-22, but it is doubtful whether these had any impact on locally made clinical or death certificate diagnoses. Since then troponin should have made a difference.

MONICA investigators trawled through all acute coronary cases, but also related diagnostic groups where coronaries could be lurking, to review the evidence and decide whether to classify an event as definite, possible, not (other diagnosis more plausible), or (for deaths only) unclassifiable (insufficient evidence to decide whether a coronary death or not).20-22 Differing patterns of clinical diagnosis versus MONICA categories (fatal and nonfatal) were analyzed in detail for 38 MONICA populations, including Lille, Strasbourg, and Toulouse (as in Table V) for 3 years of coronary event registration (1985-87) in a “special report.”21 The subject was again examined in the first of three reports on 10-year trends (with 37 populations).22

In the earlier paper it was shown that Belgian, French, and Polish centers, through reallocation of diagnoses by the registration teams, had coronary death rates adjudged for MONICA as higher than those shown in their officially compiled statistics.21 The later paper showed similar findings over 10 years.22 After allowing for some missing death certificate data, the average center registered 1882 deaths attributed officially to coronary heart disease, but registered 2213 events satisfying MONICA criteria for coronary deaths (definite, possible, or unclassifiable), a ratio of 1.2. Some 21% of these, however, were “unclassifiable.” The three French, two Belgian, two Polish centers, and Catalonia (Spain) all had unclassifiable deaths above 40% of their MONICA total. The relative increase in numbers from official coronary heart disease deaths to MONICA fatal events was greatest for the three French centers. In Lille, the local MONICA investigators identified 3608 MONICA deaths with 48% unclassifiable, as against 1723 official coronary deaths; for Strasbourg it was 2659 with 47% unclassifiable versus 1451 official coronary deaths, and for Toulouse it was 1627 with 43% unclassifiable versus 888 official coronary deaths. In each French center, numbers approximately doubled (ratio 1.94) through inclusive MONICA categories. These additions were deaths previously attributed to other causes, often cardiovascular, sometimes simply “sudden death.”21,22

It is arguable whether the near doubling of coronary deaths for French centers in MONICA is appropriate. Missing diagnostic information cannot be recreated. The problem of what MONICA called unclassifiable deaths (all men and women below age 65) is a widespread scandal for medical science not just for France. Twenty-seven of 37 populations had unclassifiable deaths at 10% or more of their total, involving 16 of 21 different countries. Results for women were worse than for men.21,22

One clue to the justice of including unclassifiable deaths as coronary deaths is the community 28-day case fatality embracing sudden deaths outside hospital.21 For men this averaged 48% across 38 populations in 1985-7 with those deaths included. Values for Lille were 58%, Strasbourg 51%, and Toulouse 45%, averaging 51%. This suggested no significant addition of noncoronary deaths despite near doubling of numbers. For women the 38-population 28-day case fatality mean was 54%. Values for Lille were 68%, Strasbourg 62%, and Toulouse 65%, averaging 65%. Perhaps these were too high. However, here another factor may have been operating. In women, not men, case fatality across different populations was inversely related to coronary event rates.21 The supposition was that where coronary disease was rare anyway, and therefore even rarer in women than men, it was less likely that nonfatal myocardial infarction below age 65 in women would be suspected by the patient, their contacts or their doctors. If nonfatal cases were completely missed they would not appear in the denominator of case fatality. As it is less easy to overlook a dead body, deaths would be recognized more readily than nonfatal events, spuriously raising the resulting case fatality. At the other...
extreme, Glasgow, with very high event rates in both men and women, implying very frequent recognition of the diagnosis, had the same 28-day case fatality of 49% in both sexes. The reallocation of deaths to the MONICA unclassifiable category, and calling them coronary deaths, leads both to higher coronary death rates, and to higher combined fatal and nonfatal coronary event rates, for the three French centers. However, even after correction, the event rates of the three French centers remain very low. In the final 3 years of event registration the three French centers ranked for men 28th (Lille), 30th (Strasbourg), and 34th (Toulouse) of the 37 populations in MONICA, mixing with Beijing (China), Catalonia (Spain), Augsburg (South Germany), two Italian centers, and a Swiss center. In women (the Swiss opted out of registering coronary events in women) Lille was 29th, Strasbourg 30th, and Toulouse 35th out of 35, competing for the bottom few rankings with Catalonia, two Italian centers, and Beijing.

Five-year averaged coronary event rates by MONICA criteria, including unclassifiable deaths, are shown for the three French centers in Table V. As stated already, they remain well below the 38-population average, and a fraction of those from northern populations, despite this adjustment. Of the three, Lille is furthest north and closest to Calais and the United Kingdom, Strasbourg is close to the German border, and not too far from Switzerland, while Toulouse is closest to the Mediterranean and nearest to Catalonia in Spain, although separated from both by mountains. Catalonia also had very low coronary event rates. Similar analyses of coronary event rates have led to the suggestion that French paradox is a misnomer and that the similarity of the French results to those from Italy and Spain make this a “Mediterranean paradox.” The latter links it to the so-called Mediterranean diet (see later), raising the question of whether France is a Mediterranean country and whether it has a Mediterranean diet.

**THE RISK FACTOR/SATURATED FAT ORTHODOXY OF CORONARY HEART DISEASE CAUSATION, AND WHAT FOLLOWED IT**

“Orthodoxy is my doxy: heterodoxy is another man’s doxy”
Bishop William Warburton

The triangle: saturated fat—serum cholesterol—coronary heart disease

The Framingham and contemporaneous cohort studies in the USA in the 1950s and 1960s generated the concept of cardiovascular risk factors, of which three, now labeled classic, dominated discussion in the 1960s and 1970s:  

Cigarette smoking, blood pressure, and blood (serum/plasma/total) cholesterol appeared of equal importance in determining risk within American populations. This did not explain what made Americans more prone to coronary heart disease than others. Comparisons were needed with populations outside America with different coronary disease rates.

Ancel Keys (Figure 5), a physiologist from Minneapolis, familiar with long-term nutritional and metabolic experiments through research on starvation and malnutrition in the Second World War, undertook two complementary sets of studies.
He and his collaborators, a quorum of the world’s cardiovascular epidemiologists, set up mini-Framingham studies of cohorts of people across countries differing in their coronary heart disease mortality, measuring baseline risk factors and diet, and monitoring incident coronary events over following years. Cohorts, totaling 13 in the 5-year results and 16 in the 10-year results, were recruited within seven countries: USA, Japan, Finland, The Netherlands, Italy, Yugoslavia, and Greece. The choice depended on local contacts and enthusiasm, and other factors. France, Germany, and the United Kingdom were not alone in being excluded.

Within America, Keys (as did others elsewhere) undertook a large series of feeding experiments to discover what determined blood levels of cholesterol and related lipids, using medical students, prisoners, and mental hospital volunteers, among others. A meta-analysis produced a formula that predicted change in serum cholesterol levels (for constant calorie intake and weight) in terms of change in intake of calories from saturated fats, polyunsaturated fats, and change in dietary cholesterol intake. Carbohydrates and monounsaturated fats were estimated to be neutral in effect; saturated fat and cholesterol led to an increase, and polyunsaturated fats to a reduction.

The Seven Countries cohorts confirmed the role of the classic big three risk factors in determining observed coronary risk during follow-up. However, the level of smoking and blood pressure in different populations did not appear to explain overall cohort event rates so well as did the mean serum cholesterol: that in turn was correlated with total fat in the diet and even more closely \( r=0.84 \), with the amount of saturated fat in the diet. There was thus a triangular relationship between the proportion of calories from saturated fat, population mean cholesterol, and the incidence of coronary heart disease. At the same time the nutritional experiments emphasized the relationship between serum cholesterol and both saturated fat and (to a lesser extent) dietary cholesterol. Saturated fat is most commonly derived from ruminant animals (cows, sheep, etc), but also came in the past from industrial manufacture of hard margarines and shortenings derived from vegetable and fish oils. Dietary cholesterol comes exclusively from animal sources, often the same sources as saturated fat, animal meat and offal, but to a lesser extent from eggs and shellfish.

The outcome of these studies assigned a central role to serum cholesterol and saturated fat (with dietary cholesterol acting as its Sancho Panza, Figure 6). At that time coronary disease causation and prevention was almost one-dimensional as far as diet was concerned. The resulting orthodoxy or dogma was called the “Diet-Heart Hypothesis.” Never universally accepted—there were eminent detractors, vehement exchanges of diatribes well loved by journal editors, agnostics who bent their sails to the prevailing wind—all roles familiar in ecclesiastical history—it was the only plausible show in town. As such it was adopted by the American Heart Association, appeared in consensus statements, and was adopted and simplified by health educators in the USA, and increasingly worldwide.

It was chance that France was not included in the Seven Countries Study. Thirteen or 16 data points, produced with enormous effort, are not ideal, yielding correlations and regressions that lack precision and robustness, and may be strongly influenced by the extremes, in this case Japan and Finland. The supposition now is that French cohorts would have been outliers on the famous Keys scatter plots, produced as they were in the decades immediately following the Second World War, when many countries had predominantly rural populations. It would subsequently be less possible,
unless non-industrialized countries are included, to show a scatter plot of spread of mean population cholesterol values correlating well with coronary disease incidence in different populations, particularly as most populations are in the middle range for both.

For example, in the MONICA Project populations, using data collected up to a quarter of a century later, in the early 1990s, participation demanded commitment of skilled personnel, resources, and local medical services. There was no African, South American, Central American, or Asian involvement other than Novosibirsk and Beijing. Mean cholesterols are tightly bunched (except for Beijing) and correlate poorly with coronary event rates.20,23 Using data for 38 populations, which are partially extracted in our Table V, in men, population coronary event rates show correlation coefficients with percentage smokers r=0.17, systolic blood pressure r=0.31, total cholesterol r=0.16, BMI (body mass index) 0.30; whereas in women, coronary event rates correlate with percentage smokers r=0.41, systolic blood pressure r=0.06, total cholesterol r=0.24, BMI r=0.35 (Tunstall-Pedoe, unpublished, calculated for this review). The sexes are not consistent; the picture is now confused.

Keys’ supporters would say he was right, but serendipitous in his choice of populations to achieve such a good correlation, detractors that he was wrong and chose his populations to make his case. The retrospecoscope would tend to vindicate him, but the diet-heart story has turned out to be more complex than the simple triangle suggested.

The Framingham9 and Minneapolis11,24 studies were the simple triangle suggested. The heart story has turned out to be more complex thanKeys chose his populations to make his case. The retrospective good correlation, detractors that he was wrong and supporters that he was right, but serendipitous in his choice of populations to achieve such a good correlation, detractors that he was wrong and chose his populations to make his case. The retrospecroscope would tend to vindicate him, but the diet-heart story has turned out to be more complex than the simple triangle suggested.

The French paradox therefore lay outside France. Earlier observers and investigators had described and commented on the low French mortality from coronary heart disease, possible differences in death certification from elsewhere, and the rich diet3-5. The French situation became truly paradoxical when put into the straitjacket of the diet-heart hypothesis, which achieved widespread currency during the 1970s.

Lipids and the diet-heart hypothesis transformed

The remainder of this review will necessarily be superficial and eclectic both in the text and referencing. There is such a great field to cover, on dietary factors and atherogenesis, that some key topics, and many key investigators, will inevitably be overlooked.

Since the 1970s diet and coronary heart disease causation has become multidimensional. Keys and others had suggested that different saturated fats might differ in their effects on serum cholesterol.5,25 The latter ceased to be the almost exclusive mediating risk factor between diet and coronary risk. (Interest in diet and blood pressure continues, but it has always received less prominence). With the recognition of the importance of HDL cholesterol,15 a subset of the total but with opposing significance for risk, it became necessary to revisit the earlier feeding experiments to see whether the changes in low-density lipoprotein (LDL) cholesterol, the main constituent of total cholesterol, were confounded by changes in HDL cholesterol within the total cholesterol previously measured. It was claimed that the role of monounsaturated fatty acids (found in animal fats as well as vegetable oils such as olive oil, where oleic acid is predominant) had been misunderstood.26

Techniques improved for identifying specific fatty acids. Among these were the so-called omega-3 and omega-6 fatty acids, long chain polyunsaturated fatty acids found in specific foods such as fish and vegetable oils. An early dietary hypothesis, originating with Hugh Sinclair of Oxford, England, had been that coronary heart disease was caused by deficiency of these “essential” fatty acids,5,26,27 but this had little support outside Britain. However, they and their metabolites have important roles in platelet function and in inflammation. Omega-3 fatty acids are found in fish oils, (Figure 7, page 170) which, with fish, have figured in many studies and trials, showing more potential effect on serum triglycerides than serum cholesterol: effects on overall disease rates are pursued in numerous analyses and meta-analyses.26,28

The potential harmful effect of the unnatural trans unsaturated fatty acids produced by the industrial process of partial hydrogenation of polyunsaturated fatty acids in vegetable and fish oils, in the manufacture of margarines and shortening, was suggested decades ago, but active research took place more recently. (Natural double bonds in the carbon-carbon chain of fatty acids,
as in the essential polyunsaturated fatty acids and oleic acid, have the alternative cis stereochemical configuration. The Keys formula would classify monounsaturated trans fatty acids as neutral in effect, without distinguishing cis from trans, but trans fatty acids are now considered to raise LDL cholesterol levels, lower HDL cholesterol, and increase coronary risk, leading to a change in the formulation of margarines and shortenings by most major manufacturers. Paradoxically, margarine was invented by a Frenchman, but figures more in the diet history of industrialized populations elsewhere.

Keys was predominantly concerned with major components of the diet, the macronutrients, whose intake could be measured in grams (or tenths of a gram for cholesterol). Later, the long-chain polyunsaturated fatty acids were given a role. The next twist in the lipid hypothesis brought in components of the diet consumed in very small quantities, the micronutrients.

In the 1960s and early 70s total cholesterol was the main lipid villain. In the late 1970s this became LDL cholesterol as HDL cholesterol achieved separate status, and the LDL receptor was identified. In the 1980s, the situation was complicated further when it was realized that LDL itself was not particularly atherogenic. It became so when oxidized. So it was oxidized LDL cholesterol, not cholesterol itself that was of interest.

Lipids, particularly unsaturated fatty acids, have a tendency to degrade or become rancid through the oxidizing action of free radicals (chemical compounds of transient existence and high reactivity through having unpaired electrons). In life, this is prevented energetically through the metabolic involvement of vitamins that are antioxidants.

**Micronutrients: the antioxidants**

Emergence of the antioxidant vitamin hypothesis opened new dimensions in diet and coronary heart disease, giving positive roles to dietary components that vegetarians and others considered “healthy,” but did not fit the Keys formula. (The legendary cardiovascular epidemiologist, Geoffrey Rose, said to me in the 1970s “what is the use of eating lettuce—it is nearly all water anyway?”—years before micronutrients and antioxidants appeared on the scene.) The excitement of the new theory precipitated numerous observational studies and experiments, which continue. Some involving dosing with antioxidant vitamins have produced disappointing results. Interest shifted from antioxidant vitamins in the diet to other antioxidants found in foods. These are too numerous to name here, but an Internet listing gives some idea of the challenge faced by investigators in trying to sort things out (Table VI).

Many are identified with particular foods, or particular colors of food. Although in foods, they may not be digested and absorbed. Experiments on them may be done in vitro, in small animals and, most expensively, in man, to test their effects on possible indices of atherogenesis. A preventive trial would be a huge undertaking. Apart from the antioxidant role, there are other potential micronutrient roles that are of interest, some of which will be briefly mentioned. Many substances have multiple roles and classifications.

**Other micronutrients: a Tower of Babel**

Man-made acetyl-salicylic acid (aspirin) is widely used in primary and secondary prevention of coronary heart disease because of its effect on platelet function (interacting with metabolites of essential fatty acids). Natural salicylates are found in many foods including fruit and wine, although weaker in effect.

Cholesterol is exclusively found in the animal kingdom. Plants have analogues of cholesterol known as phytosterols that are now being extracted for their cho-
Lesterol-lowering effects. In animals, cholesterol is metabolized into sex hormones (leading to a big court case years ago in the USA when an advertisement for "The Sexy Egg" was challenged by cardiovascular epidemiologists and the American Heart Association). Again plants contain analogues. Phytoestrogens appear to figure more in discussion of cancers than coronary heart disease.

**Vitamins cofactors and minerals**
- Coenzyme Q10
- Manganese, particularly when in its +2 valence state as part of the enzyme called superoxide dismutase (SOD).
- Iodide

**Hormones**
- Melatonin

**Carotenoid terpenoids**
- Lycopene
- Lutein
- Alpha-carotene
- Beta-carotene
- Zeaxanthin
- Astaxanthin
- Canthaxanthin

**Flavonoid polyphenolics**
- **Flavones:**
  - Luteolin
  - Apigenin
  - Tangeritin
- **Flavanoids:**
  - Quercetin and related, such as rutin
  - Kaempferol
  - Myricetin
  - Isorhamnetin
  - Proanthocyanidins, or condensed tannins
- **Flavanones:**
  - Hesperetin (metabolizes to hesperidin)
  - Naringenin (metabolized from naringin)
  - Eriodictyol
- **Flavanols and their polymers:**
  - Catechin, gallocatechin and their corresponding gallate esters
  - Epicatechin, epigallocatechin and their corresponding gallate esters
  - Theaflavin its gallate esters
  - Thearubigins
- **Isoflavone phytoestrogens**
  - Genistein
  - Daidzein
  - Glycitein
- **Stilbenoids:**
  - Resveratrol
  - Pterostilbene - methoxylated analogue of resveratrol
- **Anthocyanins**
  - Cyanidin
  - Delphinidin
  - Malvidin
  - Pelargonidin
  - Peonidin
  - Petunidin

**Phenolic acids and their esters**

| Main article: polyphenol antioxidant |
| Ellagic acid |
| Gallic acid |
| Salicylic acid |
| Rosmarinic acid |
| Cinnamic acid and its derivatives, such as ferulic acid |
| Chlorogenic acid |
| Chicoric acid |
| Gallotannins |
| Ellagitannins |

**Other nonflavonoid phenolics**
- Curcumin
- Xanthones
- Flavonolignans
- Eugenol

**Other organic antioxidants**
- Citric acid, oxalic acid, and phytic acid
- Lignan
- Bilirubin
- Uric acid
- R-α-Lipoic acid
- N-Acetyl cysteine

**Table VI. List of antioxidants in food.** Only the names are listed here, for full details refer to Wikipedia: [http://en.wikipedia.org/wiki/List_of_antioxidants_in_food](http://en.wikipedia.org/wiki/List_of_antioxidants_in_food).

Homocysteine has been shown in many studies to be a risk factor for cardiovascular disease. Blood levels in man are partly determined by specific genes. Levels are also related to dietary components including folic acid, found in green vegetables, pyridoxine, and cyanocobalamin, another means by which a varied “balanced” diet might contribute to coronary disease prevention.
Interest has recently been rekindled in cardiovascular disease and vitamin D, associated with various animal fats. Minerals are also potential micronutrients.

More recent than the antioxidant story is the realization that atherogenesis is an inflammatory disease whose activity may be exacerbated or damped down by the effects of micronutrients. This involves the measurement of activity of inflammatory markers such as fibrinogen, C-reactive protein, and many others. Underlying vascular health now is the concept of endothelial function, another series of tests remote from the original serum cholesterol. Micronutrients may also figure in activating/deactivating specific genes.

Although some complexities were anticipated in part, the simple Keys Diet-Heart triangle of cholesterol, saturated fat, and coronary heart disease of 30 years ago is now replaced by a multiplicity of dietary components and physio/pathological intermediary pathways. These will provide employment and publications for researchers for decades to come. In attempting to summarize developments in this field, your reviewer wonders with the innumerable possible mechanisms and interesting micronutrients, if we have not moved from the biblical Ten Commandments of the 1960s to the Tower of Babel in the 21st century. However, some consensus is centered on the “Mediterranean diet.”

THE MEDITERRANEAN DIET AND WHAT MIGHT MAKE IT PROTECTIVE

Which countries “serve it” and “what’s on the menu?”

In fairness to the instigator of the saturated fat—cholesterol—coronary disease triangle and the Keys formula, Ancel Keys himself positively promoted what he named the Mediterranean diet. He claims to have first seen it in Naples in the 1950s when there was virtually no disease about. He claimed subsequently the “heart of the Mediterranean diet is mainly vegetarian: pasta in many forms, leaves sprinkled with olive oil, all kinds of vegetables in season, and often cheese, all finished off with fruit, and frequently washed down with wine.” Others would add to this list (fish, for example) or subtract from it.

The Mediterranean is certainly bordered by countries with low coronary mortality, but it is a big area and supports many different diets. Pasta suggests Italy, wine the northern littoral, but there is no wine to the south. There is a problem in identifying what are the key components. Some investigators have proposed scoring systems for conformity with a model Mediterranean diet as inhabitants of Mediterranean countries abandon it, or have difficulty in pursuing it if they migrate northwards. One attempt to establish whether people in Mediterranean countries conform with current American recommendations on the prudent diet to prevent coronary heart disease found that most did not. The historical diets eaten by participants in the Seven Countries Study in the 1960s would no longer apply. The world has urbanized and now uses supermarkets. The rural idyll—of the herdsman playing his Pan-pipes to his goats, among his olive trees—scarcely exists except in folk memory and 18th century romantic pastoral paintings.

Discussion of the French paradox, the potential Mediterranean paradox, the Mediterranean, and “healthy diets” leads to them becoming conflated. It is argued that France is not a Mediterranean country, and does not eat a Mediterranean diet. Certainly the FAO figures (Table IV) show little agreement in consumption of macronutrients between Greece and France. In emphasizing the dietary world beyond cholesterol and saturated fat, Ulbricht and Southgate in 1991 listed seven dietary principles for atherogenicity and thrombogenicity. In 2004, a paper from the Netherlands suggested an evidence-based “polymeal” for coronary disease prevention as an antidote to excitement over a proposed polypill. The “polymeal” would contain wine, fish, dark chocolate, fruit, vegetables, garlic, and almonds. Missing from that list is olive oil considered by some to be a key component of the Mediterranean diet, whereas the polymeal contains fish, garlic, and almonds (nuts) missing from Ancel Keys’ list along with chocolate.

The Mediterranean-type diet has figured in two published trials of secondary prevention of coronary heart disease. The Lyon Diet-Heart study was very successful. The second, reportedly equally successful, from India, probably never took place. Unfortunately, it appears that further such trials, which are needed, may have been inhibited by the results of statin trials in the middle 1990s, although the benefits could well be synergic. It is easier to eat pills than change your diet. Very briefly we will consider specifics.

Olive oil

The monounsaturated cis fatty acid, oleic acid, is a major constituent of olive oil, but it is also found in considerable quantities in animal fats. Olive oil keeps
well without going rancid. Is olive oil directly beneficial in its own right, or simply because consumption substitutes for known harmful fats? It has been argued that olive oil goes with a healthy diet because it encourages consumption of salads (Figure 8). It has also been shown to contain innumerable micronutrients that may be beneficial and will vary with “quality” and how it is processed. It has a European marketing organization that lobbies for it. Many poorer people in Mediterranean countries substitute cheaper oils and fats because it is expensive. How many French people consume significant amounts?

**Alcohol and wine**

Your reviewer chaired the plenary session of the British Society for Social Medicine in 1978 when Professor Archie Cochrane (a father of evidence-based medicine) reported that national mortality rates from coronary heart disease were inversely related to wine consumption. Professor Alwyn Smith called out from the audience that the Queen should honor him by putting him in the House of Lords. I replied amid equal laughter that we should wait to see whether he was to be made Lord Archie of Burgundy or Lord Archie of Bordeaux. I failed to realize that this was prophetic, anticipating the pattern of much research a quarter of a century later, with competing claims made for the benefits from different antioxidant polyphenols and other micronutrients featured in different wines. It is no coincidence that the Google page for “French paradox,” alongside its announcement of finding 368,000 relevant pages, features a large advertisement for resveratrol, one of these antioxidants. There is controversy about how well some of them are absorbed and whether alcohol is needed to absorb them. Meanwhile there is full rein for extravagant claims for individual wines, and the superiority of their terroir in producing particular micronutrients (Figure 9). Were there to be an agreement on which one was the answer, no doubt plant breeders and geneticists would produce a genetically modified vine that fitted the requirement.

Epidemiologists are not well equipped to distinguish one wine from another. Indeed some large cohort studies find different forms of alcohol, beer, wine, and spirits, to be equally beneficial, others favor wine. Different patterns of consumption are confounded with other lifestyle factors—wine goes naturally with other components of the Mediterranean diet. Alcohol itself raises HDL cholesterol, a beneficial effect not involving micronutrients. There is confusion as to the cutoff at which increased consumption becomes harmful. The “J-shaped curve,” memories of prohibition, and fear of encouraging addiction, accidents, and violence, all lead to reluctance to recommend alcoholic drinks as beneficial. Which matters more, what you drink or your pattern of drinking it—slowly with food, or rapidly in concentrated doses? French inves-
tigators point out that France used to have the highest alcohol consumption per head in the world, associated with much disease, and that mortality rates have come down from all causes and coronary disease as consumption has declined. In industrial areas, many people drink beer. Some of these issues are discussed further in an accompanying Respondent Article by Joël de Leiris and François Boucher.

The wine industry seems to have a powerful lobby, and one suspects that it funds considerable positive research. Distillers of spirits and brewers of beer seem to be less well organized, less positive, and more defensive.

Onions and garlic

These have not featured so much in recent research as wine, possibly because there is less financial support forthcoming from an industrial lobby. Apart from stable antioxidants, these contain sulfur compounds that are unstable and produce a cascade of complex chain reactions, making them difficult to study in the laboratory. At one time there was debate on how much they lowered blood lipids, but benefit could be through entirely different pathways.

Fruit and vegetables

There is substantial direct and indirect evidence to support the prime importance of fruit and vegetables in maintaining health (Figure 10), despite their failure to appear in the FAO country profiles (Table IV). There is little profit in producing them, and less in marketing them fresh and unchanged, than there would be if an industrial process was involved that produced added value. This means there is not much of an industrial lobby, or consequent commercially funded research. Apart from the interest in vegetable fiber, topical some years ago, in vitamin C, an important antioxidant, and in folic acid, which is involved in homocysteine metabolism, different colored vegetables and fruits contain different antioxidants and micronutrients with differing potential for influencing disease processes, and differing claims for them (for example lycopene in tomatoes). It is not possible to do them justice here.

Fish, nuts, and chocolate

Fish (Figure 11) and nuts feature in many definitions of the Mediterranean diet, while chocolate features in the evidence-based polymeal diet, although it is a tropical product. All three have beneficial effects claimed for them, simply from observational studies, or linked to particular micronutrient constituents, but no single one can be considered the answer to coronary disease or the French paradox in isolation.

Patterns of eating

Early dietary theories featured macronutrients consumed per day. Later interest moved to micronutrients. As striking as dietary constituents are patterns of eating, which should not be ignored. The French still sit...
down to meals as a family (disappearing in some countries) and eat fresh food, and meals last considerably longer both in the preparation, the anticipation, and the consumption than elsewhere. Food is an opportunity for conversation. Much of the alcohol that is consumed is with food rather than separately. Although such traditions and behaviors may be declining, they may imply different metabolic consequences and disease patterns. French eating patterns are the subject of an accompanying Respondent Article by Michelle Holdsworth.

**CAN WE BE SURE THAT DIET IS RESPONSIBLE?**

**Genetics and other alternatives**

Our discussion so far has been concentrated on the original and then evolving versions of the “diet-heart” hypotheses. Before micronutrients provided a happy-hunting-ground for endless new hypothetical mechanisms, some researchers, resenting the straitjacket of diet and lipids, suggested alternative explanations outside diet. These included psychosocial factors and genetics. Psychosocial factors have perhaps enjoyed more support for explaining the Japanese—a country isolated for hundreds of years—than the French, and more in the past than more recently. Both countries have converged with other advanced industrial countries over the decades in their lifestyles and behaviors. Perhaps “patterns of eating” is an area where the psychological and the physicochemical can overlap.

Genetics was the hope to explain everything not explained by classic risk factors. More is now known about genetics. Ancestors of the current French population were never isolated long enough from neighboring countries for major differences in gene frequencies to emerge. Those smaller differences that have been identified are insufficient to account for major population differences in coronary event rates. Interest has shifted from single genes determining disease, to multiple genetic predispositions that interact with the environment. Those that have been identified appear to increase risk more in coronary prone populations, so the relative immunity of the French extends even to those with genetic susceptibilities.

One perennial explanation for national differences in coronary heart disease is north-south climate differences. People in northern countries now have central heating, heated transport, and work indoors. Global warming is changing outdoor temperature gradients. Historically, the crops grown depended on the climate: it is temperate farming and food practices that are blamed for coronary heart disease. The definitive test would be to swap diets between northern and Mediterranean countries. That might be considered unethical and unattractive. So we come back to diet as the main candidate to explain the paradox.

**A FRUITFUL COLLABORATION**

Among innumerable specific studies authored by others that might be mentioned, I select an ongoing collaboration of my erstwhile Belfast and French MONICA colleagues, in particular Toulouse. This has led to many publications from the MONICA, ECTIM (Étude Cas Témoins de l’Infarctus du Myocarde), and PRIME (étude PRospective de l’Infarctus du MyocardE) studies, elucidating the French and Mediterranean paradoxes in some detail, but without, however, apparently solving the mystery.

**CONCLUSION: ARE WE ANY NEARER TO ANSWERING THE PARADOX TWENTY YEARS AFTER ITS DESCRIPTION?**

As described above, the French paradox emerged within the straitjacket of the lipid or diet-heart hypothesis of coronary heart disease, which dictated that low rates of coronary heart disease mortality should be accompanied by low population levels of total serum cholesterol and low intake of animal fat from ruminant animals.

There is evidence, discussed above and also in an accompanying article, that French mortality rates from coronary heart disease are underreported compared
with other countries. Correction of these rates, however, does not bring them up to average European levels. They remain surprisingly low. The explanation that there is a long time lag between rising cholesterol levels and rising coronary rates is untestable and unconvincing if 9 years after its publication, French rates are still declining from an initially low level.50

Unraveling the French paradox would demand an explanation of why French men benefit only with respect to coronary disease mortality and not mortality overall, whereas French women get the best of both. Maybe the pattern of smoking and drinking in the two sexes has something to do with it. If steady consumption of alcohol/wine is protective, but French men are consuming way beyond the level necessary for coronary prevention, their decline in mortality with decreasing consumption might be explained. An accompanying article discusses wine and alcohol in greater detail, and another, the patterns of eating food in France, a previously neglected subject.

Would it be possible to recognize the answer to the French paradox if it did appear, and would someone blow a whistle to stop the discussion? There are large vested interests in pursuing the dietary advice being promoted to different populations already, and huge commercial interests at stake. Scientific research has identified a great number of micronutrients, metabolic pathways, and biomarkers that might be involved. Could we achieve a consensus on what the answer might be, good enough to initiate a confirmatory randomized controlled trial? How expensive might that be? How many hundreds of thousands or millions of person years would be involved, and could it be double blind? Coronary rates are declining in many countries outside France, so a long-term trial would be chasing a disappearing target. Diet is influenced as much or more by economic factors as by health promotion. Compliance with the trial protocol would be a huge problem.

Twenty years ago I queried whether the building of the Channel Tunnel between England and France, and the creation of a common European market, would lead to a merging of lifestyles; and I wondered whose mortality rates would predominate.6 We have seen the French adopting fast foods and American practices, and many Britons becoming addicted to continental, Mediterranean, and other exotic food and cuisine. Meanwhile the French paradox is diminishing in absolute terms although remaining the same relatively. Coronary heart disease rates are declining and are increasingly controlled by medical interventions (Table II). Perhaps in another twenty years, or earlier, we will have the answer. By then the question may no longer seem so important.

I finish with Samuel Black (see Figure 12):3

“As far as….professors have exerted their ingenuity in constructing brilliant theories or in dressing up fanciful speculations, their efforts have been thrown away. But so far as they have employed their talents in the observation, collection and arrangement of useful or important facts, ..to this extent they have rendered a real and important service to the science they cultivate.”

It is doubtful whether one can observe and recognize a useful or important fact without some framework for doing so. However, this professor sympathizes with Black’s opinion, and hopes that his own concentration on facts rather than fanciful speculations has been helpful to his readers.

Figure 12. Saint Patrick’s Church (erected in 1573 and restored in 1866), Newry, where Dr Samuel Black is buried. All rights reserved.
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The French Paradox: Fact or Fiction?

*Expert Answers to Three Key Questions*

1. Does wine consumption explain the French paradox?
   
   *J. de Leiris, F. Boucher*

2. Coronary heart disease in France and in Europe: where are the facts?
   
   *P. Ducimetière*

3. How important are differences in national eating habits in France?
   
   *M. Holdsworth*
Epidemiological evidence confirms that moderate intake of alcohol reduces the risk of morbidity and mortality from cardiovascular disease. Although regular consumption of any type of alcoholic beverage appears to confer health benefits, additional benefits are thought to be associated with wine—particularly red wine. Regular drinking of moderate quantities of wine has been proposed as an explanation for the “French paradox,” which designates the relatively low incidence of coronary mortality in France compared with other Western countries despite a high intake of saturated fats. The beneficial effect of wine is ascribed to the presence of ethanol and phenolic compounds. This review examines the epidemiology of cardiovascular disease and wine consumption and the mechanisms underlying the biological effects on cardiovascular disease derived from red wine compounds.

**Keywords:** French paradox; wine; alcohol; phenolic compound; cardiovascular protection

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**SELECTED ABBREVIATIONS AND ACRONYMS**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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<tbody>
<tr>
<td>CHD</td>
<td>coronary heart disease</td>
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<tr>
<td>CVD</td>
<td>cardiovascular disease</td>
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<tr>
<td>HO-1</td>
<td>heme oxygenase-1</td>
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<tr>
<td>HSP</td>
<td>heat shock protein</td>
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<tr>
<td>NF-κB</td>
<td>nuclear factor kappa B</td>
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<td>NO</td>
<td>nitric oxide</td>
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<tr>
<td>PKC</td>
<td>protein kinase C</td>
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<td>TNF-α</td>
<td>tumor necrosis factor-α</td>
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of regular wine consumption has increased considerably over the past 30 years. In 1979, St Leger and colleagues drew attention to the protective properties of wine when they described an inverse relationship between wine consumption and deaths from CVD for Europe, North America, and Australasia. Prevention of CHD is the chief potential benefit attributed to light consumption of wine—and this has been attributed to alcohol itself or other wine components. However, the possibility that this benefit may be confounded by other physical, socioeconomic, and lifestyle characteristics shared by moderate drinkers cannot be discarded.

A balanced view of wine drinking and health should take into account both the beneficial and the harmful effects, the amount of wine consumed, the variety of the grapes used in wine making, and drinking patterns. Heavy drinking (>3 standard-size drinks) carries excess mortality from cardiovascular and noncardiovascular causes, whereas lighter drinking carries a lower total mortality risk, mainly because of a lower CHD risk.

A number of epidemiologic studies in various countries have consistently evidenced substantial (at least 30%) protection against CHD with moderate amounts of alcohol (10 to 40 g per day). Total mortality is slightly favorably affected in middle-aged and older moderate drinkers as compared with abstainers.

Protection through moderate wine drinking also probably extends to ischemic stroke and ischemic damage to the extremities and possibly to diabetes mellitus and other conditions. Findings from two large studies, one in Denmark and the other in France, which looked at death from CHD and all other causes, are very important. The Danish study, conducted in more than 24,000 men and women living in Copenhagen, investigated the effect of one to three glasses of alcoholic beverage (beer or wine) per day on CHD. Support for a more pronounced cardioprotective effect with wine compared with other alcoholic beverages first emerged from this study because it showed that subjects with low-to-moderate wine intake had half the risk of dying from cardiovascular and cerebrovascular disease as those who never drank wine, whereas beer and spirit drinkers did not experience this advantage.

These results were reinforced when the same group performed pooled cohort studies in which the type of alcohol consumed, smoking status, educational level, physical activity, and body mass index were assessed at baseline. Compared with nondrinkers, light drinkers who avoided wine had a relative risk of death from all causes of 0.90, whereas those who drank wine had a relative risk of 0.66. The authors concluded that wine intake may have a beneficial effect on all-cause mortality that is additive to the protection afforded by alcohol. Serge Renaud reported similar results from a study conducted in eastern France between 1978 and 1983 in 36,250 men. As in the Danish study, both beer and wine drinkers had reduced CHD, but the most impressive result was the finding that wine drinkers who drank two to four glasses per day suffered 30% fewer deaths from all causes compared with nondrinkers or those who drank more than four glasses of wine per day. Excess consumption of any alcoholic beverage was thus associated with a significant increase in mortality.

Within the framework of Northern California Health Care program, Klatsky et al performed a prospective cohort study of 128,934 adults followed from 1978 to 1998. They concluded that drinkers of any type of wine have a lower risk of CHD and respiratory deaths and a lower all-cause mortality risk than do beer or spirit drinkers, even though each beverage type apparently protects against CHD mortality. However it remains unclear whether this reduced risk is due to nonalcoholic wine ingredients, drinking pattern, or associated traits.

Mukamal and colleagues studied the association of alcohol consumption (beer, red wine, white wine, or liquor) with the risk of myocardial infarction among a cohort of 38,077 male health professionals who were free of CVD and cancer at baseline. During 12 years of follow-up (1986-1998), there were 1418 cases of myocardial infarction. As compared with men who consumed alcohol less than once per week, men who consumed alcohol 3 to 4 or 5 to 7 days per week had a decreased risk of myocardial infarction, and the risk was similar among men who consumed less than 10 g of alcohol per drinking day and those who consumed 30 g or more. Moreover, men who increased their alcohol consumption by a moderate amount during the 12-year follow-up had a decreased risk of myocardial infarction. In contrast, among men whose consumption was stable or decreased during follow-up, a 12.5 g decrease in daily alcohol intake was associated with a nonsignificant trend toward a higher risk of myocardial infarction.

No single type of beverage conferred additional benefit, nor did consumption with meals. Even in men already at low risk on the basis of smoking, body mass index, physi-
cal activity, and diet, moderate alcohol intake was associated with lower risk for myocardial infarction. Although a number of case-control and cohort studies in different countries have reported decreased CVD rates among healthy moderate drinkers as compared with abstainers, data on the impact of moderate wine drinking in patients with established CHD remain limited. In survivors of a recent myocardial infarction, de Lorgeril and colleagues studied the association between alcohol intake (92% to 95% wine) and the risk of recurrence during a 4-year follow-up [Lyon Diet Heart Study]. In comparison with abstainers, the adjusted risk of cardiovascular complications was reduced by 59% in patients whose average alcohol intake was 7.7% of total energy intake (about 2 drinks per day), and by 52% in those whose average ethanol intake was of 16% of energy (about 4 drinks per day). Despite a small sample size (353 males), this study suggests that in a very homogenous population of patients with established CHD, after controlling for many potential confounders, wine drinking is associated with a reduced risk of CVD complications.

**MECHANISMS AND COMPOUNDS ASSOCIATED WITH CARDIOPROTECTION**

What are the likely mechanisms by which wine confers cardioprotection? What are the specific components of wine that are active on cardiovascular end points?

It is difficult to explain the effect of wine on risk factors associated with CVD by a uniform biochemical mechanism. Wine is a complex nutritional based on grape juice in which alcohol has formed following natural fermentation. Wine contains more than 500 compounds, some originating from the grapes and some metabolic by-products of yeast activity during fermentation. Most of these compounds are present in very low concentrations, but a few occur at concentrations above 100 mg/L. These include water, alcohols, organic acids, sugars, and glycerol. The most important alcohol in wine is ethanol, with concentrations ranging from 10% to 14%. Ethanol is crucial for the stability, aging, and gustatory properties of wine. It plays a role in the extraction of pigments and tannins during the fermentation of the skin and seeds of grapes.

Many active substances, such as phenols and polyphenols, have been identified in wine, but they are also found in other foods. Grape polyphenols, namely, anthocyanins, flavonols, hydrocinnamic acids, and flavanols (including catechins and proanthocyanidins) represent about one half of the polyphenol content of a 2-year-old red wine. In wine, polyphenols are responsible for the changes in color and taste that occur during aging. Quercitin, the main flavanol in the human diet, is found not only in wine, but also in apples and in many other fruits and vegetables, particularly in onions. Proanthocyanidins (including procyanidins), which are responsible for the astringency of wines, are also found in many fruits, particularly in cherries. Catechins, the main flavanol, are found in wine, but also in green and black tea, as well as in dark chocolate. Stilbenes are not widespread in food plants, and one of them, resveratrol, which was discovered during medicinal plant screening, has recently received great attention. Indeed, in the Western world, people ingest this compound only in red wine (and very little in white wine), and no other Western food (except a very low amount in peanuts and berries) contains it. Thus resveratrol is an important marker for research because the determination of ingest ed quantities in red wine is not confounded by the consumption of other beverages or foodstuffs. Finally, tyrosol, a liposoluble mono phenol, the second phenolic compound quantitatively in white wine, may be involved in the benefit associated with drinking white wine since it has been reported that this phenol is able to inhibit the release of tumor necrosis factor alpha at nanomolar doses.

Most phenols present in wine (at least 100) show a large variability in concentration according to several factors such as climate, vintage, vineyard environment, age of vine, and type of grapes. As wine is produced in many different regions, with a broad variety of grapes, and following different winemaking procedures, the final concentration of polyphenols in wine may be highly variable from vintage to vintage and from region to region. This variability may have some consequences on the biological activity of wine. Recently, it has been shown that the variability of the content in procyanidin is inversely associated with mortality across the whole population in specific European regions such as Southwest France (Saint Mont, Gers) or Sardinia.

In view of the hypothesis that all alcoholic beverages afford some benefit against CVD, both alcohol and phenolic compounds present in wine may probably contribute to biological effects of wine consumption. An overview of the links between the working mechanisms and clinical effects of ethanol and nonethanolic compounds found in wine is given in Figure 1 (page 186). The different cardioprotective effects of these constituents of wine are discussed below.
Alcohol has dose-dependent and dual effects on several physiological functions, and these effects may be either beneficial or harmful. Mechanisms underlying the cardioprotective effects of moderate alcohol consumption may be related to the well-described alcohol-induced changes in serum lipids and lipoproteins, blood clotting proteins, platelets, inflammatory cytokines, endothelial function, and insulin resistance. Recently, the concept has emerged that moderate alcohol drinking could also induce a direct cytoprotective effect on cardiomyocytes independently of any action on the aforementioned traditional targets.

Many experimental studies using animal models of chronic ethanol feeding have confirmed the cardiovascular benefits reported in human studies. In most species under investigation, a sustained consumption of ethanol (6 weeks; 2.5% to 36% vol/vol in drinking water) resulted in a significant reduction in myocardial ischemia/reperfusion injury with improved recovery of function and decreased cardiac enzyme release. In addition, ethanol administration can mimic classic ischemic preconditioning and protect the heart against ischemic damage. Different isoforms of protein kinase C (PKC) have been identified as major contributors to this protective effect. Acute ethanol exposure induces within 10 minutes the activation of both δ-PKC, an isoform that mediates the harmful effects of ischemia/reperfusion, and ε-PKC, an isoform that is required for cardioprotection against ischemia/reperfusion to develop. Therefore, immediately after ethanol administration, activation of the δ-isof orm attenuates the cardioprotective effect of the ε-isof orm. However, the δ-isof orm is able to induce ε-PKC activation through a relatively slow process (60 minutes) by a mechanism involving adenosine receptor activation. Thus, ethanol-induced activation of δ-PKC can be cardioprotective provided that sufficient time elapses to allow δ-PKC-induced activation of ε-PKC.

This effect probably accounts for the recent finding that, in patients undergoing elective coronary angioplasty, acute oral administration of 40 g ethyl alcohol (149 milliliters of Gordon’s gin) 30 minutes prior to ischemic preconditioning (2 sequential 2-min balloon inflations, separated by 5-min interval) blunted the cardioprotection. Moderate alcohol consumption also imparts cardioprotection by adapting the heart to oxidative stress. Indeed, ethanol induces a significant amount of oxidative stress to the cardiomyocytes, which then translates into induction of expression of several cardioprotective oxidative stress-inducible proteins including heat shock proteins HSP70, 27, 70, 32, and epsilon isoforms of protein kinase C; NO, nitric oxide.
fllamination. Similarly, moderate drinking also protects against CHD complications and inflammation. It was therefore hypothesized that the protection resulting from moderate drinking could be, at least partly, mediated by ω3. Recently, de Lorgeril et al demonstrated that moderate wine drinking was associated with increased plasma concentrations in marine ω3, such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) in patients with CHD. This phenomenon was observed in patients with either low or high intakes in α-linolenic acid (ALA), the plant precursor of marine ω3. Moreover, no dietary (marine foods) or nondietary factors could explain the association. Since high marine ω3 plasma levels have been associated with low mortality from CHD (sudden cardiac death), this effect of ethanol, comparable to that of fish, might also account in part for the cardioprotective effect of alcohol consumption. Finally, a very recent report by Guiraud et al has shown, through a well-controlled experimental study, that a comparable increase in ω3 plasma levels could also be achieved in animals chronically treated with moderate doses of ethanol alone.

**CARDIOPROTECTIVE EFFECTS OF POLYPHENOLS**

Polyphenols are the most abundant antioxidants in human diet and they have generated a great amount of scientific research due to their in vivo and in vitro antioxidant capabilities. These compounds cross the intestinal barrier and reach the bloodstream at micromolar concentrations that have been shown to exert effects in vitro.

Inclusion of polyphenol-rich food (fruits, vegetables, wine) in the diet may help protect endothelial function, reverse hyperlipidemia, alter the atherogeneity of the low-density lipoprotein (LDL) hypothesis particle, and protect the cholesterol in LDL from oxidation. Although there are contrasting viewpoints on their effects on LDL oxidation variables, there is increasing evidence that polyphenols possess additional cardioprotective functions including altering hepatic cholesterol absorption, triglyceride assembly and secretion, and the processing of lipoproteins in plasma. Moreover, lycopene, grape powder or red wine intake has been recently shown to significantly decrease nuclear factor kappa B (NF-κB) activation by oxidized LDL and other reactive oxygen species in monocytes. NF-κB is responsible for activating proinflammatory cytokines (tumor necrosis factor [TNF-α] and interleukin 6 [IL-6]), adhesion molecules, and procoagulant proteins. In an 11-week study comparing red wine and gin consumption in healthy men, adhesion molecules and monocyte adhesion to endothelial cells were significantly altered due to red wine. This effect on cytokines involved in cellular adhesion may explain the anti-inflammatory properties of polyphenols.

In a recent study, Toufektsian et al reported that long-term dietary absorption of anthocyanins in rats is associated with a significant increase in total glutathione and oxidized glutathione in cardiac tissue, indicating that chronic consumption of polyphenols may increase the antioxidant potential of myocardial cells. This increase was associated with a significantly reduced vulnerability to ischemia/reperfusion.

Flavonoids may have an additive effect to the endogenous scavenging compounds by interfering with different free radical-producing systems. Flavonoids can prevent tissue injury caused by free radicals. One way is the direct scavenging of free radicals. Flavonoids are oxidized by radicals, resulting in a more stable, less-reactive radical. Selected flavonoids can directly scavenge superoxides, whereas other flavonoids can scavenge the highly reactive peroxynitrite. By scavenging radicals, flavonoids may contribute to inhibit LDL oxidation, an effect that could theoretically have a preventive action against atherosclerosis. Moreover, quercetin has been shown to inhibit xanthine oxidase activity, thereby resulting in decreased oxidative injury. Finally specific flavonoids, in particular quercetin, are known to chelate iron, thereby removing a causal factor for the development of free radicals.

Initially characterized as a phytoalexin, resveratrol attracted little interest until 1992, when it was postulated to explain some of the cardioprotective effects of red wine. Since then, dozens of reports have shown that resveratrol can prevent or slow the progression of a wide variety of conditions (Figure 2, page 188), including cancer, CVD, and ischemic injuries, as well as enhance stress resistance and extend the life span of various organisms from yeast to vertebrates.

Resveratrol was found to protect the ischemic heart through an increased expression of adenosine A1 and A3 receptors, a property shared by ischemic preconditioning (Figure 3, page 188). Adenosine A1 receptor activation transmits a survival signal through phosphatidylinositols-3 (PI3) kinase-Akt-Bcl-2 signaling pathway reducing cellular apoptosis. Besides, adenosine A3 receptor activation exerts its cytoprotective effect through a cyclic adenosine monophosphate (AMP) response element binding protein (CREB)–mediated Bcl-2 pathway in addition to the Akt-Bcl-2 pathway.
Resveratrol induces the expression of heat shock proteins HSP27, HSP70, and HSP32. HSP32 is also known as heme oxygenase-1 (HO-1), whose cytoprotective effect and increased cell survival in vitro and in vivo have been extensively described. HO-1 is the first and rate-limiting enzyme in the heme breakdown to generate biliverdin, free ferrous iron, and carbon monoxide (CO). Biliverdin is rapidly converted to bilirubin by biliverdin reductase. The production of CO and biliverdin via the HO-1 system has been shown to be an important protective factor against myocardial ischemia/reperfusion injury. However, the exact mechanism by which HO-1 exerts such a protective effect still remains unclear. Procyanidin, a tetra-epicatechin, is the most abundant polyphenol in young red wines. Procyanidins are also found in apples, red wine, and cranberry juice. In wine, they may initially account for 1 to 2 g per liter of the total quantity of polyphenol (usually less than 3 g per liter). These molecules are the main source of mouth-puckering astringency in young red wines. With time, these procyanidins react with each other to form longer polymers called condensed tannins that can eventually precipitate at the bottom of the bottle. In patients with chronic stable New York Heart Association class III heart failure, a 16-week treatment, under the form of Crataegus extract (a dry extract from hawthorn leaves with flowers) containing 18.75% procyanidins, improved symptoms and increased maximum tolerated workload during exercise. In patients with chronic stable New York Heart Association class III heart failure, a 16-week treatment, under the form of Crataegus extract (a dry extract from hawthorn leaves with flowers) containing 18.75% procyanidins, improved symptoms and increased maximum tolerated workload during exercise.

**Figure 2.** Health benefits of resveratrol.

**Abbreviations:** DNA, deoxyribonucleic acid; LDL, low-density lipoprotein; NF-κB, nuclear factor kappa B; UV, ultraviolet.


**Figure 3.** Cardioprotection and preconditioning with resveratrol.

**Abbreviations:** A1/A2, A1 and A2 adenosine receptors; Bax/Bad, proapoptotic protein; Bcl-2, anti-apoptotic protein; eNOS, endothelial nitric oxide synthase; HO-1, heme oxygenase-1; iNOS, inducible nitric oxide synthase; KATP, mitochondrial ATP-sensitive potassium channels; LDL, low-density lipoprotein; MAPK, mitogen-activated protein kinase; NK-κB/AP-1, nuclear factor kappa B activation protein-1; PDE/Al, phosphatidylinositol-3 kinase/hormone-specific serine/threonine protein kinase; PKC, protein kinase C.

DOES WINE CONSUMPTION EXPLAIN THE FRENCH PARADOX?

In their seminal paper,1 Renaud and de Lorgeril hypothesized that wine consumption could be a possible explanation for the French paradox. As discussed above, many different components of wine may exert some protective effects against CVD.

The wine-heart hypothesis remains a very important, but rather controversial, concept. The discussion about the relationship between wine (and/or any other alcoholic beverages) consumption and CHD incidence is at the center of a larger concept, namely the diet-heart hypothesis. Indeed, all the facets of wine drinkers’ behavior cannot be summed up in wine consumption.48

Considering the relationship between CHD and alcoholic beverage consumption per se, not taking into account the general nutritional pattern of the population, might lead to false results, since differences in alcohol consumption might also reflect differences in nutritional intake.44 Indeed, in different studies, diet quality was found to be higher for wine drinkers than other alcoholic beverage drinkers. Wine drinkers consumed higher levels of fruit, salad and vegetables, fish, and olive oil, and lower levels of carbohydrate and saturated fat. In addition, wine drinkers smoked less and were more physically active than nondrinkers and beer or spirit drinkers. Finally, wine drinkers were more likely to have had higher education.6.48 Enlarging this observation leads to underline the importance of the attitudes to food and its role in life. Thus, the French paradox concept should encourage further research on protective CHD risk factors while conveying, in primary prevention, messages promoting healthy behavior such as regular exercise, optimal diet, and life without smoking.48

IS THERE A SPECIFIC ROLE OF PROCYANIDINS?

After extensive studies on the effect of wine consumption in various areas, Roger Corder reported an intriguing observation.6 In a number of places where heart disease was lower, wines were richer in procyanidins. He noticed that wines and wine-drinking habits were not uniformly distributed across France and raised the question of whether there might be areas where people were living longer because their local wines had special characteristics such as higher procyanidin levels.6 The factors affecting the amount of procyanidins in wine are: the vineyard, the grape, the age of vines, and the winemaking process. Finally, he identified the Gers area of southwest France where the wines are the most procyanidin-rich in France and where there was double the national average of men aged 90 or more (despite a diet that many cardiologists would consider the worst possible choice for heart health, with foods high in saturated fats such as foie gras, cassoulet, sausage, and cheese). Madiran and Saint-Mont wine appellations, made with more than 40% Tannat grape, contain 3 to 4 times more procyanidin than other procyanidin-rich wines from other countries (Figure 4). This means that one small glass of Madiran wine can provide more benefit than two bottles of most Australian wines, without the obvious danger of excessive alcohol consumption. In Sardinia (Italy), there is a very high number of centenarians, mainly in Nuoro province. Here also local red wines contain a high level of procyanidin. The grape variety more often used is Grenache, a variety that is widely grown in Spain and southern France. These observations sup-

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Figure 4. Vineyards at Madiran. © 2006 Nigel Blythe / Cephas Picture Library Ltd. All rights reserved. Madiran is a sanctuary for red wine situated right in the middle of the Gers département in Southwest France, a region otherwise known for its famous white wines (Saint-Mont, Pacherenc, Jurançon). The Madiran appellation is a red wine with a very strong character. It is made from Tannat, a typical grape from the area, and from other grape varieties such as Cabernet Sauvignon, Cabernet Franc, and a local grape called Fer or Pinenc. The Tannat grape is so rich in anthocyanins that the wines made with it are usually a deep red-purple color, verging sometimes on black. Madiran is a rough-tasting wine when young. After a few years in a cellar, it turns into a sensual and tannic wine.
port the idea that procyanidin-rich wines make an important contribution to cardiovascular health and long-term well-being.

**DRINKING PATTERN AND RECOMMENDATIONS**

Most studies on alcohol and health have focused on the quantity of alcohol consumed. Few have attempted to assess the pattern of alcohol drinking in relation to CHD. It is now clearly demonstrated that moderate drinking is associated with a lower risk of CHD whereas drinking in a heavy episodic manner (often referred to as “binge drinking”) is not. Recent research indicates that more frequent drinking, especially consumption several days per week or even daily, is associated with more favorable outcomes than only occasional or weekend drinking. Since drinking pattern has a role in health effects, the usual pattern of ingesting wine slowly with food may be important. Drinking wine with food has indeed a moderating effect on the harmful effect of alcoholic drinks. Moreover, food slows the absorption of ethanol, so levels of ethanol in the blood are lower than if the alcohol before the meal is finished. In wine-producing countries, wine is mainly drunk with food, at lunch or dinner. So blood levels of alcohol after moderate drinking (2 to 3 glasses/day) will rarely reach harmful levels. However it is difficult to generalize any recommendation and to define a safe intake because the harmful effect of alcoholic drinks is highly dependent on age, sex, weight, height, medical history, and ability to metabolize alcohol.

Another problem relates to social drinking and conviviality. In a social context it is tempting to exceed a safe intake of alcoholic beverage. Finally, irrespective of whether wine consumption affords health benefits, some people should not drink any alcoholic beverage, such as pregnant women, patients taking prescriptions that might interfere with alcohol, and anyone who has a history of excess alcohol consumption.

However, the same report claims that “there are beneficial relationships with CHD, stroke, and diabetes mellitus, provided low-to-moderate average volume of consumption is combined with non-binge patterns of drinking.”

According to the 2004 WHO–Global Status Report on Alcohol, CHD is a chronic condition where alcohol has harmful and beneficial consequences. The most important health benefits of alcohol have been found in the area of CHD at low-to-moderate levels of average volume of alcohol consumption. While some studies have found that alcohol may offer protection against CHD not only at low-to-moderate average intake, but across the continuum of alcohol consumption, they nevertheless show that most of the protective effect is gained at low levels of consumption such as one drink every other day. The epidemiological evidence that light-to-moderate average alcohol consumption protects against CHD is strengthened by substantial evidence concerning the biological mechanisms by which a protective effect could be mediated. Several studies showed that cultural drinking patterns are related to differential effects of volume on CHD mortality and morbidity. Another indirect line of research on the effect of heavy drinking on CHD shows that countries with a tradition of heavier or binge-drinking occasions on weekends show proportionately high CHD or CVD mortality on or immediately after the weekend.”

Although it is clear that a regular and moderate consumption of wine may contribute to protect against heart disease, whereas binge drinking occasions may precipitate myocardial ischemia or infarction, additional studies should be conducted to: (i) specify whether there...
is a true French paradox or only re-
gional paradoxes like in the Gers
département in southwest France
or in Nuoro Province in Sardinia;
(ii) develop research on the primary
prevention of CVD, with the objec-
tive of providing a better definition
of optimal diet, pattern of wine
consumption, and lifestyle; and
(iii) evaluate psychological factors
involved in wine drinking and atti-
dudes to food.

In the meantime, we might all do
well to follow the advice of Jeanne-
Louise Calment, the oldest docu-
mented woman in the world (she
died at 122 years and 164 days in
1997). At 100, she was still riding a
bicycle and she smoked until she
was 117. She claimed her longevity
was due in part to wine, and would
say, with a twinkle in her eye: “Wine,
I am in love with that” (Figure 5).

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Coronary heart disease in France and in Europe: where are the facts?

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The 1980s saw a vogue for the “French paradox” contradicting the diet-heart dogma of direct correlation between coronary heart disease (CHD) and saturated fat intake. However, epidemiologic evidence, notably the MONitoring of trends and determinants in Cardiovascular disease (MONICA) registry, favors “moderate” rather than “exceptionally low” susceptibility to CHD in France, consistent with latitude. Many other European countries display similar north/south gradients. CHD etiology also depends on factors irreducible to animal fat intake, some cultural (regular vs binge drinking), others environmental, as suggested (but unproven) by the geographic gradient. French CHD rates are not so low, nor animal fat intake so high, nor the diet-heart concept so unique, as to sustain the “French paradox” any further, except as cultural fantasy or a marketing ploy.

Keywords: coronary heart disease; epidemiology; French paradox; fat intake; alcohol intake

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Apparently the first paper to use the expression “paradoxe français” was published in 1981, in a French-speaking medical journal, by Richard et al., following the report of coronary heart disease (CHD) incidence in a cohort of policemen enrolled in the Paris Prospective Study I. Later, the same expression appeared in the title of a follow-up paper also published in French in 1987 by Richard. From then onwards, the concept gained increasing fame, growing into something of an international media hit, albeit also generating heated debate.

In the Paris cohort, the incidence of the CHD was found to be distinctly lower (one third) than that reported in US cohorts grouped together in the Pooling Project. This could be only partly explained by Framingham between-population risk factor levels. The findings appeared to corroborate the lower mortality ascribed to coronary causes at that time in French national statistics in comparison with other OECD (Organization for Economic Cooperation and Development) countries.

The independent epidemiological observations by Richard et al, which showed a level of fat—especially animal fat—consumption in France similar to that of northern and central European countries, appeared to be at odds with the so-called “diet-heart concept,” defended by Key, who was involved in the Seven countries study. According to the diet-heart concept, a given population should experience CHD in proportion to its saturated fat (and cholesterol) intake. It is this discrepancy that formed the basis for the formulation of the “French paradox” concept.

But, in actual fact, what of this purported discrepancy? Before jumping to conclusions, reason dictates that one should question successively assertion A (CHD rates are low in France), assertion B (animal fat intake is high in France), as well as the theory (the diet-heart concept) based on which the two above assertions are claimed to be mutually incompatible.

In this short review, we will focus the discussion on assertion A, analyzing the statistics of CHD in France and Europe stemming from mortality, cohort, and registry data, and, before concluding, we will also add a few comments about the two other points of the argumentation.

MORTALITY DATA

National and regional mortality data obtained from national statistics have been playing an important role in the development of chronic disease epidemiology ever since the 1950s, even though pitfalls in interpreting ecological associations are well acknowledged. Conspicuous among such pitfalls are the differences in habits in medical cer-
tification of death according to place and time, a topic that seems to have received less attention than it should have.

In a special issue of the *Revue du Praticien* published in 1958, the then leading cardiologist Lenègre elaborated on the total number of deaths attributed to “cardiovascular diseases” in 1953 in France and some other European countries with comparable population numbers. Some examples speak for themselves: “coronary atherosclerosis”—France 22,124, England-Wales 131,436, Italy 73,633; “other cardiac diseases”—France 70,944, England-Wales 75,309, Italy 12,080.

Lenègre’s conclusion was unambiguous and right to the point: “Les diagnostics… dans le cas des morts cardiaques sont, en France, fantaisistes ou erronés [Diagnoses… of cardiac deaths in France are either fanciful or wrong].” It is evident that French doctors, at that time, were reluctant to ascribe a cause of death to coronary atherosclerosis without any strong argument, especially without autopsy data, which was and still remains the rule in the country.

It is remarkable that whereas these differences have diminished since the early postwar period, the phenomenon has nevertheless persisted and, in the 1981 paper, the authors proposed to add ICD (International Classification of Diseases) codes in the 8th revision: A83 (coronary deaths), A84 (other cardiac deaths) and A136-137 (sudden or unexplained deaths), in order to gain a better picture of true between-country variations in CHD mortality. As a consequence, combined rates in France remained lower than in northern and central European countries, but much more comparable to those of southern countries.

The most recent European statistics available from “Eurostat” exhibit the same features (Table I) although cardiovascular mortality rates have been falling sharply since the 1980s in all industrialized countries. Age-standardized rates (ICD-10th revision) in France in 2002 were still the lowest for ischemic cardiac disease, but adding together the three categories yielded similar rates in France, Italy, and Spain.

Causes of deaths given by French national statistics and those determined by the French MONICA registries (MONItoring of trends and determinants in Cardiovascular disease) in 2002 were compared on an individual basis in the three regions that participated in the World Health Organization (WHO) Project in 1985-1993. Nearly all deaths reported by the MONICA registries in 2002 (310 coronary deaths and 420 presumed coronary deaths with insufficient data) could be matched with the death certificates (270 initial coronary causes and 460 other initial causes), but with a low concordance index (kappa = 0.46).

According to the MONICA convention, which grouped together coronary deaths and deaths with insufficient data as an indicator of global coronary mortality burden in the population, taking into account only initial coronary causes of death in the French statistics resulted in gross underestimation of the global indicator (59%). Interestingly, taking into account multiple causes of death on the certificates improved the concordance (kappa = 0.51) and reduced the underestimation of the global indicator (42%).

This latter result suggests that, in France, coronary causes can be considered as noninitial causes of death in a large proportion of cases, which is at variance with reporting habits in other countries.

However that may be, strictly defined coronary death rates in French national statistics, both in the past and nowadays, should be considered as negatively biased estimates at the population level and cannot be used validly in ecological correlation studies.

### Table I. Age-standardized mortality rates (2002) in various European countries (/100000). Based on data from reference 6.

<table>
<thead>
<tr>
<th></th>
<th>Finland</th>
<th>Sweden</th>
<th>UK</th>
<th>Italy</th>
<th>France</th>
<th>Spain</th>
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<tbody>
<tr>
<td><strong>Men</strong></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>I20-125</td>
<td>234</td>
<td>167</td>
<td>182</td>
<td>102</td>
<td>70</td>
<td>90</td>
</tr>
<tr>
<td>“Ischemic”</td>
<td></td>
<td></td>
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<tr>
<td>I30-152</td>
<td>24</td>
<td>38</td>
<td>23</td>
<td>60</td>
<td>56</td>
<td>45</td>
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<tr>
<td>“Other forms”</td>
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<td></td>
</tr>
<tr>
<td>R96</td>
<td>5</td>
<td>8</td>
<td>3</td>
<td>5</td>
<td>23</td>
<td>10</td>
</tr>
<tr>
<td>“Ill-defined”</td>
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</tr>
<tr>
<td><strong>Total</strong></td>
<td>263</td>
<td>213</td>
<td>208</td>
<td>167</td>
<td>149</td>
<td>145</td>
</tr>
</tbody>
</table>

| **Women** |         |        |    |       |        |       |
| I20-125  | 115     | 80     | 87 | 50    | 28     | 39    |
| “Ischemic” |        |        |    |       |        |       |
| I30-152  | 14      | 29     | 19 | 41    | 36     | 39    |
| “Other forms” |   |        |    |       |        |       |
| R96      | 3       | 5      | 1  | 2     | 11     | 5     |
| “Ill-defined” | |        |    |       |        |       |
| **Total** | 132     | 114    | 107| 93    | 75     | 83    |
CHD morbidity incidence (both fatal and nonfatal) in the Paris policemen cohort was also compared with the incidence reported in the various subcohorts of the Seven Countries Study in the 1970s. Interestingly, the 5-year incidence rate was found nearly at the median of the distribution, much lower than the 5-year incidence rates of, eg, East Finland and the Netherlands, and much higher than those of, eg, Greece and Serbia, but similar to those of Italian subcohorts. Thus, for the first time, the possibility of an intermediate ranking of French CHD morbidity indicators among European populations (rather than an exceptionally low ranking) could be documented. However, the specificity of the Paris cohort and the between-study heterogeneity of follow-up methods precluded any generalization.

A much more satisfactory comparison of CHD incidence during the 1990s between France and a high-risk northern European population (Northern Ireland) was able to be made thanks to the PRIME study (étude PRospective de l’Infarctus du Myocarde) [Prospective Epidemiological Study of Myocardial Infarction]). At least as far as men aged 50 to 59 were concerned.

The same protocol was rigorously applied for initial examination (1991-1992) and case-validation over a 10-year follow-up of three sociodemographic quota population samples in France (Lille, Strasbourg, Toulouse, 2500 subjects each) and one in Belfast (2500 subjects). After common validation by a unique independent committee, new events were identified in participants free of any coronary symptomatology or history at entry. Lost-to-10-year follow-up subjects totaled 4.8% in France and 5.5% in Belfast. Some CHD incidence data (unpublished) are given in Table II, with a relative risk of 1.7 for total CHD incidence in Belfast, confirming, if necessary, the lower incidence in France.

Looking at specific categories of deaths reported as first events, it is remarkable that both coronary deaths and sudden deaths (<1 hour) with cardiac symptoms were more frequent in Belfast, whereas, contrary to France, there were very few other sudden deaths (<1 hour). This finding parallels that concerning deaths with insufficient data in France, and has similar implications to those discussed above. However, the fact that the validating experts judging all events were the same enables differences in interpretation to be practically ruled out. The most likely explanation is that details on the circumstances of death were more easily obtained in Belfast, which resulted in a near-total absence of witnessed sudden deaths without any other indications. We should add that 3 coronary deaths in Belfast were diagnosed as first events from autopsy data and none in France. As expected, higher autopsy rates in Belfast than in France accounted for the differences in certification, but probably only to a small extent.

<table>
<thead>
<tr>
<th>Total CHD</th>
<th>After MI</th>
<th>Coronary</th>
<th>Cardiac sudden</th>
<th>Other sudden</th>
</tr>
</thead>
<tbody>
<tr>
<td>France</td>
<td>5.8</td>
<td>0.1</td>
<td>0.2</td>
<td>0.2</td>
</tr>
<tr>
<td></td>
<td>(425)</td>
<td>(7)</td>
<td>(18)</td>
<td>(15)</td>
</tr>
<tr>
<td>Belfast</td>
<td>9.8</td>
<td>0.3</td>
<td>0.8</td>
<td>0.6</td>
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<td>(236)</td>
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*28-day period after MI

Table II. 10-Year CHD incidence data in PRIME Study (/100) according to the country of living (numbers of cases in brackets). CHD, coronary heart disease; MI, myocardial infarction. PRIME = étude PRospective de l’Infarctus du Myocarde (Prospective Epidemiological Study of Myocardial Infarction). Based on data from reference 8.

In a short review published in 1992, which challenged the concept of the "French paradox," we discussed in particular the necessity of comparing geographical CHD incidence data (and not only mortality) and, whenever possible, obtained from similar methods. The WHO MONICA Project offered this opportunity, as three French regions, among many European ones, participated in it. Summarized 9- to 10-year incidence data, mostly recorded during the 1980s, were published in 1994 and have been further analyzed since. Those data have been repeatedly used to discuss the so-called paradox.12,13
Project and given by the national statistics in the same regions and years are shown.11

Country ranking according to MONICA event and mortality rates was nearly identical for both sexes and correlated with north-south geographical location, including France, a result that is consistent with our previous discussion of mortality data. This confrontation of French and European CHD data can be made more precise by comparing event rates at a more local geographical level. Figure 1 represents mean age-standardized event rates in individual French registries, each one being matched with the nearest foreign one.11 Interestingly, differences seemed much larger between French registries than within French/non-French pairs. This illustrates the claim that location in terms of north-south latitude may be more important than belonging to a given country itself, which, after all, is globally coherent with geographical and historical knowledge.

To conclude, all available epidemiological evidence (mortality, cohort, and registry) suggests there is a “moderate” and not an “exceptionally low” CHD susceptibility of the French population, which correlates with latitude within the country according to an east-south gradient. Furthermore, such a gradient can be evidenced within many European countries as well, and not only France.

**FURTHER REMARKS**

**Dietary data**

Discussing assertion B (animal fat intake is high in France) would require as close a scrutiny of existing data as assertion A. It is remarkable that the data predominantly used in this field also come from official statistics and specifically from the national food supply or...
food balance sheet data collected by the Ministry of Agriculture. Although beyond the scope of this review, it should be pointed out that the validity of these data for estimating average individual food intake, and all the more so nutrient intake in a given population, is controversial at best and no assurance can be given about the absence of bias of these estimates according to countries.14
The paucity of data on dietary intake in general population samples, using a similar protocol as at the individual level, should be stressed. Such an attempt was made in the 1980s with the first MONICA population survey.15 As far as we know, the results were only published separately, but collation of some key data was included in an unpublished thesis.16

Table IV gives the mean intake of fat and fatty acid in samples of men (200 to 900) aged 45 to 64 in various MONICA regions (averaged at country level) based on 3-day (or 7-day) recordings and providing weight estimates of foodstuffs. One clear finding was that fat intake, and especially saturated (mostly animal) fat intake, was not higher in French men than in those of northern countries. No comparable data were available for men from other Mediterranean countries.

Although these data are partial and clearly insufficient to firmly reject assertion B, they do suggest that epidemiology should mistrust alleged “commonsense evidence” that equates “eating well” and “eating fatty.”

Diet-heart concept

Although periodically disputed, the diet-heart theory remains the cornerstone of CHD etiology and a key to prevention. Most of its strength comes, on the one hand, from the relationship between saturated fat and cholesterol intake and circulating cholesterol levels and circulating cholesterol levels to current CHD mortality in various countries, including France. In our opinion, difficulties of at least three types are raised by their analysis. First, no sound biological explanation is available for such a long time lag (the analogy with smoking and cancer cannot apply here). Second, estimating time trends in dietary habits and cholesterol at the population level and using them in ecological correlation analyses is a risky task. Last, but not least, these authors forecasted an increase in CHD mortality risk in France since the increase in fat intake was more recent than in other countries. However, 15 years after their study, which covered the 1988-1990 period, CHD mortality rates were still decreasing in the French regions covered by CHD registries.18

Among the various points discussed by Law and Wald as alternative explanations, alcohol consumption is indisputably a serious contender, even though the authors considered it as a simple confounder of animal fat intake rather than an actor in its full right.

Thirty years ago both ecological19 and cohort studies20 exhibited a negative association of moderate alcohol intake with CHD risk, which has been repeatedly described since, even though much heterogeneity.
exists, which needs to be explained. It is alcohol as such rather than the type of alcoholic beverage that seems to be involved in the decrease in CHD risk, which is consistent with the usual causality criteria in epidemiology. However, the way in which alcohol is consumed is now considered to play an important role, risk reduction being associated with regular intake rather than binge drinking. The high proportion of regular drinkers in France (and other Mediterranean countries) in comparison with northern populations is very likely a modulating factor in the determination of CHD risk at the population level.

Clearly, the diet-heart concept does not tell the whole story and CHD etiology at the population level depends on many factors that cannot be simply restricted to the amount of animal fat intake. Some of these factors are cultural (like regular moderate alcohol drinking vs binge drinking), others environmental as suggested (though still unproven) by the north/east-south gradient in Europe.

CONCLUSION

Returning to the question raised in the introduction of this review, we can now say that CHD rates are not so low in France, animal fat intake not so high, and the diet-heart concept not so unique that the existence of a “French paradox” may be sustained any longer, except as cultural fantasy or a marketing ploy.

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Great importance in France is placed on the pleasurable and convivial aspects of eating, as well as more traditional practices, such as cooking meals from basic ingredients and having structured meal times. The data from several studies reviewed suggest that the “French paradox” can be partly explained by eating habits (what is eaten, when, how, and with whom), but also how food is bought, cooked, and celebrated, rather than by specific nutrients or foods that afford protection against coronary heart disease and obesity. As there appears to be nothing exceptional about the nutrient content of the French diet, compared with other European countries, “l’exception française” would seem to reside instead in the positive attitudes and culture of eating.

The Health Barometer study, conducted on a nationally representative sample of French adults, reported that olive oil consumption had increased sharply (+86%) to the detriment of sunflower oil between 1996 and 2002. But the same study reported that various fatty products are still commonly put on the table at mealtimes to add flavor, for example, mayonnaise, butter, and olive oil are set out by nearly 20% of French people.

Unexceptional intake of fruit and vegetables

The consumption of fresh vegetables increased in the 1970s but has been static since (Figure 2). In the Health Barometer study, only 10.2% of the population ate at least five portions of fruit and vegetables, which is the current recommendation from the World Health Organization (WHO). Average consumption of fruit and vegetables was 2.4 times a day, which is less than the recommended 5 times a day. This percentage did not change significantly.
cantly between 1996 and 2002, indicating that intake is static, although the recent INCA2 study (Étude Individuelle Nationale des Consommations Alimentaires—2) reported a 16% increase in fruit consumption. But fruit and vegetable intake in France is not sufficiently high compared with other European countries to explain the French paradox.6

**Dairy consumption still high: milk intake is falling, replaced by cheese and yogurts**

Since the 1970s, there has been a steady fall in consumption of fresh milk, and a recent study reported that consumption fell by 24% in a 6-year period.1 Conversely, since the 1970s, the consumption of cheese and yoghurt has steadily increased.7 Cheese is highly appreciated and intakes are marginally higher than the European average.6 The Health Barometer surveys found that adults consumed dairy products 2.3 times a day on average, also reporting that cheese consumption is higher among men and increases with age, while yogurt consumption is higher among women and young people.

**Less red meat, more poultry**

The consumption of red meat increased up to the 1980s; since then there has been a steady decrease (Figure 3, page 202).5 The INCA2 study1 suggests that it is mainly women who are moving away from red meat, with a 16% fall in intake between 1998 and 2002. The consumption of poultry increased consistently between 1970 and 2000, as households transferred some of their meat budget to the purchase of poultry. The consumption of fresh fish and shellfish increased up to 1990, then leveled off at around 14 kg per person/year. Egg consumption has remained stable since 1980. However, intakes of red meat, poultry, and eggs remain marginally higher than the European average.6

**Decreasing alcohol, but red wine still popular, with a healthy drinking pattern**

Overall, there has been a considerable decrease in the consumption of alcohol (beer and wine) since 1970 (Figure 4, page 202).5 The INCA2 survey suggests that the decrease in alcohol intake is particularly due to women (27% reduction), compared with a reduction of only 9% in men.1 Red wine remains the most popular alcoholic drink, although the trend is downwards, as one study reported that red wine consumption fell from 30% in 1996 to 23% in 2002, among both men and women.4 However, men still drink alcohol more often than women, consuming more units/day, and proportionally more men than women exceed the limits recommended by the WHO.
Previous authors have reported that the French drink more than other Europeans, but this appears to be no longer the case, as data from the WHO European region suggests that there are 10 countries in the European region with higher consumption, although there are still 39 countries with lower consumption. It has been suggested that it is not the overall quantity that may contribute to the protective effect of alcohol, but the drinking pattern, taken with meals in small quantities, rather than drinking large quantities without food, as is often the case in Northern Europe. For example, one study found that in Belfast, 66% of alcohol is consumed on Fridays and Saturdays, whereas it was consumed evenly throughout the week in France.

Drinking wine in France is associated with eating a healthier diet. For example, Ruidavets et al reported that moderate alcohol drinkers or wine drinkers have a healthier diet compared with other types of drinkers, including those who abstain.

**Besides red wine mainly coffee and bottled water are drunk**

Coffee is drunk by the great majority of the population (>70% drink it every day), while tea is drunk less often (<20% every day). More coffee is drunk by men, and more tea by women. These are both drunk without milk, but sugar is often added, especially to coffee. More than half of those questioned in the Health Barometer study drank only bottled mineral water, increasing from just over a third in 1996.

**Diet in France is not similar to other Mediterranean countries**

A Mediterranean diet is widely accepted as being one that is rich in olive oil, with a high fruit and vegetable intake, and is considered as an optimal diet in health terms. Whether France is a Mediterranean country is a subject of controversy. France is geographically diverse, and it has been estimated that only 20% of the population live in Mediterranean areas in the South. However, some have argued that to be able to shed light on the links between geography and CHD, what is of greater importance is not where individuals live, but whether they follow a Mediterranean diet. Indeed, age-standardized mortality rates for CHD do not differ between the north and south, nor do obesity rates, suggesting that there are no regional health trends.

The findings from the Data Food Networking (DAFNE) project comparing 11 European countries, indicate that the French pattern is more similar to that of Northern European countries than of those in the Mediterranean region (Greece, Italy, and Spain) as there is less
availability at a household level of olive oil, fish, fruit, and vegetables, and more butter/other vegetable oils is consumed than in Greece, Italy, and Spain. However, these data are from 1991 and the trend of increasing consumption of olive oil throughout France may have shifted this, but in terms of when the concept of the French paradox emerged, the diet at that time did not resemble that of Mediterranean countries. The French diet contains more than the average “European diet” of butter, other vegetable oils, juices, pulses, and wine, with a marginally higher intake of cheese, red meat, poultry, and eggs. The DAFNE databank consists of country representative standardized household budget surveys and collects information on foods available at the household level.

A further example comes from dietary patterns of countries participating in the European Prospective Investigation of Cancer (EPIC) study that began in the early 1990s. The findings indicated that the diets of Greeks and Italians are characterized by high intakes of plant foods and vegetable oils and less animal and processed foods compared with all the other countries, including France. Hence, France did not follow this same Mediterranean pattern. However, what could be argued as being similar to the Mediterranean diet is the diversity of the French diet and the cultural importance attached to eating, such as using fresh seasonal foods, eaten with pleasure.

**Evidence of a north-south divide in France in eating habits**

There is still some evidence of a healthier diet in the south compared with the rest of France, as was reported by the MONICA study in the mid 1990s, which found that those living in the south adopted a diet closer to that of other Mediterranean regions, ie, higher in fruit, vegetables, fish, olive oil, and wine, whereas the north was characterized by high intakes of sausages, ham, butter, eggs, and beer.

The Health Barometer study found a better dietary diversity score in the southern Languedoc–Roussillon region compared with the north, and slightly better than the rest of France. More beans and lentils are used, consumption of fruit and vegetables is higher, and olive oil is put on the table more often than elsewhere in France, where butter and crème fraîche are preferred. But there were also less healthy habits in the south, as people reported eating more ice cream, biscuits, sugar, and confectionary than elsewhere. Alcohol appears to be drunk in similar quantities throughout France.

**Small portion sizes**

Rozin et al have suggested that the French paradox could be explained in part by the fact that the French eat small portion sizes. They report that although the French eat more courses than you would typically find in Anglo-Saxon countries, the amount they eat is less. Rozin’s study found that portion sizes served in France were smaller compared with those in US restaurants, ready-meals in supermarkets, and portion sizes in cookbooks.

**Less snacking in France**

In a study comparing French and English eating habits, very few (6.6%) of the French reported snacking once a week on crisps or fried snacks, which was markedly less than the English. This concurred with the Health Barometer study, which reported that only 7.2% of inhabitants of Languedoc-Roussillon were regular snackers. The different snacking patterns in Southern France have been reported previously, finding that snacking among nurses in Toulouse was rare, but when they did snack they chose bread, cheese, yogurts, and fresh fruit rather than cakes, sweet biscuits, or confectionary.

**CULTURE OF EATING FOR PLEASURE AND CONVIVIALITY**

**A regular meal pattern**

The “traditional” eating model in France is based on three meals spread over the day, consisting of several courses and shared with others. The French still have a regular meal pattern as the vast majority (9 out of 10) report eating breakfast, lunch, and evening meal most days. All three main meals are still usually eaten at home, including the midday meal (67.7%), and this is even higher in the Mediterranean region, as three quarters of adults report eating lunch at home.

Eating a four-course traditional meal at lunchtime (starter, main course, cheese, dessert) has fallen, from 25.2% (in 1996) to 19.9% (in 2002). Even so, lunch still usually consists of two (30.3%) or three courses (37.7%). The evening meal is usually two (38.9%) or three courses (30.3%).

Both these mealtimes are becoming simpler as there is a trend to reduce the number of courses. In the Mediterranean region, this simplification is less evident, as more people still eat three or four courses than in the rest of France, for example, at lunchtime 55.2% have a starter, 98.2% a main dish, 62.7% cheese/yogurt, and 63.2% a dessert.
Social aspects of eating together are valued à table

Culture has a major role in determining where and how foods are consumed and food is a way of expressing hospitality, as mealtimes bring groups together, both physically and symbolically. The kitchen in France has been described as a convivial room where everyone meets, and this still appears to be true as nearly two thirds of French report eating together as a household on a daily basis. This is significantly more than in England, for example, where just over half of adults report eating together as a household daily. These findings support those of an earlier study, which reported daily. These findings support those eating together as a household where just over half of adults report more than in England, for example, with every meal, however simple. You are eating with “bon appétit” fied by the habit of wishing those celebrating food daily is exemplified by the habit of wishing those you are eating with “bon appétit” with every meal, however simple.

Taking time to eat

Average meal periods in France were 38 minutes for the midday meal and 40 minutes for the evening meal in 2002, which have not changed from an earlier study. Including breakfast, this means an average 93 minutes are spent eating every day. This is around one third longer than that spent in the US for example, where an estimated 67.2 minutes are spent eating by men and 63.6 minutes by women. Rozin et al reported that the French take longer to eat than US citizens, even when eating at fast-food restaurants. Time spent eating appears to be no longer in Mediterranean France, so it is a widespread national habit to take time to eat, which is reinforced by a culture in which it is the social norm to stop what you are doing to eat a meal between midi et deux (twelve and 2 PM).

Positive and healthy attitudes to food-pleasure of eating

Pleasure, attitudes, and social aspects of eating are well known to be important factors in the choices people make about food. Some have suggested that positive attitudes to food could even lower CHD incidence. Much pleasure seems to be derived from eating in France, both from food and of sharing company. Far more of the French agree that providing someone with food is a way of showing them how you feel about them, than a comparable English population. Rozin et al found a similar trend in their study comparing attitudes of the French with people from the US, Japan, and Flemish Belgium, finding that the French were the most food-pleasure-oriented and least food-health-oriented. They concluded that there appeared to be substantial cross-cultural differences in whether food was seen as a source of pleasure or stress, which they go on to suggest may influence health, including cardiovascular disease.

One reflection of positive French attitudes to food is the language around eating, for example, the use of the term gourmand, which has no equivalent in English, where it is translated into greedy, with negative connotations of gluttony. However gourmand is not pejorative in France, and a gourmand is respected as someone who appreciates good food.

Pride of national traditional food-positive food culture

Recently, Nicolas Sarkozy became the last of a succession of French presidents to proclaim the superiority of French cuisine, suggesting that “We have the best gastronomy in the world. It is an essential part of our heritage.” He goes on to explain how France will apply to have its cuisine recognized by the United Nations Educational Scientific and Cultural Organization (UNESCO) as part of the world’s cultural heritage. Indeed, France does have an international reputation for an elaborate cuisine, as well as regular and traditionally structured meals, and it forms an intricate part of national identity. More recently, there are fears that a more “American-style” diet is becoming popular in France, often referred to as “the MacDonaldization of culture,” with “fast food” being more widely eaten, often between meals. Even so, food does tend to “follow the flag” and national traditions have held their own more than many other European countries, such as England.

Spending money on quality food is valued

Quality is a key influence on consumers’ food choices. In a study comparing the French and English, French respondents clearly agreed more than the English that they were prepared to wait in a queue
order to get fresh and quality products, a home-cooked meal is the basis of healthy eating, and that money spent on food is money well spent. The French were more likely to agree that quality was more important than cost when choosing food.  

**COOKING AND SHOPPING**

Cooking from raw ingredients over convenience: still a mainly female task

Convenience has become an important influence on food choice in many developed countries due to time pressures in people’s daily lives and the growing number of working women, restructuring cooking and meal patterns. However, this does not appear to have spread as much to the French as they still value a home-cooked dinner as the basis of healthy eating and cooking from scratch. An astonishing two thirds of the French cook a meal from raw ingredients on a daily basis compared with less than a quarter of the English in the same study, and the French were prepared to make time for cooking. This is perhaps to be expected, given the great pride that the French associate with their national cuisine.

Women still cook more and work less than men, as the same study reported that three quarters of French females (74.0%) compared with less than half (44.8%) of French males said they cooked daily. The gender division of cooking meals from raw ingredients was more defined in France than it was for England. One explanation could be the fact that a lower proportion of French women are in paid employment, therefore having more time for cooking.

In the Health Barometer survey, one third of those surveyed said that they produced and ate their own food. Although growing food at home is more common in rural areas, more than a quarter of the urban population report that they grow their own food. Home-grown food seems set to stay in France and did not change significantly in the 6 years between the two surveys (34.3% in 1996 and 34.6% in 2002).

Making time for and enjoying shopping for food

As in most industrialized countries, food in France is mainly purchased in large supermarkets, but this is less frequent than in England, for example (74.5% versus 89.9% at least once a week). Using supermarkets less often avoids exposure to seductive marketing techniques to buy cheaper, less healthy foods, which are often on special offer. Food shopping is done “under one roof” less often in France, as the French still continue to frequent small specialist shops regularly, including bakers, butchers, fishmongers, greengrocers, and markets. They still use these more than the English do, for example. The fact that smaller shops are used more may mean more physical activity (walking and carrying). However, use of local shops may be changing, as data from the Health Barometer study suggested that, in 2002, fewer people did their shopping in corner shops than in 1996.

The French appear to even enjoy food shopping, placing great value on its pleasurable and social aspects, with many agreeing that “making time for food shopping was a priority in their life.” Even waiting in a queue to buy fresh, quality products is seen positively.

The quality of food seems to be a more important influence on where French people shop than convenience or price, as 41.2% of French adults report quality as their reason for choosing to purchase from a particular shop, compared with proximity (31.0% agreement) or price (15.5% agreement).

**EATING OUT AND TAKEAWAY FOOD**

To be able to say whether France is atypical in how often they eat out, we need to compare with trends for eating out Europe-wide. The only data published at present are those within the EPIC study, which provide estimations of the percentage of energy from calories eaten at home compared with those away from home in 10 European countries—unfortunately data are only available for women in France. They suggest that women living in the three Mediterranean countries in the EPIC study (Greece, Italy, Spain) get far less of their daily calorie intake from eating away from home (13.2% to 13.5% energy) compared with Northern European countries, ie, Denmark, Germany, Netherlands, Norway, Sweden, UK (19.1% to 27.6% energy). France alone sits almost midway, with 17.0% energy coming from food eaten away from home. So France does not follow the Mediterranean pattern of eating out less frequently, but it is nearer to this pattern than the northern European countries are. In a study conducted in the South of France, no difference was apparent in how often the French went out for a sit-down meal, compared with the English. Very few French (7.0%) reported purchasing a takeaway meal, and this is reflected in the fewer takeaway food outlets in France.

**HOW MIGHT DIETARY HABITS AND ATTITUDES INFLUENCE HEALTH?**

Adult obesity/overweight is on the increase, but still less than many other countries. Obesity and over-
weight prevalence in adults has increased gradually in France since 1991. Table I shows the extent of the problem with an average increase in adult obesity of 5% per year from the ObEpi studies.26-28

The findings from INSEE (Institut National de la Statistique et des Études Économiques) suggest an increase in the prevalence of obesity from approximately 6% to 11% between 1980 to 2003 and overweight also increased. As a result, over 40% of the adult population (>15 years of age) is now affected by either obesity or overweight. An earlier study of adults that did not include younger adults (age 35 to 64 years) showed that the prevalence of obesity and overweight remained stable between 1985 and 1997,28 but the suggestion is that these data reinforce the fact that it is only in recent years that obesity has begun to increase in French adults. However, compared with many European countries, this is still modest, as data in the 25 EU member states available from the International Obesity Task Force database show that the prevalence of adult obesity in France ranks low, in 23rd position among the 25 EU member states.

Is it true that “French women don’t get fat?”

Contrary to the title of a recent best-selling book French Women Don’t Get Fat, evidence is mixed.29 French women are as likely to be obese as men, but they are less likely to be overweight. Data indicate that obesity is more prevalent in younger women (15 to 45 years), but prevalence in men supersedes that of women between 45 and 65 years (Figure 5).26 Although after 65 years of age, prevalence in men and women merges. Overweight (Figure 6) still remains more prevalent in men at all ages.26

Hu recently investigated whether there was a French paradox regarding the adverse effects of overweight on cardiovascular disease incidence and mortality, but found no evidence to support this, ie, the French are no more protected from the effects of overweight than other populations.30
An aesthetic society, self-control and motivation to eat well

Weight control/body image are known to influence food choice decisions, especially by females. In a survey comparing French attitudes with those in England, more of the French were satisfied with their current weight, but they also seemed more likely to take action early on as more also reported dieting, even though they were already slimmer than their English counterparts. This could partly be explained by the more prominent aesthetic concerns in France.

The “locus of control” is the way individuals view certain important health-related issues. The French appear to have a more marked internal locus of control than the English, indicating that they believe events to be a consequence of their actions and are more likely to be in control of their health. This suggests that they may be more effective at changing and controlling their eating habits, but that includes men as well as women.

CONCLUSION

Returning to the original question of “How important are differences in national eating habits in France?” the data from several studies reviewed here suggest that the “French paradox” can be partly explained by eating habits (what is eaten, when, how, and with whom), but also how food is bought, cooked, and celebrated, rather than about specific nutrients or foods that afford protection against CHD, as there appears to be nothing exceptional about the nutrient content of the French diet, compared with other European countries. The substantial cross-cultural differences observed in some of these studies seem to show that when food is seen as a source of pleasure, rather than of stress, it may contribute to the lower prevalence of cardiovascular disease and obesity we see in France.

This paper has shed light on a distinct French pattern of eating, where pleasure and conviviality are valued. So there certainly seems to be little risk and possible great gain in eating as the French traditionally do:
• Eat slowly, while discussing what you are eating
• Prioritize quality over quantity
• Don’t do anything else at the same time as eating (except talking about it . . .)
• Eat a varied diet, using fresh ingredients, however simple
• Don’t eat in between meals
• Make time to shop, at local specialist shops (butcher, baker, fishmonger, grocer)
• Eat together as a household every day
• Eat with friends, family, colleagues, or neighbors to celebrate food daily
• Eat a variety of courses at a main meal (starter, main course, cheese; dessert), but small portions
• Take lunch breaks with colleagues, friends, or family
• Go home for lunch

Lastly, but by no means least
• Savor the wonderful pleasure of eating—so, bon appétit!

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As a child my parents took me to the source of the River Danube, a mere trickle of water destined to become a mighty river flowing past Vienna and Budapest to the Black Sea. I have chosen two examples, the discovery of p53, a tumor suppressor, and the discovery of insulin to show how great discoveries, like rivers, are insignificant and vulnerable at the beginning, but develop into mighty streams of science and medicine. There is as yet no end to these rivers of discovery, and their impact will be felt for years to come.

p53

The earliest publications on p53 appeared in 1973. They described that after infection or transformation with a tumor virus, the simian virus SV40, an immunogenic protein could be precipitated. Further evidence showed that this protein is of cellular origin and is expressed in several murine carcinoma cell lines. The p53 protein is precipitated only by specific antibodies and is also found in tumors of nonviral etiology. At this point, like a meandering river, research on p53 took on a new course. It was the period in cancer research when oncogenes were the main and most fruitful topic. It was only natural to assume from these findings that p53 was an oncogene. Cloning of p53 furnished further evidence of its role in oncogenesis.

Now, the course of discovery changed again. It was found that the oncogenic effect of p53 was due to its mutations. Several mutants of p53 species were found, one containing a two-point mutation, the other a single different point mutation. It is the wild type of p53 which effectively interferes with the ability to elicit neoplastic transformation. Soon more evidence of the tumor inhibitory properties of p53 became available. Chromosomal changes in colon cancer had been known for a number of years, affecting primarily chromosome 17 where allelic deletions are expressed as mutations of the gene expressing p53. In colon cancer this deletion leads to tumor progression. Another evidence for the tumor inhibition by p53 was that mice lacking p53 are developmentally normal,

p53 bound to DNA. The p53 molecule is colored according to the frequency of mutations (blue, very few; red many). Two of the most mutated residues are indicated with arrows. From: Cho Y, Gorina S, Jeffrey PD, Pavletich NP. Crystal structure of a p53 tumor suppressor–DNA complex: understanding tumorigenic mutations. Science. 1994;265:346-355. © American Association for the Advancement of Science.
but are very susceptible to spontaneous tumor formation. p53 accomplishes suppression of tumors by the triggering of apoptosis, programmed cell death. Apparently there are a multitude of mediators of p53-induced apoptosis, but in normal cells p53 is latent. A number of factors activate it, among them oncogenic activation, telomere attrition, nitric oxide and others. Like Moshe Oren writes in his Harvey Lecture, “all this extensive understanding will culminate in the development of new strategies to treat cancer”. We only can hope that he is right.

**INSULIN**

The discovery of insulin occurred about 80 years before that of p53. At the time of the discovery of insulin, the nature of the gene and most of the biochemical processes were unknown. But the human drama of the discovery of insulin, with its small beginnings could have happened at any time in the history of science. The small brook of discovery was many times in danger of drying up.

It started with Frederick Banting who practiced surgery in London, Ontario, at the beginning of the twentieth century. His practice was not lucrative and gave him time to think of advancing the cure of diseases, especially diabetes. One day he came across an article which described that ligation of the pancreatic duct leads to the digestion of the exocrine tissue while leaving the Islets of Langerhans intact. This became Bantings idée fixe. Why not, he reasoned, tie the pancreatic duct in dogs and then extract the sugar-lowering substance from the remaining tissue? With this idea he went to Professor Macleod, the head of the department of Physiology at the University of Toronto. On his way to his native Scotland for vacation, Macleod gave Banting inadequate facilities in his department. He obviously expected little from a country surgeon. A young student, Charles Best, joined Banting during the summer and the two started to work on dogs by ligating their pancreatic ducts and extracting the remaining pancreatic tissue. The original idea of ligating the pancreatic duct was soon discarded in favor of using the whole pancreas. By the time Professor Macleod returned from Scotland,
Banting and Best were on the way to discovering insulin. When Macleod saw the progress, he tried to take over the project which he previously had considered with scorn.

I cannot help but speculate how Banting and Best’s idea would play today. The animal rights committee would never have given the go-ahead for the use of dogs under these circumstances. As far as the granting agency is concerned, it would have written a scathing report, calling it a fishing expedition and the investigators unfit to undertake this task. On the other hand, they would have approved a sophisticated application submitted by Professor Macleod to study the effect of low carbohydrate diet on diabetes. Almost 100 years have passed between the discoveries of insulin and p53. As to be expected there are many differences, foremost in technique. The work on insulin was confined to tissue extraction with hydrochloric acid and alcohol. For p53 there was a long chain of techniques: cell cultures, transfection, transcription, immunoprecipitation, radiolabeling, hybridization, northern and southern blot, and others. Working with p53 needed thousands of dollars for equipment, running expenses, and salaries. In contrast, Banting and Best received no salary. In the case of insulin the idea came first, while the significance of p53 was recognized only later as a result of many experimental findings. Banting was a country surgeon and Best was a student, while workers on p53 were highly trained scientists.

Banting and Best’s discovery of insulin was the triumph of an idea, the discovery of p53 as a tumor inhibitor was the result of sophisticated techniques leading to significant experimental results. And yet, both discoveries had something in common: like the source of a river, the beginnings were modest, but then the river became a mighty stream, still coursing toward the distant sea. Both the discoveries of insulin and of p53 will influence the progress of medicine for years to come.

FURTHER READING

Best HBM.
The personal story of Dr Charles Best: The co-discoverer of insulin.
Toronto, Canada: The Dundurn Group; 2003.

Oren M.
The p53 saga: The good, the bad, and the dead.
The French Paradox: Fact or Fiction?

Summaries of Ten Seminal Papers

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Clinical and Pathological Reports

1. Clinical and Pathological Reports
   S. Black. Newry, N. Ireland: Alex Wilkinson. 1819

2. Cardiopathies par athérosclérose coronarienne
   [Cardiac disease caused by coronary atherosclerosis]
   J. Lenègre. Rev Prat. 1958

3. The effect of dietary fats on the blood lipids and their relation to ischaemic heart disease

4. Coronary heart disease in seven countries. American Heart Association Monograph No. 29

5. How to Eat Well and Stay Well the Mediterranean Way

6. Factors associated with cardiac mortality in developed countries with particular reference to the consumption of wine
   A. S. St Leger and others. Lancet. 1979

7. Coronary heart disease in middle-aged Frenchmen. Comparisons between Paris Prospective Study...
   P. Ducimetiere and others. Lancet. 1980

8. Nutrients, platelet function and composition in nine groups of French and British farmers
   S. Renaud and others. Atherosclerosis. 1986

9. Myocardial infarction and coronary deaths in the World Health Organization MONICA Project...
   H. Tunstall-Pedoe and others. Circulation. 1994

10. Autres pays, autres cœurs? Dietary patterns, risk factors and ischaemic heart disease in Belfast and Toulouse
    A. E. Evans and others. QJM. 1995

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Selection of seminal papers by Hugh Tunstall-Pedoe, MA, MD, FRCP(London), FRCP(Edinburgh), FFPH, FESC - Emeritus Professor of Cardiovascular Epidemiology and Senior Research Fellow - Cardiovascular Epidemiology Unit - Institute of Cardiovascular Research - University of Dundee - UK

Highlights of the years by Ian Mudway, MD
For Biomedical Sciences - Division of Life Sciences
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www.dialogues-cvm.org
Clinical and Pathological Reports

S. Black

Newry, N. Ireland: Alex Wilkinson; 1819

Born in 1763/4 in the north of Ireland, Samuel Black attended Edinburgh University in the age of the Scottish Enlightenment, graduating MD in 1786. Entering clinical practice in Newry, County Down, in 1792, he continued to live and work there until his death in 1832. He showed an early and sustained interest in angina pectoris, publishing his first case in 1795, but this book came 24 years later, in 1819. Major events such as the Napoleonic Wars and the United Irishmen's 1798 rebellion had come between.

Like many physicians of the 18th, 19th, and (to a lesser extent) early 20th centuries, he studied his patients and their symptoms in life, and, as a matter of routine (for him), carried out necropsies on them to correlate the pathology after death. His writing shows an astute interest in the antecedents of disease, and its relation to living habits, now called lifestyle, and environmental factors.

While studying his own patients and researching what others had written about angina pectoris, he was struck by the absence of disease reports from France, a country he obviously admired for its savants and other features. Where others, after 20 years of what amounted to a world war, might have dismissed the lack of French observations in a bigoted chauvinist manner, Black, like the Sherlock Holmes he was (“the curious incident of the dog that failed to bark in the night”) searched for deeper significance: “If the reader should be surprised or confounded by this seeming inadvertence of enlightened British physicians, equally distinguished for industry, zeal and extensive erudition, I beg permission to present to his attentive consideration the following circumstance:—A work has been published in a neighbouring nation, distinguished by the successful cultivation of every department of science, on the diseases of the heart and great vessels: I allude to the Essai sur les Maladies du Cœur et des Gros Vaisseaux, par I. N. Corvisart, Paris 1811. The author, the imperial physician, holding the highest professional rank, was deservedly elevated to a high civil rank also, and the "Essai" was ushered into the world under imperial auspices, being dedicated by permission "à sa majesté, l’empereur et roi."

The work is beyond contradiction one of great merit, and the number of dissections it contains evinces that the author was in possession of the most ample opportunities of investigation and research. These opportunities have been rendered available by the application of ability, ingenuity, and accurate observation. Yet, in this work, such as I have represented it, there is not one word of the disease I have been endeavouring to explain and illustrate. In what light then are we to consider this fact? Can we presume that the author has altogether overlooked or neglected a disease of the heart so serious and important as that under consideration? I can scarcely admit of such a supposition. Shall we then allege that the disease is less known and of less frequent occurrence among our neighbours, than among the inhabitants of these islands? That, I think, is sufficiently probable. I can readily conceive that French habits and modes of living, coinciding with the benignity of their climate and the peculiar character of their moral affections, may have a less tendency to favor this peculiar disorganization than the same circumstances, considered in their application to the inhabitants of the British islands. It is not to be imagined that a disease of the heart, attended with such marked lesion of structure, should be altogether omitted in a work of this kind, if it were of frequent occurrence.”

1819

Thomas Jefferson, the third President of the United States and the principal author of the Declaration of Independence, founds the University of Virginia; Spain cedes Florida to the United States as part of the Adams-Onís Treaty of 1819; and Queen Victoria, the United Kingdom’s longest serving monarch, is born.
Jean Lenègre was born in Paris in 1904, pursued his medical career there, dying suddenly while walking in the Latin Quarter in 1972, despite attempted resuscitation. A former President of the French Society of Cardiology, his obituary in the *British Heart Journal* was by Dr Evan Bedford whom he succeeded in 1960 as President of the European Society of Cardiology (in an era when bilingual meetings were held). Taking an early interest in cardiology, from 1936 to the outbreak of World War II he was responsible for pathological anatomy at Broussais Hospital in Paris, conducting the necropsy examinations. Afterwards, he was appointed Professor of Clinical Cardiology at Boucicaut Hospital. He had an interest in electrocardiography and pathology of the Bundle of His, but was also a pioneer of cardiac catheterization. His publications show him as a general cardiologist, with publications on arrhythmias, heart failure, antiarrhythmic drugs, the relationship between cardiac and renal disease, and rheumatic heart disease. Papers on coronary disease were less numerous.

In the 1950s coronary (ischemic) heart disease was a minority interest of cardiologists, who had other preoccupations—even more true in countries where the coronary epidemic was less developed. However, such was the breadth of the author’s experience that this review covers hundreds of cases, including necropsy findings.

The subject at issue, the apparent low incidence of coronary disease in France, however occupies very little of this major review, which runs to 153 pages. The author devoted a very small section in the Introduction to the question of the very low mortality for ischemic heart disease recorded in France, in contrast to its neighbors. The subject was not mentioned in the General Conclusions. Lenègre presents cardiovascular disease mortality data for 1953, for (West) Germany, England and Wales, Italy (1952), and France, four countries with populations of roughly equal sizes. Although each country had fairly equal numbers of cardiovascular disease deaths, apart from England and Wales which had 50% more, there was a large discrepancy in “arteriosclerotic coronary” deaths with France having only a quarter of deaths from this cause compared with Germany and Italy, and a sixth of that in England. He stated that France had 15 times the mortality of England in terms of other “cardiac pathology” but this was in fact closer to 10 times. He admitted that atherosclerotic coronary disease is not always well known to French doctors, and he felt that many cardiac deaths had been misclassified as renal failure or senility. He accepted that some of the mortality statistics relating to cardiac disease in France were fictitious or wrong. “On peut donc admettre que les diagnostic portés sur les feuilles d’état-civil, dans les cas des morts cardiaques sont, en France, fantaisistes ou erronés.”

As shown elsewhere, this problem, though worse there, is not confined to France, and applies to coronary deaths, particularly those outside hospital. Diagnosis of nonfatal events is a different problem.

This study predated the eighth edition of the International Classification of Diseases (ICD, 1968) which, while not necessarily standardizing its usage, introduced modern terminology.

It is still debated whether the phenomenon described by Lenègre is part of, or the complete explanation of, the French paradox. He was the first and most eminent author to draw it to the attention of cardiologists and practitioners in France, and internationally.

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1958

Mao Zedong starts the “Great leap forward” movement in China; Neil Finn, New Zealand singer and songwriter, is born; and British playwright Harold Pinter’s play the “Birthday Party” premieres in London
The effect of dietary fats on the blood lipids and their relation to ischaemic heart disease

B. Bronte-Stewart


Briam Bronte-Stewart graduated and worked in Cape Town, South Africa, before going to St Mary's Hospital in London to join Sir George Pickering, moving with him to Oxford when he became Regius Professor of Medicine. Publication of this systematic review in 1958 marked a move back to Cape Town. He returned to head the Medical Research Council Atheroma Research Unit in Glasgow in 1962, but died only 3 years later aged 42 from bladder cancer, conceivably related to dyes used in his animal experiments on cholesterol and atherogenesis. This review embodies much of his own and contemporary work on diet, lipids, and coronary disease. Its publication in a dedicated issue of the *British Medical Bulletin* shows the perceived importance of the subject at that time. It covers much of the early history of the subject, subsequently dominated by the doctrines of Ancel Keys in Minneapolis (who lived to reach the age of 100).

Had Bronte-Stewart continued for another 20 years as he had started, British medical and public opinion might not have been so determined over the next three decades that cholesterol was for American hypochondriacs, and that diet did not contribute to coronary disease risk. It is now forgotten that in the early 1950s the idea promoted by others that different fats differed in their effects on serum cholesterol was strongly resisted by Ancel Keys, who was then proved wrong by strictly controlled feeding experiments by several researchers, including Bronte-Stewart. The original distinction among fats was made between animal and vegetable fats, but this was later refined to consider the degree of saturation (measured as iodine number). Even now this early simplification is still reflected in some health promotion suggesting the lowering of total fat consumption (difficult to achieve), rather than specific fats.

Bronte-Stewart, like many future epidemiologists, was sensitized to disease causation by the different pattern of diseases in the different races living in one country, in this case South Africa, and their relation to different risk factors, diet, and lifestyles. Cholesterol levels followed different patterns by age and wealth in the Bantu, Cape Coloreds (many of Malay ancestry), and what he called Europeans. These differences could be abolished and even reversed by feeding with animal and vegetable fats, implying that the differences were environmental and not genetically determined.

It could be asked what the relevance of this review is to the French paradox. France is conspicuously absent from the discussion, although there is mention of olive-oil consuming countries and their low fat consumption (not true in France’s case). The paradox is that (like the Seven Countries study) this superb review is relevant to the French situation without actually mentioning it. At the time that it was written the French paradox was not specifically identified as such in the lipid or cardiovascular epidemiological literature. It is ironic that some French authors quote this review as if it supported a particular statement on the French situation, although careful examination suggests that it did not. Maybe in 1958 it was the best statement on coronary disease and lipids that was available to other researchers, and this still applied for those not wishing to endorse Keys uncritically. It remains an excellent statement of the state of play in lipids a half century ago, illuminating the French paradox from one side without stating it.

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1958

Jack St. Clair Kilby invents first integrated circuit for which he is awarded the Nobel Prize for Physics in 2000; in France, a majority vote for a new constitution establishing the fifth republic replacing the former parliamentary government with a semipresidential system; and Guinea votes for independence from France
Ancel Keys, born in 1904, died in 2004. Peripatetic for the first third of his life, his outstanding research followed appointment age 36 to the Laboratory of Physiological Hygiene, at the University of Minnesota's Minneapolis football stadium (address: Stadium Gate 27). Born in Colorado, a refugee from the San Francisco earthquake aged 2, he studied chemistry at Berkeley, economics, and political science, earned a master's degree in zoology, a PhD in oceanography and biology, won a fellowship in physiology to Copenhagen, and did a second PhD in physiology in Cambridge, England, becoming interested in high-altitude physiology. Offered a permanent post in Cambridge, he went to biochemistry at Harvard, and then to the Mayo Foundation, Rochester, Minnesota researching human biochemistry and physiology, before accepting the Minneapolis post in the same university.

Not medically qualified, Keys might not have achieved what he did with conventional medical education. After his appointment he worked on subsistence rations for soldiers during World War II, (named K rations after him) and conducted a classic study of starvation/malnutrition and recovery in conscientious objectors.

Post-War, coronary heart disease became prominent in the USA. Keys was impressed by reported declines in heart disease in Europe with wartime malnutrition. He investigated a Wisconsin dairy farmer with a blood cholesterol over 1000 mg/dL (26 mmol/L), which fell on a low-fat diet. Keys wrote in 1949 “the physico-chemical characteristics of the individual should have predictive value.” His earlier work on altitude, starvation, and refeeding had shown how population differences in hemoglobin, blood pressure, cholesterol, etc, could be determined, but also modified, by environmental factors, especially diet.

English coldness and disbelief contributed to Keys’ achievements. In Oxford University on a Fulbright scholarship in 1952 he found the paucity of winter heating unbearable (fuel still rationed, and central-heating uncommon) and traveled to somewhere warmer (Naples) to study the apparent absence of coronary disease in the general population. He gained collaborators and did pilot studies on cholesterol. His developing dietary theories on coronary disease were later challenged in a forensic cross-examination at a World Health Organization meeting by Sir George Pickering, leaving him worsted, but determined to produce the necessary, missing evidence.

Keys mounted the first longitudinal study of cardiovascular disease in Minnesota business and professional men, just anticipating the Framingham study, and carried out important preliminary studies before mounting the Seven Countries Study in 1958.

This 200-page monograph sadly does not have summaries or text available through PubMed, so you need the original, but the titles of the multiple individually authored sections reflect the large range of studies done on 13 cohorts of men from seven countries (five European, Japan, and the USA), predicated on diet, cholesterol and other risk factors, and the incidence of coronary heart disease. Baseline data are complemented with crucial 5-year incidence of coronary heart disease. 10-Year data on 16 cohorts appeared in a book in 1980, but it was this monograph, published by the American Heart Association in *Circulation*, complemented by his laboratory feeding experiments, that crucially established the Keys dogma on coronary disease causation for the next two decades. It created the French paradox.

1970

Paul McCartney announces that the Beatles have disbanded; President Nixon signs the Public Health Cigarette Smoking Act into law, banning television advertisement of cigarettes in the United States; and a jury finds the Chicago Seven not guilty of conspiring to incite a riot at the 1968 Democratic National Convention.
A n advantage of an eminent and lucid old age is one’s reminiscences, but the retrospec-
toscope shows rosey tints, even distortion. Keys in 1999 quoted this book as showing his en-
thusiasm for the Mediterranean diet, going back to a visit to Naples in the early 1950s. Written with his wife, trained as a biochemist, by request for the public, it describes dietary causation and prevention of coronary heart disease, followed by discussions on different food-
stuffs and culinary principles, and then practical help in numerous recipes that follow prudent, heart-healthy, prin-
ciples. It was deservedly a bestseller and widely quoted among Keys’ achievements in his obituaries in 2004 when “Mediterranean diet” was in common parlance.

Inquisitive readers may be puzzled on finding that the term “Mediterranean diet” does not appear until page 38, although there are earlier eulogies of the beauty of four Mediterranean countries. The Seven Countries study is featured prominently, including as it did, Italy, Yugoslavia, and Greece.

Although a “first edition” it is a rewrite of a book by the same authors published in 1959 (when Seven Countries was starting) entitled Eat Well and Stay Well—the modified title came 16 years later. The 1959 book is interesting for what it does not say as well as what it does. There are discussions on wine and olive oil, but not in the context of “Mediterranean diet,” which is not mentioned. The first references to olive oil state that its calorific value is more than coal and less than fuel oil, and it is of intermediate status between fats and unsaturated oils. But, the authors’ preface was written in Makarska in Yugoslavia. There is a foreword by Paul Dudley-White, (President Eisenhower’s cardiologist) written in Heraklion, Crete, stating that he worked on his book on heart disease in Anacapri, Southern Italy, but relaxed by hiking in the hills with his wife, taking half a loaf of bread, a bottle of Capri wine, some cheese, and two oranges. He then describes a cycling tour, eating French food in the Dordogne in France, and how much he enjoyed the local, low-fat diet on a visit to Sardinia. So, in some ways, Dudley-White in 1959 said as much as Keys but the phrase “Mediterranean diet” did not appear. It is first indexed by PubMed in a paper by Anna Ferro-Luzzi and colleagues from Rome in 1984.

The close support given to epidemiologists like Ancel Keys by Paul Dudley-White, a leading and influential cardiologist, made their studies possible. Sir James Mackenzie, a pio-
neering British cardiologist, who, before World War I, had moved from general practice to hospital practice and then community epidemiological research had infected Dudley-
White, as a postgraduate student, with enthusiasm for the latter, and Dudley-White infected his cardiologist col-
leagues in the USA. This enthusiasm was sadly missing in British cardiologists, despite Mackenzie. One of your re-
viewers attended the international 10-day teaching seminar on cardiovascular epidemiology in Ireland in 1970 featuring both Keys and Dudley-White. The latter had donated fees from his (semiretirement) private practice to support it.

Keys liked Mediterranean countries for their warmth as well as their diet. Having escaped to there from an Oxford win-
ter in 1952, he later commuted from the Minnesota winter to a village in south Italy where Jerry Stamlner and Martti Karvonen, fellow epidemiologists, also established homes. One of the recipes in this book was Jerry Stamlner’s—nice to think of legendary epidemiologists sharing recipes.
Factors associated with cardiac mortality in developed countries with particular reference to the consumption of wine

A. S. St Leger, A. L. Cochrane, F. Moore

Lancet. 1979;1:1017-1020

Cambridge undergraduate in the 1930s, Archie Cochrane’s placard in a demonstration demanding socialized medicine had the word “effective” qualifying the statement that medical care should be free. Joining the ambulance section of the International Brigade in the Spanish Civil War, he found the British contingent, unlike others, was not victimized on returning home. Later he was medical officer in German prisoner-of-war camps. Without the then standard therapies, his young male charges, although poorly nourished, recovered from most illnesses. After the War he researched on miners’ pneumoconiosis for the British Medical Research Council (MRC). Disappointed not to be promoted Unit Director, he might then have been lost to wider evidence-based-medicine. Instead, he headed an MRC epidemiological unit in South Wales, studying what interested him, including effectiveness and efficiency in medical care.

Previously, his team compared mortality rates from all causes from 18 developed countries with data on indices of medical care: numbers of doctors and nurses, gross national product, and diet, etc, but found no good associations. They then moved to specific causes of death using similar data, with more on foods and alcohol, finding that wine consumption was inversely correlated with mortality from coronary (ischemic) heart disease. The effect could not be made to go away, whether or not France, an extreme case, was included.

This paper was neither completely original, nor conclusive. Countries were limited to those with often doubtful data. Correlation is not causation. Results begged questions, many still relevant, including the ecological fallacy. Why was it important?

Archie Cochrane received modest recognition in life, but is now eulogized in the “Cochrane collaboration.” Although his work could leave contemporary epidemiologists and progressive clinicians hugging themselves with delight, there was a vast rump of others, particularly in countries where randomized controlled trials were considered unorthodox, even immoral, where his thinking was considered offensive and threatening. A medical qualification or specialist training had been thought sufficient to justify ex-cathedra statements and decisions for the rest of one’s career. This paper was iconoclastic in several respects. It failed to support demands for more doctors and nurses. It failed, using crude data, to support the diet-heart concept of fats causing coronary disease promoted by Keys, Stamler, and others. It challenged the orthodox message that alcohol was bad for you and caused heart disease. Many people then were teetotal and alcohol was considered evil. Avoiding heart disease implied unwelcome advice. Even preventive factors, such as exercise, were considered punishment.

So here was a bizarre Cochrane finding—both a positive result and one implying that coronary prevention might be enjoyable.

Socialism aside, Archie Cochrane was wealthy in his own right. At a time when a bottle of wine in Britain was still considered a luxury, the ending of this paper reveals opinion not scientific rigor.

If wine is ever found to contain a constituent protecting against ischemic heart disease (IHD) then we consider it almost a sacrilege that this constituent should be isolated. The medicine is already in a highly palatable form (as every connoisseur will confirm). We can only regret that we are as yet unable to give information to our friends about the relative advantages of red, white, or rosé wine.

1979

Nottingham Forrest wins the 24th Europe Cup defeating Malmö FF [1-0] in Munich’s Olympic Stadium; American Airlines Flight 191 crashes during takeoff at O’Hare International Airport, Chicago, killing 275; and the Conservative Party wins the British general election.
Research on common diseases should attract professional and public interest and good funding. One center can accumulate reasonable numbers for publication. What is true of clinical research holds true in epidemiology. Following people up to see who develops coronary heart disease in a cohort study is cheaper and easier in middle-aged men in a high incidence country than it is in women, and it is correspondingly more difficult in low incidence countries where you wait longer or accept fewer end points. Hence the former absence of data on risk factors in women and in low-incidence countries.

Classic coronary risk factors were identified in Framingham and similar studies in the USA when disease rates were high. Travelers’ tales and small studies raised the question whether risk factors were the same everywhere or whether they differed in their impact and relative importance by time and place. This was relevant to France. How did the French relative immunity operate? Did risk factors operate in the same way as in the USA?

An answer was provided by the Paris Prospective Study, organized by a group of researchers working with support from INSERM, the French Medical Research body, and the Paris Prefecture. This group studied men aged 42 to 53 working for the Paris Police Administration recruited between 1967 and 1972, followed for an average of 6.7 years from measurement of their coronary risk factors, and experiencing 165 major coronary events.

The results from this study were compared with those published in 1978 from a Pooling Project of American prospective studies, (Albany, Chicago Gas Co, Chicago Western Electric, Framingham, and Tecumseh) and also the Seven Countries study 5-year follow-up. The authors wished to compare the incidence of coronary heart disease in men of similar ages in the three groups, to see whether differences in incidence were explained by different levels of risk factors, and to determine whether logistic functions for combining the effect of major risk factors in the different studies were consistent.

Results appeared to demystify the French paradox. French incidence rates were claimed to be similar to those for southern European cohorts in the Seven Countries study; risk factor levels were slightly higher than the average for Europe; serum cholesterol was lower than that in American railroad workers. Logistic function coefficients for different risk factors were very similar for all three groups—Paris had a slightly lower coefficient for blood pressure, but higher for smoking. Three different logistic functions derived from the different studies were used to predict numbers of events in each decile of risk, showing correlation coefficients of 0.99 and over. However, absolute levels of risk showed less agreement—Paris and the European component of the Seven Countries showed good agreement, but incidence rates in American studies were much higher than predicted from the Paris formula.

This study showed that coronary risk factors behave similarly in France to other countries. It also anticipates many recent studies reporting that the Framingham formula “overpredicts” in European populations—no surprise after this 27-year-old study. More arguable is the comparison of an urban, sedentary Paris occupational group with the limited incidence data from largely rural populations in southern Europe.

This paper dismisses the French paradox, replacing it with an American one. Some of us are impressed but unconvinced.

The Cable News Network (CNN) is officially launched; “Blues Brothers” starring Dan Aykroyd & John Belushi premieres; Vigdis Finnbogadottir is elected president of Iceland, becoming the first woman to be elected head of state in a democratic election...
Nutrients, platelet function and composition in nine groups of French and British farmers


Atherosclerosis. 1986;60:37-48

Serge Renaud, the first author, lived with his parents and grandparents on a vineyard near Bordeaux, France, interrupting his medical training after two years in 1951 to go to Canada where medical research was better funded. There he discovered the problem of coronary heart disease, returning to France in 1973. Considered a maverick at one time, he later was considered a guru on the French paradox, responsible for the explosion of interest in the United States in that and red wine, through appearing on television in 1991. There is now a Renaud Society in America “for medical professionals with an interest in better health and a passion for wine”—perhaps an antidote to the hangover from prohibition after World War I.

Renaud’s interest has been on thrombosis in atheroma, and dietary influences on platelet function such as alcohol and α-linolenic acid. He was an architect of the Lyon Diet Heart Study, which produced dramatic results in secondary prevention, unfortunately not yet replicated, a side-effect, no doubt, of the advent of statins.

The paper is one of several studies on small groups of subjects in France and Britain subjected to sophisticated investigations. The authors state the argument for using farmers (an almost vanishing species in Britain now in terms of numbers), but one suspects that it is partly based on the French winegrowers’ almost mystical sense of terroir. These studies are an antidote to the discredited idea that research can only be done in ivory-towered, massive temples, where patients with advanced disease come like pilgrims to help the researchers. Renaud established his laboratory in a caravan that was towed to the rural areas concerned, processing blood specimens immediately after capture. He also succeeded in persuading two of his nine groups of recruits to completely change their diet for a year, a remarkable achievement. However, he used a central laboratory for analyzing the composition of replicated dietary intakes. The study is based on a total of 260 male farmers aged 40 to 45, in nine groups, six from France, two from Scotland and one from England. Some results are given by groups, but most analyses are of correlations and regressions across the 260 subjects of coagulation, platelet aggregation, lipemia, fatty acids from plasma lipids, and platelet phospholipids in relation to food intake evaluated by chemical analysis of the diet.

The authors concluded that their studies indicated that dietary saturated fats, calcium, and alcohol influence platelet behavior in a way strictly parallel to their known effect on coronary heart disease. One of the potential problems in the study was how long a period of abstinence was needed from cigarettes, food, alcohol, and aspirin before taking blood: it was 10 hours for most and 10 days for aspirin, but arguable. The food intake data showed the three British groups of farmers had the lowest intakes of polyunsaturated fats, and two of the three highest intakes of saturated fat; the extreme for both was from the West of Scotland, which has most coronary disease. Although based on small numbers these results, unlike most dietary data, were based on laboratory analyses.

Lipidologists have it easy compared with those studying ephemeral coagulation factors. Long ago platelet function tests were so difficult to standardize that researchers were unable to replicate each other’s findings. Renaud’s meticulous work reminds us that thrombogenesis runs in parallel with atherogenesis, and that the influence of diet is not confined to effects on lipids.

A treaty ends the 335 Years’ War between the Netherlands and the Isles of Scilly off the SW coast of England—the war in which not a single shot was fired, was one of the world’s longest wars and the war with the fewest casualties; US actor Clint Eastwood is elected mayor of Carmel, California; and British journalist John McCarthy is kidnapped in Beirut where he will be held hostage for more than 5 years.
Myocardial infarction and coronary deaths in the World Health Organization MONICA Project. Registration procedures, event rates and case-fatality rates in 38 populations from 21 countries in four continents

H. Tunstall-Pedoe, K. Kuulasmaa, P. Amouyel, D. Arveiler, A. M. Rajakangas, A. Pajak; WHO MONICA Project

Circulation. 1994;90:583-612

Before MONICA (MOlItoring of trends and determinants in Cardiovascular disease), the epidemiology of coronary heart disease was patchy, depending on local enthusiasm, or unusual disease rates, to precipitate research. Methods were not standardized. Comparability was questionable.

Disease rates meant mortality. Death certification was subject to medical judgment, but also how medicolegal services operated in different countries. Sudden death posed a problem, occurring outside hospital and not necessarily leading to necropsy. It was questioned whether excess coronary deaths occurred from more prevalent coronary heart disease or a greater susceptibility to fatal arrhythmias in the populations concerned. Population frequencies of nonfatal myocardial infarction were not known, as diagnostic criteria were not explicit where it shaded off into angina pectoris, and there was no central registration.

Some questions were answered in the European Myocardial Infarction Registers of the 1970s, but diagnostic criteria had been only descriptive and definite and possible cases had been combined. For MONICA, diagnostic criteria were quantitative, including Minnesota coding of electrocardiograms. In 38 population centers round the world, data on presumed cases of myocardial infarction and coronary deaths in men and women below age 65 were collected and subjected to diagnostic coding. External quality control for criteria and coding were provided in Dundee, Scotland and for Minnesota coding in Budapest, Hungary.

This first paper comparing results of registration in 1985-1987 appeared in 1994. As Paul Hugenholtz, former president of the European Society of Cardiology, stated, “it is a labor of love.” The results were important for both negative and positive reasons. They confirmed large differences in disease rates between men and women and between populations. Although subject to adjustment through applying MONICA diagnostic criteria, findings broadly confirmed what ordinary death certification had been telling about differences in disease rates in different countries. Rates of nonfatal myocardial infarction strongly correlated with rates of coronary deaths: evidence against high mortality populations having more sudden coronary deaths than predicted from their rates of nonfatal myocardial infarction. Inclusion of three French centers among the 38 in MONICA provided an opportunity to study the French paradox. Their official mortality rates were very low, but French investigators identified almost equal numbers of additional potential coronary deaths, corroborated by rates of nonfatal myocardial infarction. French disease rates overall were therefore higher than official mortality rates suggested, but remained very low compared with centers in other countries.

This paper reported poor availability of corroborative diagnostic data in many potential coronary deaths in many countries, including France. Detailed tables showed inconsistencies between populations in the final MONICA diagnostic categories and the International Classification of Diseases (ICD) codings of clinical and death certificate diagnoses from which the cases had been found. In 1994, the World Health Organization MONICA criteria were the only published international standard for diagnosing myocardial infarction, creating interest and rivalry on that account. The advent of troponins has since stimulated several attempted redefinitions, but no apparent general consensus. Unfortunately, troponins do not help solve the problem of poorly documented sudden deaths.

Colombian footballer Andrés Escobar is shot dead in Bogotá in retaliation for the own goal he scored in the 1994 World Cup against the United States; Israel and Jordan sign the Israel-Jordan Treaty of Peace, formally ending the state of war that had existed between the nations since 1948; and Dorothy Crowfoot Hodgkin, the renowned British x-ray crystallographer and Nobel prize laureate, dies.
One advantage of large epidemiological studies is that they may be used to answer questions for which they may not have been designed. The data items must be there in a usable form so that it is not necessary to torture or abuse them to get a plausible answer. This study is an offshoot of the WHO MONICA (World Health Organization–MONItoring of trends and determinants in Cardiovascular disease) Project, which involved 38 populations in 21 countries and was concerned with trends in cardiovascular disease and risk factors. It involved measuring them in a standard manner, providing an opportunity to explore the French paradox. This involves men alone in two populations, rather than whole countries: Belfast and neighboring areas, in the north of Ireland, an old industrial city and port (shipbuilding, tobacco, textiles), and Toulouse in southern France (aeronautical engineering, modern industries). It was part of an ongoing collaboration between the three French centers and Belfast, which continued into genetic factors, and has proved productive. A two-center comparison of similarities and differences is useful for generating hypotheses, but not proof—statistical testing of multiple differences in findings must be interpreted with extreme caution. Large differences in conceivably causal factors may not be relevant, but it is also possible to imagine similarities in contributory factors that are misleading through being confounded by others, as what is true of these two centers may not be so for others.

Belfast was near the top of the MONICA ranking for incidence of coronary events, and Toulouse near the bottom. All-cause mortality was higher in Belfast, but Toulouse had higher rates for some categories of death including violence. Coronary event rates, after using the explicit MONICA criteria, were several times higher in Belfast than Toulouse. However, conventional coronary risk factors did not explain the difference, as two different risk scoring systems produced very similar scores for the two centers with their risk factors cumulated in multiple logistic functions.

The authors therefore had to look elsewhere. Measurement of diet was an optional item in MONICA because of the difficulties and expense of measurement. Both centers used a MONICA optional-study protocol which included 3-day food records, in Belfast all weighed, in Toulouse 3-day diaries with 10% weighed. Response rates in the men concerned were 52% and 58%, but the weighed results were used for analyses. Total energy intake was similar as was total fat and carbohydrate intake. Belfast ate more sugar, Toulouse more protein, more dietary cholesterol, and more alcohol, their saturated fat intake was lower, monounsaturated fat the same, and polyunsaturated intake higher giving them a P/S ratio of 0.51 to that of 0.30 in Belfast.

Not surprisingly, given the geographic situation of the two cities, there were many differences in individual food items—but not all in the direction one might expect. Meat consumption was higher in Toulouse, as were total dairy products, particularly cheese. Belfast men ate more potatoes, biscuits, and cakes, and more onions. Bread consumption was similar, but Toulouse ate more green vegetables of several sorts, carrots, and six times as many tomatoes. This study both restates the French paradox, and may contain clues to its explanation. Looking at the data overall however, it is difficult to accept that the factors listed account for a three to fourfold difference in coronary disease rates in men aged 45 to 64 without results from a randomized controlled trial—more difficult for wine than for tomatoes.

1995

Italian cyclist and an Olympic gold medalist Fabio Casartelli dies in a crash during the 15th stage of the 1995 Tour de France;

UN Dutch peacekeepers leave Srebrenica as Bosnian Serb forces march into the city, prompting the Srebrenica massacre; Juan Manuel Fangio the Argentinean five-time Formula One World Driver’s Champion, dies aged 84.
The French Paradox: Fact or Fiction?

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