Novartis Foundation Symposium 216

ALCOHOL AND CARDIOVASCULAR DISEASES

1998

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Chairman's introduction

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In most Western countries the production, purveying and pathology of alcohol beverages is a multibillion dollar business. We have vacillated between its beneficial and detrimental effects throughout the last century. Of recent interest is the apparent beneficial effect of modest alcohol consumption, one to three drinks per day, on mortality and morbidity rates, particularly relating to cardiovascular disease. The objectives of this symposium were to bring together speakers and discussants from a wide range of disciplines to evaluate the evidence for the so-called J-shaped curve and to seek a biological explanation for the apparent beneficial effects of low levels of consumption. The final aim was to discuss how the conclusions from the symposium might be translated into effective and acceptable public health measures.

The physical and intellectual objectives of the programme were clearly achieved: the participants and readers will clearly have a view as to whether worthwhile conclusions were reached.

Alcohol and cardiovascular diseases: a historical overview

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Abstract. Evident disparities in relationships make it desirable to consider several disorders separately. (1) Alcoholic cardiomyopathy was perceived 150 years ago, but understanding was clouded by recognition of beriberi and of synergistic toxicity from alcohol with arsenic or cobalt. (2) A report of a link between heavy drinking and hypertension in WWI French soldiers was apparently ignored for >50 years. Epidemiological and intervention studies have now firmly established this association, but a mechanism remains elusive. (3) The 'holiday heart syndrome', an increased risk of supraventricular tachyarrhythmias in alcoholics, has been widely known to clinicians for 25 years; data remain sparse about the total role of heavier drinking in cardiac rhythm disturbances. (4) Failure of earlier studies to distinguish types of stroke impeded understanding; it now seems probable that alcohol drinking increases risk of haemorrhagic stroke but lowers risk of ischaemic stroke. (5) Heberden reported angina relief by alcohol in 1786, and an inverse alcohol–atherosclerosis association was observed by pathologists early in this century. Recent population studies and plausible mechanisms support a protective effect of alcohol against coronary disease. International comparisons dating back to 1819 suggest beverage choice as a factor, but this issue (the 'French Paradox') remains unresolved.

1998 Alcohol and cardiovascular diseases. Wiley, Chichester (Novartis Foundation Symposium 216) p 2–18

Those who cannot remember the past are condemned to repeat it.
George Santayana, The Life of Reason, 1905

The effects of ethyl alcohol upon the cardiovascular system have excited the interest of clinicians and investigators for well over a century. While much has been learned, many areas of knowledge remain incomplete. Physiological, clinical and epidemiological evidence cannot yet be integrated into definitive general concepts. Past attempts to generalize and simplify have probably had the effect of slowing progress in understanding this area. Disparity in relations of alcohol drinking to various cardiovascular conditions (Klatsky 1995a) has become increasingly clear.

To this must be added the disparity between the effects of lighter and heavier drinking. The choice of topics for this book recognizes these differences. In this historical overview, each of the following will be considered separately: cardiomyopathy, arsenic and cobalt beer drinkers' disease, cardiovascular beri-beri, systemic hypertension, cardiac arrhythmias, cerebrovascular disease, atherosclerotic coronary heart disease (CHD), total mortality and definitions of safe drinking limits. Emphasis is on aspects less likely to be covered in detail by other papers in this book; the latter are only briefly summarized. Hopefully, some light will be cast upon previous mistakes, so that we can proceed less burdened by the condemnation of repeating them.

Alcoholic cardiomyopathy

Circumstantial evidence only raises a probability.
Mr Justice Pollock, 1865

A number of famous nineteenth century physicians commented about an apparent relationship between chronic intake of large amounts of alcohol and heart disease (Friedreich 1861, Walsche 1873, Strumpell 1890, Steell 1893, Osler 1899). A German pathologist (Böllinger 1884) described cardiac dilatation and hypertrophy among Bavarian beer drinkers, which became known as the 'Munchener bierherz'. He reported an average yearly consumption of 432 litres of beer in Munich, compared with 82 litres in other parts of Germany.

In 1900, an epidemic of heart disease due to arsenic-contaminated beer occurred in Manchester, England. Before this event, Graham Steell (1893), in a report of 25 cases, stated 'not only do I recognize alcoholism as one of the causes of muscle failure of the heart but I find it a comparatively common one'. Following the arsenic beer episode Steell (1906) wrote in a textbook that 'in the production of the combined affection of the peripheral nerves and the heart met with in beer drinkers, arsenic has been shown to play a conspicuous part'. In his textbook *The Study of the Pulse* William MacKenzie (1902) described cases of heart failure attributed to alcohol and first used the term 'alcoholic heart disease'. Early in the 20th century, there was general doubt that alcohol had a direct role in producing heart muscle disease, although some (e.g. Vaquez 1921) took a strong view in favour of such a relationship.

After the detailed descriptions of cardiovascular beri-beri (Aalsmeer & Wenckebach 1929, Keefer 1930), the concept of 'beri-beri heart disease' dominated thinking about the effects of alcohol upon the heart for several decades. For the past 40 years or so, increasing interest has been evident in possible direct toxicity of alcohol upon the myocardial cells, independent of, or in

addition to, deficiency states. The sheer volume of clinical observations, indirect evidence of decreased myocardial function in heavy chronic drinkers, and a few good controlled studies have now solidly established the concept of alcoholic cardiomyopathy. The absence of diagnostic tests remains a major impediment to epidemiological study, since the entity is indistinguishable from other forms of dilated cardiomyopathy. Most cases of dilated cardiomyopathy in 1997 are of unknown cause, with a post-viral autoimmune process the leading aetiologic hypothesis. The most convincing circumstantial evidence that alcohol can cause cardiomyopathy consists of extensive data, in animals and humans, of non-specific cardiac abnormalities related to alcohol. A landmark study (Urbano-Márquez et al 1989) showed a clear relation in alcoholics of lifetime alcohol consumption to structural and functional myocardial and skeletal muscle abnormalities. The amounts of alcohol were large — the equivalent of 120 grams alcohol/day for 20 years. Thus, Walshe's term 'cirrhosis of the heart' seems very appropriate.

In view of the history just cited, it seems noteworthy that there has been little work so far about possible cofactors or predisposing traits for alcoholic cardiomyopathy. In this context, it seems appropriate to consider further the arsenic and cobalt beer drinker episodes and thiamine (cocarboxylase) deficiency — or beri-beri heart disease.

Arsenic beer drinkers' disease

Synergy: (def.) combined action or operation.
Webster's 7th Collegiate Dictionary

In 1900 an epidemic (6000+ cases with 70+ deaths) occurred in and near Manchester, England, which proved to be due to contamination of beer by arsenic. There were skin, neurological and gastrointestinal signs and symptoms, but cardiovascular manifestations, especially heart failure, were especially prominent. A superb clinical description (Reynolds 1901) included: (1) 'cases were associated with so much heart failure and so little pigmentation that they were diagnosed as beri-beri. . . .'; (2) 'so great has been the cardiac muscle failure that . . . the principal cause of death has been cardiac failure. . . .', and (3) 'at post-mortem examinations the only prominent signs were the interstitial nephritis and the dilated flabby heart . . .'.

Lively entries in *The Lancet* over the next few years included allusion to a possible earlier (by 12 years) outbreak in France due to contaminated wine, and the probable source as contaminated sulfuric acid used to treat cane sugar. It was determined that the affected beer had 2–4 parts per million of arsenic, not — in itself — an amount likely to cause serious toxicity. It was pointed out that some persons seemed to have

a 'peculiar idiosyncrasy', that 'many persons became ill who drank less beer than others not affected', and that 'the amount of arsenic . . .was not sufficient to explain the poisoning'. One entry (Gowers 1901) mentioned that the author prescribed 10 times the amount of arsenic involved for epilepsy over long periods of time with no toxicity. An appointed committee report (Royal Commission 1903) suggested that 'alcohol predisposed people to arsenic poisoning'. As best one can determine, no one suggested the converse.

Cobalt beer drinkers' disease

History repeats itself.
Thucydides; History, I, c. 410 B.C.

Recognized 65 years after the arsenic beer episode, this condition was similar in some respects. In the mid-1960s reports appeared of epidemics of heart failure among beer drinkers in Omaha and Minneapolis in the USA, Quebec, Canada, and Leuven, Belgium. The condition developed fairly abruptly in chronic heavy beer drinkers. The North American patients suffered a high mortality rate, but those who recovered did well despite return, by many, to previous beer habits. The Belgian cases were less acute in onset, longer in duration and had a lower mortality.

The explanation proved to be the addition of small amounts of cobalt chloride by certain breweries to improve the foaming qualities of beer. Widespread use of detergents (new at that time) in taverns had a depressant effect upon foaming. This aetiology was tracked down largely by Quebec investigators (Morin & Daniel 1967), and the condition became justly known as Quebec beer-drinkers' cardiomyopathy. The largest Quebec brewery had added cobalt to all beer — not only draught beer. Removal of the cobalt additive ended the epidemic in all locations.

In Belgium, where the cobalt concentrations were lower and the cardiac manifestations less severe, there were more of the usual findings of chronic cobalt use, such as polycythemia and goiter. However, even in Quebec, where cobalt doses were greatest, 12 litres of contaminated beer provided only about 8 mg cobalt, less than 20% of the dose sometimes used as a haematinic. The haematinic use had not been implicated as a cause of heart disease, whereas the first cases of this dramatic heart condition occurred 4–8 weeks after cobalt was added to beer.

Thus, both cobalt and substantial amounts of alcohol seemed needed to produce this condition. Most exposed persons did not develop the condition. Despite much speculation, biochemical mechanisms were not established. One observer (Alexander 1969) summed up the arsenic and cobalt episodes thus: 'This is the second known metal induced cardiotoxic syndrome produced by contaminated beer'.

The arsenic and cobalt episodes raise the possibility of other cofactors in alcoholic cardiomyopathy, such as cardiotropic viruses, drugs, selenium, copper and iron. Deficiencies of zinc, magnesium, protein and various vitamins have also been suggested as cofactors, but deficiency of thiamine is probably the only one with solid proof of cardiac malfunction.

Cardiovascular beriberi

Things are seldom what they seem.
W. S. Gilbert, HMS Pinafore, 1878

As already stated, for many years this condition dominated thinking about alcohol and cardiovascular disease. The classical description (Aalsmeer & Wenckebach 1929) defined high-output heart failure in Javanese polished-rice eaters, with decreased peripheral vascular resistance as the physiological basis. It became assumed that heart failure in heavy alcohol drinkers in the West was due to associated nutritional deficiency states. Although some heart failure cases in North American and European alcoholics fitted this clinical pattern, most did not. Many had low output heart failure, were well-nourished and responded poorly to thiamine. Some felt that these facts were due to the chronicity of the condition, which ultimately might become irreversible. However, Blacket & Palmer (1960) stated the following view: 'It (beriberi) responds completely to thiamine, but merges imperceptibly into another disease, called alcoholic cardiomyopathy, which doesn't respond to thiamine'. Modern physiological techniques have established that in beriberi there is generalized dilatation of peripheral arterioles, with creation of an effective large arteriovenous shunt with resultant high resting cardiac outputs. A few cases of complete recovery with thiamine within 1–2 weeks were documented.

It is evident that many cases earlier called 'cardiovascular beriberi' would now be called 'alcoholic heart disease'. Does chronic thiamine deficiency play a role in some cases of alcoholic cardiomyopathy? This currently unpopular thesis has not been proved or disproved.

Hypertension

There is nothing new save that which has been forgotten.
Mme. Bertin, milliner to Marie Antoinette, c. 1785

Epidemiological studies

A threshold relationship between heavy drinking and hypertension was reported in WWI middle-aged French servicemen (Lian 1915). Unless Dr Lian's French

soldiers were exaggerating, they were prodigious drinkers: the hypertension threshold appeared at >2 litres of wine per day. It was almost 60 years before further attention was paid to this subject. Since the mid 1970s, dozens of cross-sectional and prospective epidemiological studies have solidly established an empirical alcohol–hypertension link (Beilin & Puddey 1992, Klatsky 1995b). Almost all studies show higher mean blood pressures and/or higher hypertension prevalence with increasing alcohol drinking. These studies involve both sexes and various ages and include North American, European, Australian and Japanese populations. The apparent threshold amount of drinking associated with higher blood pressure in the more modern studies is at approximately 3 drinks/day. The studies show independence of the link from adiposity, salt intake, education, cigarette smoking and several other potential confounders. Alcoholic beverage type (wine, liquor or beer) seems to be a minor factor. Most studies do not show any increase in blood pressure at lighter alcohol drinking; several show an unexplained J-shaped curve in women, with lowest pressures in lighter drinkers.

Intervention studies

The landmark study of Potter & Beevers (1984) showed in hospitalized hypertensive men that three to four days of drinking four pints of beer raised blood pressure and that a similar period of abstinence resulted in lower pressures. These changes occurred in several days to a week without evidence of withdrawal increases in pressure. Similar results were later seen in ambulatory normotensives and hypertensives (Beilin & Puddey 1992). Other interventional studies have shown that heavier alcohol intake interferes with drug treatment of hypertension and that moderation or avoidance of alcohol supplements or betters other non-pharmacological interventions such as weight reduction, exercise or sodium restriction (Beilin & Puddey 1992). Even in the absence of an established mechanism, the intervention studies strongly support a causal hypothesis. It now seems probable that alcohol restriction plays a major role in hypertension management and prevention.

Arrhythmias

If all the year were playing holidays,
To sport would be as tedious as to work.
Shakespeare; Henry IV, I, c. 1598

An association of heavier alcohol consumption with atrial arrhythmias has been suspected for decades, with occurrence after a large meal accompanied with much alcohol. The concept of the 'holiday heart phenomenon' was popularized (Ettinger

et al 1978) on the basis of the observation that supraventricular arrhythmias in alcoholics without overt cardiomyopathy were most likely to occur on Mondays or between Christmas and New Year's Day. Some have suggested that atrial flutter was especially likely to be so associated, but various atrial arrhythmias have been reported to be associated with spree drinking. Atrial fibrillation is the commonest manifestation. The problem typically resolves with abstinence, with or without specific treatment. A Kaiser Permanente study (Cohen et al 1988) compared atrial arrhythmias in 1322 persons reporting 6+ drinks per day to arrhythmias in 2644 light drinkers. The relative risk in the heavier drinkers was at least doubled for atrial fibrillation, atrial flutter, supraventricular tachycardia, and atrial premature complexes.

Stroke

The cautious seldom make mistakes.
Confucius: Analects, IV, c.500B.C.

Earlier studies of relationships of alcohol drinking to stroke were made difficult by imprecise diagnosis of stroke type before modern imaging techniques improved diagnostic accuracy. All studies of alcohol and stroke are greatly complicated by the disparate relationships of both stroke and alcohol to other cardiovascular conditions.

Several reports suggested that alcohol use, especially heavier drinking, was associated with higher risk of stroke (Van Gign et al 1993). Some studies examined only drinking sprees; some others did not differentiate between haemorrhagic and ischaemic strokes. The importance of these deficiencies is highlighted by several recent studies suggesting that regular lighter drinkers are at higher risk of haemorrhagic stroke types, but at lower risk of several types of ischaemic stroke (Van Gign et al 1993).

At this time there is no consensus about the relations of alcohol drinking to the various types of cerebrovascular disease and agreement only that more study of this important subject is needed.

Coronary heart disease

Wine and spiritous liquors — afford considerable relief.
William Heberden, 1786

After the classic description of angina pectoris (Heberden 1786), alcohol was widely presumed to be a coronary vasodilator (White 1931, Levine 1951). However, data from exercise ECG tests (Russek et al 1950, Orlando et al 1976)

suggest that alcohol does not improve myocardial oxygen deficiency and that symptomatic benefit is subjective and, possibly, dangerously misleading. Few data suggest any major immediate effect of alcohol upon coronary blood flow (Renaud et al 1993, Klatsky 1994).

In the first half of this century there were reports of an apparent inverse relationship between alcohol consumption and atherosclerotic disease, including CHD (Cabot 1904, Hultgen 1910, Leary 1931, Wilens 1947). One explanation offered was that premature deaths in heavier drinkers precluded development of CHD (Ruebner et al 1961, Parrish & Eberly 1961). Since 1974 several dozen population and case-control studies have solidly established an inverse relationship between alcohol drinking and either fatal or non-fatal CHD. Data supporting plausible protective mechanisms have also appeared (Renaud et al 1993, Klatsky 1994). It now seems likely that alcohol drinking protects against CHD.

The cause is hidden, but the effect is known.
Ovid; Metamorphoses, IV, c.5.

In 1819 Dr Samuel Black, an Irish physician with a great interest in angina pectoris and of considerable perception with respect to epidemiological aspects, wrote what is probably the first commentary pertinent to the 'French Paradox'. His anecdotal observation (Black 1819) was based upon lack of discussion of the condition in the French medical literature, but his interpretation is noteworthy. With respect to the disparity in CHD between Ireland and France, he attributed the low angina prevalence in the latter to 'the French habits and modes of living, coinciding with the benignity of their climate and the peculiar character of their moral affections'. It was to be 160 years before data were presented from the first international comparison study to suggest less CHD in wine drinking countries than in beer or liquor drinking countries (St Leger et al 1979). We now have several confirmatory international comparison studies as well as reports of non-alcohol antioxidant phenolic compounds or antithrombotic substances in wine, especially red wine (Renaud et al 1993, Klatsky 1994). However, prospective population studies show no consensus about the wine/liquor/beer issue (Rimm et al 1996, Klatsky et al 1997). This question remains unresolved at this time.

The J-shaped alcohol–mortality curve

There are more old wine drinkers than old doctors.
German proverb

This scientifically unsound (no denominators) proverb suggests general scepticism about medical reports. There was one report of the J-curve alcohol–mortality

phenomenon which preceded other population study reports by half a century. A Baltimore investigator (Pearl 1926) described this relationship in a study of 5248 tuberculosis patients and controls. 'Heavy/steady' drinkers had the highest mortality; 'abstainers' were next; and 'moderate' drinkers had the lowest mortality. His interpretation was cautious; he concluded that moderate drinking was 'not harmful'. Perhaps his major contribution was to realize the fallacy in comparing all drinkers to abstainers, which masks the J-curve.

The 'sensible drinking limit'

Drink not the third glass.
George Herbert: The Temple, 1633

The medical risks of heavier drinking and the relative safety of lighter drinking have long been evident. Thus, attempts to define a safe limit are hardly new. Probably the most cited such limit has been known for more than 100 years as 'Anstie's Rule' (Anstie 1870), which advised an upper limit of approximately three standard drinks daily. Although his limit was intended to apply primarily to mature men, Sir Francis Anstie was a distinguished neurologist and public health activist who emphasized individual variability in the ability to handle alcohol. Individual risk/benefit considerations should be a major focus of any discussion and the primary consideration when a health practitioner advises his or her client. It is noteworthy that several contemporary data-based definitions are similar to Sir Francis Anstie's common-sense-based concept.

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DISCUSSION

Keil: You told us that the protective effect of alcohol on coronary heart disease (CHD) was first shown in 1974 (Klatsky et al 1974). However, in a recent paper by Seltzer (1997), he claimed that he had been the first to examine the alcohol–CHD relationship with Framingham data. He produced a manuscript, but not a paper, showing its protective effects, which he submitted to the National Institutes of Health (NIH). Dr Zukel from NIH said that this was scientifically and socially unacceptable, and that Dr Seltzer should instead produce a paper showing a detrimental effect of alcohol. In this area we are obviously continually dealing with questions that have both scientific and moral aspects.

Klatsky: I didn't know Dr Seltzer, but when we presented the first report about the inverse relation between alcohol drinking and CHD at a medical meeting, somebody else from the Framingham study came up to me and told me that they had found this association in the Framingham data, but they didn't know what to make of it. It was barely statistically significant, and so they didn't publish it. When one looks over the various earlier reports on alcohol and coronary disease, it's hard to come to any firm conclusions from the Framingham cohort data. It is a wonderful landmark study in many respects, but they didn't have enough information about alcohol — and, in particular, they didn't have enough people who reported heavy drinking — to clearly show the relationship between alcohol and CHD. I think they also failed to separate lifelong abstainers from past drinkers. So, everything considered, I think that Dr Seltzer's memory of the remote past is probably only partially correct: there must have been political pressures involved, but I also don't think the data would have been solid enough to make a statement on a subject that seemed so controversial and difficult to present. When we published our first study, we faced a real dilemma about how to present the findings. In the original article we actually tried to attack the protective hypothesis, because it seemed on one level to be a frightening conclusion.

Keil: In an editorial in the *Journal of the American Medical Association* in 1979 a comment was made: 'This is a message for which this country is not yet ready'

(Castelli 1979) — another statement showing that people were initially hesitant about the conclusions.

Shaper: It's interesting how the pendulum has swung. We have now reached the stage where it is difficult to get results suggesting that alcohol is not protective through to the public!

Peters: You mentioned that for a long time alcoholic cardiomyopathy was misattributed to thiamine deficiency. Why did cardiologists have that 50 year hiatus, when they ignored the effects of alcohol? In a similar manner, alcoholic liver disease was thought for a long time to be nutritional in origin.

Klatsky: I think one sees what one knows. If one knows that thiamine deficiency can cause heart failure, even if it's clear that acute thiamine deficiency responds to acute administration of thiamine, it's a logical jump to assume that if there is an acute syndrome, there's also a chronic syndrome. That must have been the thinking at the time. I was taught at the Boston City Hospital to try administering thiamine, but not to expect it always to work when the heart failure becomes chronic.

Marmot: With regard to the current Russian scene, more than half of the excess mortality in Russia is attributed to cardiovascular disease. Some would attribute the roughly six-year decline in life expectancy of males over the last five years to alcohol. Is this at all credible?

Klatsky: There is no question that heavier drinking, however one wants to define it, is associated with increased mortality for a number of reasons. If a large proportion of a population drinks heavily, an increase in mortality will be seen, particularly among young people, in whom the relationship between heavier drinking and mortality is especially clear. I don't know whether alcohol is more lethal to young people or whether the people who drink heavily and survive to old age are those who are resistant to cirrhosis and other alcohol-related illnesses. But in Russia there is a high prevalence of very heavy drinking in a binge drinking pattern, which may be particularly unfavourable. As a consequence there likely is no J- or U-shaped alcohol–risk curve in Russia. Thus it's very probable that a lot of the excess mortality is due to alcohol. However, there may well be many unfavourable lifestyle traits among younger and middle-aged Russian men, such as cigarette smoking, unfavourable diet and lack of exercise. Consequently, it may be hard to sort out what proportion of mortality is attributable to each of these risk traits.

Marmot: My question is not whether alcohol can kill people, because clearly it can: rather, it concerns the magnitude of the effect. If one tried to do an estimate of the relative risk of cardiac death from heavy drinking, what would the prevalence of heavy drinking and relative risk of death have to be in order to account for a six year decline in life expectancy in men in the space of five years?

Klatsky: I don't know what the prevalence of cardiomyopathy is. It is probably lower than cirrhosis. Lelbach (1974) in Germany was interested in the proportion

of heavy drinkers that would develop cirrhosis: I think he said that the figure was 18–20%. The decline of life expectancy is related to not only the prevalence of the conditions, but also the age at which people die. If people die young of accidents, suicide or cirrhosis, this will reduce overall life expectancy a lot more than if people are dying older.

Marmot: But most of the excess mortality is in middle-aged men.

Shaper: It is the temporal relationship that is important. When the Russian authorities clamped down on alcohol drinking some years ago, the mortality rate seemed to be steady or falling. Later, when alcohol became cheaply and freely available, the mortality rate rose rapidly: the excess mortality developed in only a few years. Therefore we are dealing with something that is not a chronic phenomenon but may have to do with large intakes of alcohol in young people, possibly with resulting myocardial instability.

Anderson: If you look at the trends in premature mortality in Russia from 1980 to present (Fig. 2 on page 242), the striking feature is the rapid increase in cardiovascular disease deaths. This is what we need to account for. We have been looking at this, and although it is clear that some are due to misclassification (some of the deaths are from direct alcohol poisoning rather than cardiovascular disease deaths), it is very important to try to unravel the mechanism behind this trend.

Rehm: It is not possible to simulate the increased mortality due to alcohol in Russia with the normal relative risks. However, it is possible if you take into account the specific pattern of drinking in Russia, which involves binge-drinking. The majority of epidemiological studies do not take this into account. The large cohorts, such as Framingham or the Nurses' health study, do not include people who habitually binge drink. Without taking drinking pattern into account we won't be able to explain the Russian excess mortality data.

Keil: An interesting point is raised by the meta-analysis published by Maclure (1993) and covering over 50 studies. The Finnish studies show an increased risk for coronary heart disease, which could well be a consequence of binge drinking. In Scandinavia, even in the higher social classes, a common pattern of drinking is for people to get drunk at the weekend, whereas in Central Europe drinking is more likely to be spread through the week. Many studies don't pick up these different drinking patterns.

Criqui: In the last two months there has been an analysis of this mortality pattern and an accompanying editorial in *The Lancet* (Leon et al 1997, Kromhout et al 1997). The conclusion is that much of this excess is due to alcohol *per se*. There is one discrepancy that's not addressed too often in population studies: everybody agrees that there is a U-shaped curve with total mortality increasing above about three drinks a day, but in some studies the risk of coronary disease goes up sharply after three drinks a day, whereas in other studies it stays down to up to six or seven drinks a day. It is interesting that this dichotomy exists.

Atherosclerotic disease is one issue, but sudden cardiac death is perhaps a separate cause of death that could be occurring in the former Soviet Union. In the early 1980s there was a program established in the USA, the Lipid Research Clinics Program, looking at blood lipids in 10 US populations, a population in Israel and two clinics in what was then the Soviet Union. When we looked at the first mortality data, it was very clear that high-density lipoprotein (HDL) cholesterol was very protective in all US populations and in Israel, but in the two Russian populations it was not: there was this clear anomaly where the higher the HDL cholesterol the higher the death rate, even then suggesting that perhaps the very heavy drinking produced an anomalous relationship between lipids and coronary disease.

Farrell: The issue of measurement of drinking is likely to be at the core of much of the discussion at this meeting. It is clear that in the future we are going to have to be more refined in our measurement of drinking, not just discriminating between binge and continuous drinking, but also tackling the problem of the assumption of stability of drinking patterns across years. We don't really have a good population understanding of fluctuations in patterns of drinking.

Farchi: Some unpublished results (G. Farchi, A. Menotti) obtained from the analysis of data collected on the Italian rural cohorts of the Seven Countries Study, may partially answer the question raised by Michael Marmot about alcohol consumption and survival. Men aged 45–64 in 1965 were followed for 30 years, until 1995. The maximum mean survival, 21.6 years, was experienced by men drinking between 49 g and 84 g of alcohol every day; above this threshold one year of life is lost for every 30 g/day alcohol.

Shaper: Is there really any significant difference between any of the figures?

Farchi: Differences between any of the figures are not statistically significant, but if a model is used, the coefficient of the quadratic terms is statistically different from zero, so highlighting a U-shaped significant trend.

Shaper: Arthur Klatsky, I'm delighted that you referred to Raymond Pearl. His book (*Alcohol and longevity*) has recently been reprinted (Pearl 1981), and one cannot but feel affectionate towards a man who dedicates his book 'To my friends of the Saturday Night Club'!

Pearl looked at an interesting group of people: he was studying tuberculosis and in order to get a control group, the non-tuberculous individuals were taken at random either from those persons who had committed some trivial offence (such as playing baseball in a vacant lot!) or from patients registered at the general dispensary of the Johns Hopkins Hospital. Interestingly, the group included many younger people: 50% of them were under 40. Pearl was also was interested in a relatively small group of people in whom he found change in alcohol consumption: those people who either increased their alcohol intake or who became abstainers. Thus, even at that very early stage there was interest in the

question that Dr Farrell has raised of changing alcohol patterns. Finally, in his summary of the work, Pearl trod very cautiously, saying that moderate drinking of alcohol did not shorten life but, on the contrary, moderate steady drinkers exhibited somewhat lower rates of mortality and greater expectation of life than abstainers. He concluded that this superiority was not great in the male moderate drinkers and may not be significant.

Peters: The arsenic and cobalt poisoning episodes you described in your paper raise the question of individual susceptibility factors. Did the authors of these reports speculate as to what these might be?

Klatsky: They did not do so specifically. Particularly interesting in this respect, however, are the letters that were published in *The Lancet* at the turn of the century: they made it clear that some people who drank less beer got ill and died, as compared with others who drank substantially more. Incidentally, in both of these poisoning epidemics, the beer drinkers involved were big-time drinkers — they were not drinking just two or three pints a day!

In general, the study of cofactors for alcohol-induced toxicity is rather neglected. Some analogy can be drawn here with alcoholic cirrhosis. There are references in the older literature to previous or ongoing viral infection as a susceptibility factor in alcoholic cirrhosis. In the modern literature there are suggestions that ongoing low-level post-viral infection factors could be involved in myocardial toxicity to alcohol.

With regard to Dr Shaper's reference to Raymond Pearl, I believe that in his book he also talks about the possible 'constitutional weakness' of the abstainers. This is an interesting point.

Shaper: Yes. Pearl was very concerned with what he calls 'racial aspects': he started with 'racial' studies of alcohol and poultry. It is my understanding that by 'racial' he was referring to genetic differences, and he was concerned with the fact some poultry and some people might be more susceptible to alcohol.

Fillmore: On this issue, I would like to add a footnote to the observations regarding the former Soviet Union (Korolenko et al 1994, White 1996, Tarchys 1993). There is currently a real need for epidemiological work in that country. There is tremendous illicit alcohol production, and we don't really know what else might be present in the alcohol that is consumed: this brings us back to the cobalt and arsenic observations Dr Klatsky made. Does anyone here know of any analysis of what is going on there with respect to additives? The critical question here concerns the degree to which these deaths are attributable to alcohol.

Shaper: I attended a meeting recently with some of the Russians who were involved with this work, and they were saying that there is a tremendous amount of illicit brewing and distilling going on. It is almost like the prohibition days in the USA.

Gaziano: As I was listening to Dr Klatsky's talk, it dawned on me that from an epidemiological standpoint alcohol is a unique factor. Compared with other risk factors that we follow, which typically have an effect that is qualitatively in one direction, alcohol has so many competing effects on many diseases with multiple mechanisms that it's one of the few risk factors that I know that takes a qualitative turn from beneficial to harmful. Aside from the social and political aspects, this may well contribute to the difficulty of studying this risk factor.

Klatsky: I think you're absolutely right: not only are there competing effects, but I think there's a fairly consistent difference in the relationships even within coronary disease studies of the two major endpoints: non-fatal events (usually hospitalization for infarction) and fatal coronary disease. Most studies of fatal coronary disease show a U-curve, whereas most studies of non-fatal events show a levelling off: heavier drinkers also seem to have a lower death rate. There could be real difference in terms of the effects of heavier drinking on non-fatal and fatal coronary disease, because of the possibility of arrhythmias or other factors. There is also the classification problem in terms of the correctness of the diagnosis of coronary disease in heavier drinkers who are found dead.

Keil: You mentioned cobalt and arsenic, but you could also include lead. When we made our studies in the Augsburg area and were looking for blood lead, we found out that most of it comes from beer and wine (Hense et al 1994). Is it present at harmful levels?

Klatsky: I imagine that it could be. There is some older literature about lead-contaminated wine, and there's a fair amount of literature about congeners in distilled spirit as factors for toxicity, but there's more interest in them as factors in causing hangovers than in organ toxicity.

Puddey: I want to comment on the emerging concept, championed by some, that alcohol-related hypertension may be a benign phenomenon. I guess this has had its genesis in the J-shaped relationship described for alcohol and coronary disease, and alcohol and ischaemic stroke, the two major endpoints of hypertension *per se*. I was quite struck in Arthur Klatsky's presentation by the congestive cardiomyopathy caused by alcohol. In three of the earliest cases that he described, cardiac hypertrophy was the major feature of the pathology. To what extent is that a unique feature of alcoholic congestive cardiomyopathy, or could it be dictated by alcohol-related hypertension?

Klatsky: That's impossible to say. Obviously, hypertension is probably one of the major factors in left-ventricular hypertrophy of any sort. It is not unusual in idiopathic dilated cardiomyopathy for there to be hypertrophy along with the dilatation and the flabby weak heart. I think a pattern of hypertrophy on the cardiogram and total increased left ventricular mass is not uncommon in idiopathic dilated cardiomyopathy, which I think cannot be distinguished clinically from alcoholic cardiomyopathy without knowledge of the alcohol

history of the patient. I would be interested to hear more about the benignity of alcohol induced hypertension: it is an unresolved issue.

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Metabolic consequences of alcohol ingestion

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Abstract. Many of the pathophysiological effects of alcohol ingestion relate to the pathways of ethanol metabolism. However, some of the acute and chronic effects of ethanol use are also attributable to the direct effects of ethanol, e.g. on membrane fluidity. Oxidation of ethanol to acetaldehyde is catalysed by alcohol dehydrogenase (ADH). There are at least six classes of ADH, some of which show inter-individual variation, i.e. genetic polymorphism, that influences the rate of ethanol oxidation. A consequence of ethanol oxidation is an increase in the NADH/NAD redox potential within the cytosol and mitochondria with subsequent alteration in several tissue metabolites. The popular hypothesis that most, if not all, of the consequences of chronic alcohol ingestion can be explained by these redox changes is still unproven. This should be considered in the context that most metabolic pathways of the liver are affected by alcohol, as are several endocrine axes in the whole body. In fact most, if not all, tissues and organs are deleteriously affected by chronic ingestion. Acetaldehyde, the product of ethanol oxidation, is chemically highly reactive, toxic and immunogenic. However, the concentrations achieved *in vivo* usually fall short of those used to produce these toxic effects in experimental situations. Oxidation of acetaldehyde is also coupled to redox changes, although primarily affecting the intra-mitochondrial redox. In addition, further oxidative pathways of ethanol metabolism can lead to the formation of fatty acid ethyl esters, hydroxyethyl free radicals and reactive oxygen species via the ethanol-specific cytochrome P_{450}-2E1 system. There is no conclusive evidence that nutrient supplementation has beneficial effects on overall ethanol-mediated tissue damage.

1998 Alcohol and cardiovascular diseases. Wiley, Chichester (Novartis Foundation Symposium 216) p 19–34

All the effects of alcohol ingestion, beneficial or detrimental, are directly or indirectly related to the metabolic consequences of ethanol. The claims during the 1940s and 1950s of Best, Daft and Himsworth amongst others that the toxic effects of chronic alcohol misuse relate to associated nutritional impairment were decisively disproven by the seminal studies of Charles Lieber during the 1960s. A caveat, however, remains that specific vitamin deficiency syndromes, such as