

# The French Paradox in the 21<sup>st</sup> Century: *Is Wine Still*

by Richard A. Baxter, MD, FACS

*It's hard to believe that it has been almost two decades since the iconic French Paradox report on CBS-TV's "60 Minutes." The researchers interviewed in the report, Serge Renaud of the University of Bordeaux and R. Curtis Ellison, Professor of Medicine and Public Health at Boston University, were vilified by anti-alcohol activists and lauded by wine lovers. The spark of the idea ignited not just a firestorm of controversy but also an explosion of basic science and clinical research, which continues actively today.*



# *a Prescription for Health?*

One result of this was the discovery of resveratrol, a molecule in red wine with a range of properties so promising that Sirtris—a biotech company founded to develop resveratrol-based pharmaceuticals—was acquired by GlaxoSmithKline in 2008 for some \$720 million. A Medline search returns nearly 3,000 citations for red wine, revealing positive implications for conditions from Alzheimer’s disease to diabetes, along with controversies on cancer risk and whether there is indeed such a thing as healthy drinking. We have clearly moved beyond the heart health question to the broader topic of degenerative disease with wine, but even that remains subject to debate.

The issue of what to advise patients about drinking remains sensitive despite this new wealth of information. For example, in January the American Heart Association released updated lifestyle recommendations, with the only mention of drinking a caution that those who choose to drink should have no more than one per day for a woman and two for a man. There’s no lack of data here though. In 1973, a review of the role of alcohol and heart disease in the first 25 years of the

Framingham Heart Study was prepared. One of the authors of the report, Carl Seltzer, divulged years later that senior NIH officials reviewing the report responded with a written directive that it was to state there was “no significant relationship of alcohol intake to the incidence of coronary heart disease,” citing concerns that it would be “socially undesirable.” In fact, the data showed a clear benefit of moderate alcohol consumption, since confirmed in multiple studies.

What Framingham revealed was a J-shaped curve of alcohol vs. relative risk, a pattern consistently repeated in analyses of wine drinking and a range of age-related diseases. Plotting average daily consumption versus odds ratio, incidence drops as compared to teetotalers, then rises again crossing the abscissa at somewhere between three and five drinks, increasing rapidly above that. Moderate (healthy) drinking is therefore defined as the lowest point on the curve, which may be as much as 40 percent below the baseline defined by nondrinkers. This generally translates to one or two 5-ounce glasses of wine daily for a woman, and two to three for men.

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So while the benefits of moderate alcohol consumption are reasonably well-established, the question of a special role for red wine is what prompted the French paradox hypothesis. Epidemiologic surveys have tended to show a greater benefits for red wine in a range of conditions, while the role of alcohol seems limited to heart health (via elevation of HDL and cyclo-oxygenase inhibition). Large-scale surveys of lifestyle factors and Alzheimer's disease have all found regular wine consumption a defining characteristic of the lowest risk group. Diabetes, overall cancer risk, osteoporosis and other age-related diseases all occur at lower rates among moderate drinkers of red wine, and on average they outlive non-drinkers by about five years.

Certainly the habit of moderate regular wine consumption is to some degree a marker for a healthy lifestyle, though available data indicates that wine drinking is an independent variable. Is there something unique in red wine to explain this? Attention in the 1990's turned to polyphenol antioxidants, in particular a phytoalexin (botanical antimicrobial) known as trans-resveratrol. In vitro studies on resveratrol find correlates to epidemiologic patterns, with specific properties to explain the observed benefits of wine drinking. One example is anti-cancer activity via induction of apoptosis, suppression of angiogenesis, and down-regulation of cell activation pathways at the epigenetic level. Anti-Alzheimer's potential has been attributed to inhibition of beta-amyloid plaque formation and protection of neurons from oxidative insult. Selective estrogen receptor modulation may impart osteoporosis protection by way of resveratrol's phytoestrogenic properties.

Anti-aging research was given a boost with a 2003 report in Nature that resveratrol is a unique activator of epigenetic enzymes called sirtuins, thereby extending replicative lifespan in primitive organisms. Sirtuins are the basis for a well-known lifespan-extension phenomenon associated with severe caloric restriction, by altering mitochondrial metabolic pathways. Glaxo's Sirtris is developing resveratrol analogues targeting diabetes and cancer, with the hope of lifespan extension as an added benefit. However, debate has recently resurfaced as to the testing methodology used to assay sirtuin activation, and much remains to be proven.

Meanwhile, resveratrol supplements flood the market, promising "all the benefits of wine without the alcohol" and other claims. However, resveratrol levels in wine are too low to explain the observed epidemiologic patterns, and the bioavailability of resveratrol is low regardless of source. Clinical trials are all but nonexistent for these supplements. The family of wine polyphenols is complex, and one prominent researcher, Roger Corder, believes the French paradox

is entirely attributable to oligomeric proanthocyanidins from seeds of a specific wine grape called Tannat. Most wine polyphenols derive from the skins, where they are manufactured in response to stress, and extracted during fermentation. (This is why table grapes and grape juice have much lower levels, in addition to high sugar content.)

In any case, benefits of wine-derived supplements and pharmaceuticals remain speculative, despite the potential for breakthrough anti-aging therapies that may be in the offing. Meanwhile, populations with traditional lifestyles defined by consistent patterns of drinking have all but vanished, making current epidemiologic studies on the relationship of drinking and disease more difficult to decipher. A Lancet article from 1979 found a clear inverse correlation of per capita wine consumption by country and heart disease and the authors concluded that "if wine is ever found to contain a constituent protective against ischemic heart disease then we consider it almost a sacrilege that this constituent should be isolated. The medicine is already in a highly palatable form." Though we know a lot more now about these constituents today, that advice still rings true. ■

*Disclaimer: The author receives royalties from his book Age Gets Better with Wine, published by The Wine Appreciation Guild, South San Francisco.*

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