The Marcia Wilkinson Lecture

2009

Has headache any purpose?

Richard Peatfield.

I feel enormously privileged to have been asked to give the Marcia Wilkinson lecture, particularly as I know Marcia personally and she was one of the two examiners for my degree of MD at Cambridge in 1982. It gave me great pleasure to act as an MD examiner myself for Marcia's last student, Anne MacGregor, who I am pleased to see is in the audience this afternoon.

I thought I would get in the mood for this lecture on the train by reading Marcia's 1967 book on cervical spondylosis (1), which she wrote with the late Lord Brain, perhaps the most distinguished neurologist of his generation. It is certainly a book well worth a read even after 42 years.

It is also certainly a privilege not to have one's thoughts surveyed by referees! This lecture is, therefore, offered not in the spirit of Archimedes and his bath, but in the hope that someone will be either inspired or annoyed enough to prove me wrong.

Is having migraine a biological advantage?

Many of you will know that there is a marked overlap between the distribution of the sickle cell gene among Africans and the distribution of *Plasmodium falciparum* malaria (Figure 1) (2), and there is now very strong evidence that the heterozygous sickle cell trait confers some advantage in malaria, which (in population terms) outweighs the disadvantage of the minority with homozygous sickle cell anaemia, whose life expectancy is greatly shortened. I wondered by analogy if there were reasons why migraine (which is a genetic condition) is maintained in the population gene pool in every country in the world.

Protection From Information Overload

Jean Schoenen from Liege in Belgium has published many papers on reflex habituation in migraine patients. He has shown that the nociceptive blink reflex habituates rapidly in normal subjects without a family history of migraine but fails to do so in patients with migraine, or indeed in patients without migraine who have migrainous relatives (3). This led Schoenen and his colleagues to speculate that migraineurs are vulnerable to ‘information overload’ and perhaps less capable of

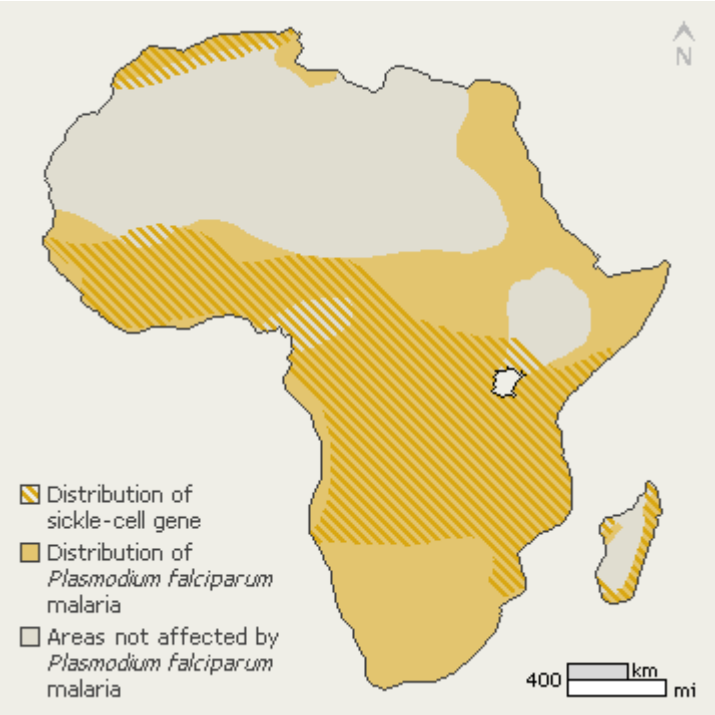

Figure 1 - **Malaria and Sickle-Cell Trait**
http://encarta.msn.com/media_461546922/malaria_and_sickle-cell_trait.html

dealing with sensory inputs (4). I must say that I find it difficult to believe this confers advantage on migraine sufferers; it is all very well being able to pay attention to lots of things at the same time but surely the essence of the human brain is to concentrate on things that are actually important. It is difficult to avoid the conclusion that Schoenen's observations, which although robust enough, are actually a consequence of the attacks rather than the cause of them.

Benefit of incessant activity

There is, of course, ample evidence that headache is a parasympathetic phenomenon. Headache is particularly prone to strike when a patient is relaxing after a period of activity. Many of these ideas lead back to Marcia Wilkinson herself, who wrote a paper entitled "*Analysis of symptoms of patients with headache and their response to treatment with ergot derivatives*" (5). Much of this paper is concerned with the pharmacology of a drug now considered almost obsolete but the paper is also known for one of the first tables (Figure 2) showing that migraine is more common on Saturdays than on other days of the week. Attacks seem to become more prevalent on Thursdays before settling on Fridays, with a much greater peak on Saturdays before reducing on Sundays. The argument, of course, is that most of us relax on a Saturday - we get up later and have a much less structured day.

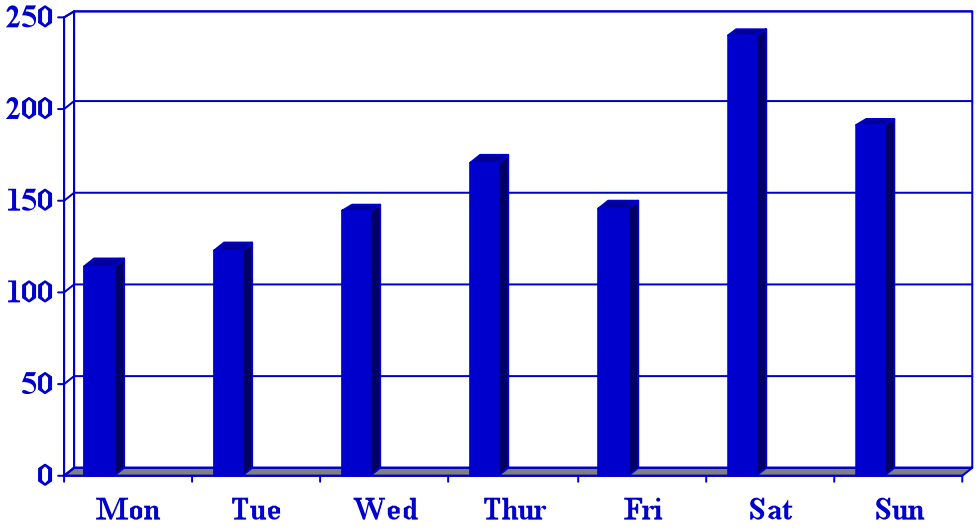

Figure 2 - Frequency of migraine attacks on different days of the week (*from* Reference 5)

In Table 1, I list evidence for sympathetic hypofunction in migraine, taken from the review by Steven Peroutka (6). Noradrenaline levels are lower, with a relatively blunted increase in blood pressure on standing but yet some receptor hypersensitivity to noradrenaline. Occasional patients have a mild Horner's syndrome and comparable findings in respect of the pupillary response. This, of course, fits in well with the elegant experiments done by Peter Goadsby and his colleagues on experimental animals when he was still in Australia, which showed that nervous control of the blood vessels in the dura and scalp has an efferent parasympathetic arm, which leaves the brainstem in the VIIth nerve before passing into the pterygopalatine ganglion, and then on autonomic nerve fibres towards the blood vessels (Figure 3) (7). The afferent arm, of course, is trigeminal and this is the pathway through which patients feel headache. It is of interest that there is parasympathetic innervation only to the blood vessels of the head, the neck and the pelvis, which are the principal sites of pain in the apparent absence of pathology.

- Lower plasma noradrenaline levels than controls.
- Normal increase on standing, but levels when upright remain lower than controls.
- Receptor supersensitivity to injections of noradrenaline lead to more a prolonged increase in blood pressure
- Mild orthostatic hypotension. Dizziness.
- Impaired increase in BP during isometric exercise
- Occasional mild Horner's syndrome.
- Supersensitivity to sympathomimetic amines
- Impaired pupillary response to noradrenaline releasing agents (Fenfluamine, Reserpine)

Table 1 – Evidence for sympathetic hypofunction in migraine (*from* Reference 6)

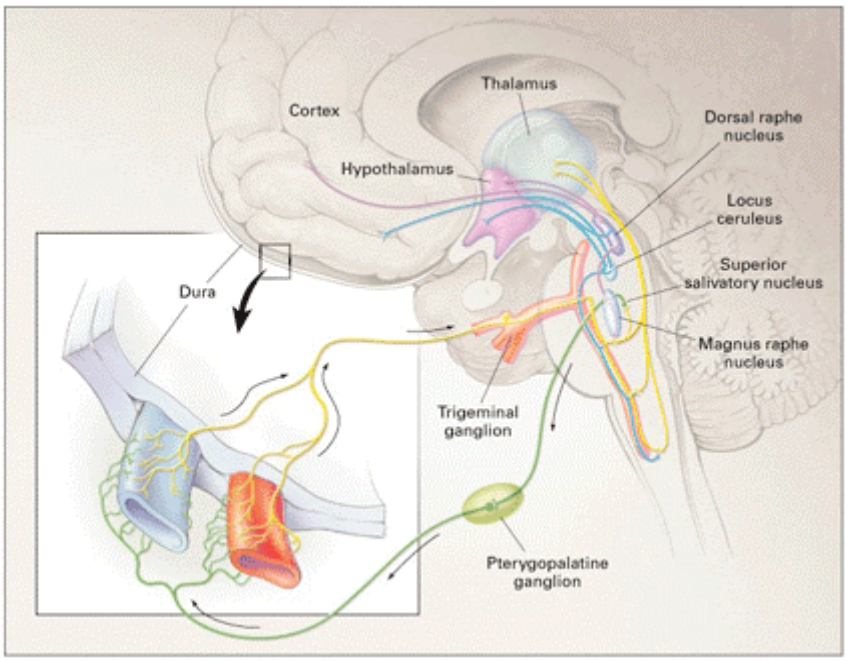

Figure 3 - Autonomic wiring in migraine (from reference 7)

This topic was a great interest to Harold Wolff, who must still be considered to the original pioneer of headache research. In his 1948 textbook on headache, he gave details of what he called the "migrainous personality"(8). He used a wide variety of adjectives including “stubbornness and inflexibility, obstinacy, orderliness, perfectionism, an unusually ambitious driving personality and the loss of the ability to feel tired”. Migrainous adults certainly have difficulty delegating, preferring to do many tasks themselves. Children tend to be very obedient, well-mannered and conscientious, "taking good care of their toys." I have to say that these comments are a synopsis of 30 pages of the book and that he does acknowledge the concept of "let down headache." Wolff argued that the reason why patients have migraine is because of their inflexible personality. I wonder if this is in fact the reverse of the truth and that migraineurs find through bitter experience over many years that incessant activity will keep the headache at bay and that they cannot afford to relax! On balance of course, employers are going to be impressed with this kind of individual, even if he/she is absent for one or more days each month.

Moderate Drinking of Alcohol

My family and I often spend our holidays in continental Europe, including Holland and Belgium. It is notable that in most of these countries, there is a thriving cafe culture, where well-behaved people sit at pavement tables drinking wine and beer in relatively modest quantities, enjoying the sunshine. The British, and by this I mean not only our football supporters, have behaved differently for centuries. St Boniface, in a message from in the 8th Century AD to Cuthbert, the Archbishop of Canterbury, reported how "in your diocese, the vice of drunkenness is too frequent. This is an evil peculiar to pagans and to our race. Neither the Franks nor the Gauls nor the Lombards nor the Romans nor the Greeks commit it" (9). It would appear, then, that drunken hooliganism is not a new feature in the 21st century! We are reminded of Hogarth's

famous print 'Gin Lane' (Figure 4) showing the evils of alcohol in a stylised dissolute London street. There is no doubt that this print had an immediate impact, as in the same year it was published Parliament passed the Gin Act, regulating the sale of alcohol by imposing a heavy duty, which soon reduced consumption to far more reasonable levels. Drunkenness was soon under much better control.

Figure 4 - Hogarth's *Gin Lane* 1822

Alcohol consumption in Europe seems relatively constant - indeed there is surprisingly low consumption in Norway, Sweden, and Poland, with the highest consumption in Germany, France, Spain, Ireland and Czech Republic. Britain, Holland, Belgium, Switzerland and Italy are somewhere in the middle (Figure 5) (10). There is a recognized association between alcohol drinking and food in many countries in Europe, most notably in Italy, Portugal and France, whereas the Irish, the Dutch, the Finns and the British tend to drink alcohol largely on its own, rather than in the context of a restaurant or home meal. The distribution of binge drinking in Europe is very different, with much higher levels of binge drinking in Norway, Sweden, Denmark, and the British Isles, including Ireland, as well as in Holland and Belgium, and relatively low levels in both Spain and Germany (Figure 6). This picture is almost exactly paralleled by the taxation levels of alcohol in different European countries (Figure 7) (10). This is at its highest in Norway but is also high in the other Scandinavian countries, the Baltic Republics, Poland and the British Isles, and very low in Germany, France, and Spain. There is a well recognised inverse correlation between alcohol consumption and the price of alcohol in Britain over the last 40 years. Prices are high when governments consider this necessary to curtail excessive drinking.

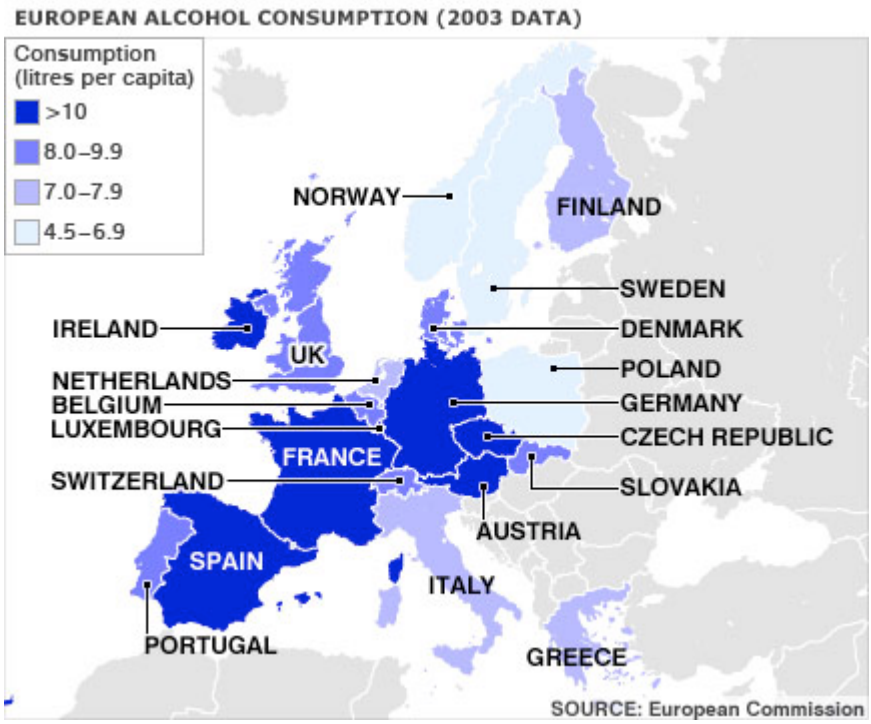

Figure 6

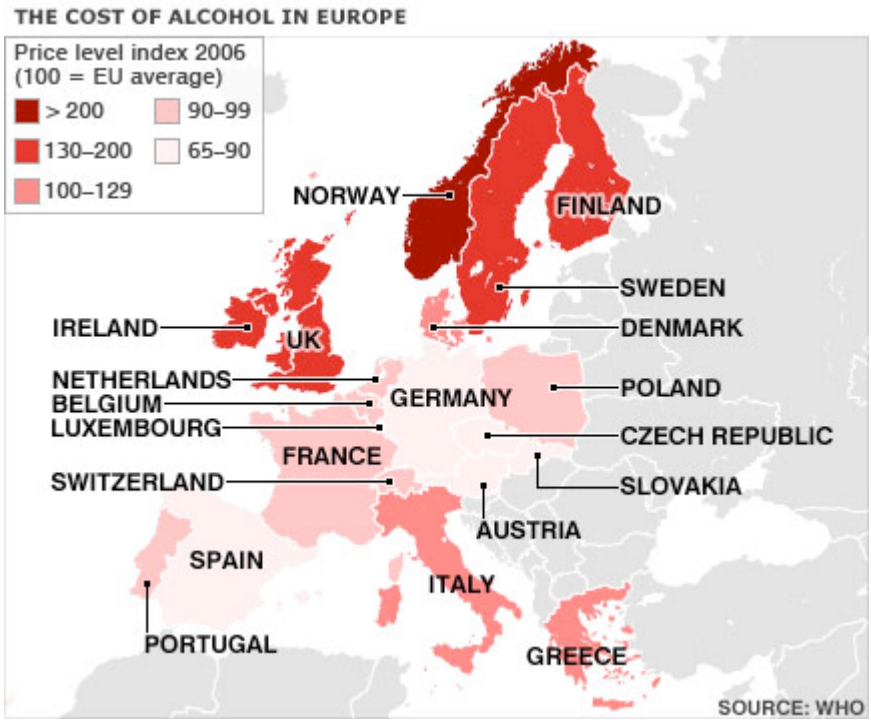

Figure 7

My experience in the Princess Margaret Migraine Clinic (11) is that 20 to 25% of migraine patients are unduly sensitive to alcohol in some form, though most say they would develop headache after relatively large quantities of alcohol. The threshold is around half a bottle of wine at one sitting. There is known to be a higher prevalence of alcoholism in the sons of alcoholic parents, even if they are adopted into 'non-alcoholic' households, and there is a lot of evidence that alcoholics are disproportionately likely to seek solace in alcohol for their headaches rather than the Aspirin, water and bedrest that come to mind to the majority of the population. There seems a little doubt that there are two kinds of "hangover symptoms." (Table 2). The majority of the population have thirst, headache, malaise and a little nausea, and seek relief from water. There are some people who developed tinnitus, pruritus, tremor, nystagmus, hallucinations and anxiety without headache, and they seem to gain much greater relief from further alcohol, sometimes known as "the hair of the dog." It is from this that the distinction between so called 'problem drinkers' and so called 'addicted alcoholics' has been derived. Problem drinkers present to doctors with liver or pancreatic disease. They often drink in binges, are able to abstain, and have a wide range of other dependencies. In contrast, addicted alcoholics seek detoxification from a psychiatrist and have a craving for alcohol, with high dependency scores.

	Typical	**Atypical**
	Thirst	Tinnitus
	Headache	Pruritus
	Malaise	Tremor
	Nystagmus	
	?Nausea	Hallucinations
		Anxiety
		Guilt
		No headache
Relief by	Water	Alcohol

Table 2- Hangover symptoms

Some years ago, together with my colleagues Dr Charles Tannock and Dr Roger Bullock, I conducted a small survey of headache in patients exhibiting alcohol abuse behaviours categorised as follows (12)

1. Patients seeking detoxification
2. Medical admissions with alcohol induced complications
3. Social drinkers attending in the Accident and Emergency Department at Charing Cross Hospital.

The patients completed a headache questionnaire (Table 3). All were Caucasian males aged between 30 and 65. The first two groups drank a minimum of 50 units of alcohol weekly, and the social drinkers 10 to 30 units.

1. Have you had a headache in the last year?
2. Have you ever had a headache in your life?
3. Have you ever had a headache after drinking alcohol?
4. Have you ever had a spontaneous headache?
5. Do you gain relief from hangover headache by taking further alcohol?

Table 3 –. Questions to patients in each of the three categories

There were 12 patients in the 'medical admissions' category, 19 in the 'detoxification' group and 16 'social drinkers', who comprised the control group. Virtually all the detoxification patients had had a headache in the past year (Figure 10), and usually had headache induced by alcohol, with most of them having spontaneous headaches from which they gained relief by drinking further alcohol. In contrast, the medical patients hardly ever had headaches and had a relatively low prevalence even of spontaneous headache. Only one of the 12 gained relief from alcohol. The control subjects all had spontaneous headaches and the majority had headache induced by alcohol; only one gained relief from alcohol.

	Detoxification	**Medical**	**Controls**
n	19	12	16
Headache			
In past year	17	3	12
In life	17	5	16
From alcohol	16	1	12
Spontaneous	8	5	16
Relief by alcohol	16	1	1

Table 4 – Survey of headache prevalence in relation to alcohol use behaviour. Results from questionnaire

We concluded that the problem drinkers (with liver failure) had a relatively low prevalence of headache and seem quite unable to control their drinking. The prevalence of headache among the addicted subjects was comparable to that in the control subjects (and therefore we assume the general population); yet they resorted to alcohol to ameliorate their headaches. It has been speculated that the chemical combination of acetaldehyde molecules (from alcohol) and catecholamines can

synthesise tetrahydroisoquinolines, which interact with opioid receptors to produce a pleasurable sensation (13). We have to wonder if this phenomenon is more powerful than the deterrent effect of the alcohol and might lead the patient to drink excessively even in the presence of a conventional headache-type hangover.

Conclusions

I wonder, therefore, if some headache is actually good for you! I think the risk of headache probably controls the drinking habits of the majority of the population; most people are deterred from excess by the development of headache, particularly after they have been drinking for a few years. I have to say, as an aside, that I have grave doubts whether hangover free alcoholic drinks are such a good idea after all.

I also think that migrainous subjects are particularly conscientious and that any weakening of this resolve can immediately lead to a headache. Migraineurs are particularly valued in the workplace as a result. I do not feel that the inability to habituate over stimulation can be anything but a disadvantage and I doubt its relevance in this particular context.

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