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GUEST EDITORIAL

Vascular depression: myth or reality?

The Oxford English Dictionary defines myth as "a traditional story, typically involving supernatural beings or forces, which embodies and provides an explanation, aetiology, or justification for something such as the early history of a society, a religious belief or ritual, or a natural phenomenon" or "a widespread but untrue or erroneous story or belief; a widely held misconception; a misrepresentation of the truth." Myths are attractive because they offer plausible explanations of phenomena that we could not otherwise understand, and they become powerful cornerstones of society when cultural leaders embrace them, thereby further propagating the myth, blurring the boundaries between the imaginary and reality.

One might assume that science, in its supposed objectivity, would never be tempted by mythological constructs, but that is not the case. In fact, myths are often the starting point of science. Scientific experiments are based on theories, from which working hypotheses are derived. However, theories can be passionately embraced without conclusive experimental proof, and that is when we risk allowing them to become scientific myths. The history of medicine is littered with examples of scientific myths. In their most benign form, they contribute to create false hopes and to waste of resources; in some instances, however, they are associated with significant costs to individuals and society. The story of Dr. Henry Aloysius Cotton is a tragic illustration of the damage scientific myths can cause (Scull, 1987).

Cotton was a prominent American psychiatrist working during the first part of the twentieth century. He was mentored by Adolf Meyer at Johns Hopkins University who, having been impressed by his intellectual prowess, organized a postgraduate attachment for him at the renowned clinics and laboratories of Emil Kraepelin and Alois Alzheimer in Munich in the early 1900s. On his return to America he was appointed, at the early age of 31 years, as superintendent of the New Jersey State Hospital in Trenton, where he worked from 1907 until his death in 1933. He had a highly successful career and received many awards and accolades for his innovative and groundbreaking work with the "insane." His work influenced the practice of psychiatry in America and Europe, with many health services adopting his theory of the septic origin of mental illness.

Cotton observed that almost all patients living in mental health asylums had infected teeth. He argued that the toxins associated with those infections were the underlying cause of mental illness and moved to extract the infected teeth of his patients. As this intervention was not always successful, he reasoned that hidden foci of infection were lying dormant elsewhere. This led to the progressive removal of all teeth (over 10,000 extractions between 1919 and

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1921), tonsils (90% of patients) and even colectomies (20% of patients). The 43% mortality associated with the last was plausibly attributed by Cotton to the high "virulence" of the underlying infection. Nonetheless, Cotton claimed that his septic treatment cured 85% of patients and concluded that septic toxins had already caused irreversible brain damage amongst those who failed to improve (Scull, 1987). Not surprisingly, he went on to suggest that prevention was the key in avoiding mental health morbidity (i.e. preventive extraction of teeth and tonsils), and oversaw the introduction of a preventive program for those he considered to be at risk (i.e. young people prone to delinquent behavior). Even his two sons were stripped of their teeth as a prophylactic measure prior to their enrolment at Princeton University – both committed suicide some years later (Scull, 2005).

An independent review of Trenton Hospital carried out by Phyllis Greenacre in the 1920s showed that Cotton's claims were preposterously out of accord with the facts (Scull, 1987), but the report was suppressed, and thousands of people continued to be maimed or killed well into the 1960s as a direct result of Cotton's legacy (Scull, 2005).

Cotton's story may seem unusual, but similarly unusual theories are more common than we might be willing to admit. Some have even been awarded Nobel Prizes in Physiology or Medicine. Julius Wagner-Jauregg, from the University of Vienna, received the prize in 1927 "for his discovery of the therapeutic value of malaria inoculation in the treatment of dementia paralytica," and Antonio Egas-Moniz, from the University of Lisbon, became a Nobel laureate in 1949 "for his discovery of the therapeutic value of leucotomy in certain psychoses" (http://nobelprize.org/nobel_prizes/medicine/).

But new knowledge can only be acquired through the systematic evaluation of new ideas, regardless of how odd they might seem at first. Marshall and Warren revolutionized psychosomatic medicine and gastroenterology by demonstrating that most cases of gastritis and peptic ulcer are caused by bacterium infection. Their initial observation was ridiculed (Marshall and Warren, 1984), but later randomized trials confirmed that *Helicobacter pylori* was indeed the cause of gastritis and peptic ulcer (Marshall *et al.*, 1988; Hentschel *et al.*, 1993). Millions of people worldwide continue to benefit to this day from this new knowledge.

What is vascular depression?

Since its introduction 10 years ago, the concept of "vascular depression" (VaD) has gained wide acceptance amongst clinicians and researchers working with older adults and, at the time of writing (September 2007), approximately 6000 papers were listed on PubMed under this heading. In their seminal paper published in 1997, Alexopoulos and colleagues argued "that cerebrovascular disease can predispose, precipitate, or perpetuate a depressive syndrome in many elderly patients. . ." and introduced the term "vascular depression" "because it is broad and encompasses entities with diverse pathogenetic mechanisms." They acknowledged that "direct testing of the vascular depression hypothesis is

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impossible because the mechanisms of depression are unknown," but went on to describe the "cardinal" and "secondary" features of VaD.The cardinal features, which should be present in all patients, included:

- depression onset after the age of 65 years or change in the course of depression after the onset of vascular disease in patients with early-onset depression (development of more frequent and persistent episodes);
- clinical or laboratory evidence of vascular disease or vascular risk factors, such as history of stroke or transient ischemic attack, focal neurological signs, atrial fibrillation, angina, history of myocardial infarction, carotid bruit, hypertension and hyperlipidemia. The laboratory evidence mentioned included significant white matter hyperintensities, infarcts, or evidence of carotid occlusion or stenosis of the Willis circle arteries.

Secondary features of VaD, which should be present in most but not necessarily all patients, were:

- cognitive impairment involving executive functions with/without deficits of other cognitive domains;
- psychomotor retardation;
- limited depressive ideation;
- poor insight;
- disability;
- absence of family history of depression.

Should we embrace the concept of VaD?

One of the stated aims of Alexopoulos and colleagues (1997) was to provide a theoretical framework to encourage "studies of the epidemiology, clinical presentation, outcomes, pathogenesis, and treatment of a large subgroup of geriatric patients with depression." Undoubtedly, their wish was granted. Numerous studies have been carried out over the past 10 years on the epidemiology of depression associated with cerebrovascular disease (e.g. Hackett *et al.*, 2005), its clinical features (e.g. Naarding *et al.*, 2007), pathogenesis (e.g. Carson *et al.*, 2000; Thomas *et al.*, 2002; Almeida *et al.*, 2007), course (O'Brien *et al.*, 1998) and treatment (e.g. Almeida *et al.*, 2006). But how valid is the VaD construct?

By definition, any person who develops depression after the age of 65 years will have vascular depression if they have a positive history of cardiovascular events or risk factors. This is a rather arbitrary and problematic starting point. The prevalence of cardiovascular diseases increases exponentially with increasing age, with nearly 60% of older Australians having heart, stroke or other vascular illnesses (Australian Institute of Health and Welfare (AIHW), 2004). In addition, 90% of adults (not necessarily old) have at least one risk factor for cardiovascular disease (AIHW, 2004). For example, approximately 70% of Australians aged

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65 years or over have hypertension and a similar proportion have high blood cholesterol (AIHW, 2004). Moreover, data from the Rotterdam Study showed that only 5% of a community representative sample of 1077 adults aged 60 to 90 years did not have periventricular or subcortical white matter lesions on magnetic resonance imaging scanning (de Leeuw *et al.*, 2001). In other words, very few people who develop depression in later life would fail to meet criteria for vascular depression. Or as Cotton would put it, all insane people have infected teeth!

Epidemiological evidence is also inconsistent with the concept of vascular depression. As previously stated, the prevalence of cardiovascular diseases increases exponentially with increasing age (AIHW, 2004), but the prevalence of depression does not. On the contrary, current evidence suggests that depression becomes less prevalent with increasing age (Australian Bureau of Statistics, 1998; Kessler *et al.*, 2003). Surely, if cardiovascular disease predisposes, precipitates and perpetuates a depressive episode, then we should be seeing a growing epidemic of increasingly more severe and difficult to treat depression in our aging developed societies. Fortunately, this is not the case.

A recent investigation showed that only a small proportion of cases of depression could be attributed to cardiovascular risk factors and diseases in a community sample of 4204 men aged 70 years or over (Almeida *et al.*, 2007). Hypertension and hypercholesterolemia, key risk factors for cardiovascular disease, made no obvious contribution to the presence of depression in the sample. The population attributable fraction of depression associated with myocardial infarction was not significant, whilst stroke accounted for 3–13% of cases. High total plasma homocysteine ($\geq$ 15 μmol/L) was associated with the highest population attributable fraction (15%), but the vast majority of cases of depression could not be adequately explained by the presence of angina, myocardial infarction, stroke, diabetes, smoking, total plasma homocysteine, cholesterol or triglycerides.

There is also limited evidence that treatment of cardiovascular risk factors or diseases changes the incidence or the course of depression. For example, the frequency and severity of depressive symptoms is positively associated with the concentration of total plasma homocysteine (Tiemeier *et al.,* 2002; Almeida *et al.,* 2004; Almeida *et al.,* 2007), which is a well-established risk factor for cardiovascular events (Wald *et al.*, 2002). Treatment with vitamins B12, B6 and folate reduces total plasma homocysteine by more than 30% (Flicker *et al.*, 2006), but has a questionable effect on the remission of depressive symptoms (Taylor *et al.*, 2003). Preliminary results from a randomized placebo-controlled trial of 299 men aged 75 years or over showed that treatment with 400 μg B12 + 2 mg folic acid + 25 mg B6 is no better than placebo at reducing the severity of depression or the incidence of clinically significant depressive symptoms over a period of two years (Ford *et al.,* unpublished data). Even more concerning was the NORVIT trial's observation that treatment with B vitamins increased, rather than decreased, the occurrence of cardiovascular events (Bonaa *et al.*, 2006). In fact, there is no evidence at present that the adequate management of risk factors for cardiovascular disease, such as hypertension or hyperlipidemia, decreases the incidence of depression or the severity of existing depressive symptoms (Stewart

et al., 2000; Fletcher *et al.*, 2002; Ried *et al.*, 2005), as predicted by the VaD hypothesis.

The usefulness of the "secondary features" of VaD, as proposed by Alexopoulos and colleagues (1997), is also questionable. A recent analysis of two large Dutch cohorts of older adults was unable to show an association between anhedonia/psychomotor retardation and a large list of cardiovascular risk factors and diseases (history of stroke or myocardial infarction, smoking, blood pressure, total cholesterol, body mass index, diabetes, peripheral arterial disease, carotid intima media thickness, carotid plaques, aortic calcifications) (Naarding *et al.*, 2007). Not surprisingly, loss of energy was more frequent amongst those with prior history of myocardial infarction or peripheral arterial disease (Naarding *et al.*, 2007).

Depression in later life has been associated with a relative loss of frontal lobe tissue and symmetry (Almeida *et al.*, 2003), and with executive dysfunction (Beats *et al.*, 1996) (deficits of executive function are supposedly secondary features of VaD). Previous studies had assumed that these changes were secondary to concomitant subcortical vascular disease (Almeida *et al.*, 2003), but data from the VITA Study suggests this is unlikely. Rainer *et al.* (2006) examined 606 adults aged 75–76 years, of whom 51 had late onset depression. They compared these subjects with 204 people matched for age, gender, education and area of residence, and found that the groups did not differ in the frequency of magnetic resonance images of deep and periventricular white matter hyperintensities, lacunes and infarcts. The authors concluded that there was no evidence that cerebrovascular disease had played a role in the clinical presentation of their subjects and argued that their findings were not consistent with the VaD hypothesis.

Conclusion

Two recent systematic reviews showed that up to one in three people develop clinically significant depressive symptoms after a stroke (Hackett *et al.*, 2005) or myocardial infarction (Thombs *et al.*, 2006). These findings are consistent with cardiovascular disease having a role in predisposing, precipitating and perpetuating the symptoms of depression in later life. However, one should not overlook the fact that the prevalence of depression is equally increased in numerous other chronic medical conditions, such as cancer, neurological disorders (for example, Parkinson's disease), rheumatological illnesses and chronic obstructive pulmonary disease, among others (Dickens *et al.*, 2002; Krishnan *et al.*, 2002; Norwood, 2006).

Epidemiological data show that the prevalence of cardiovascular diseases increases exponentially with increasing age, whereas the prevalence of depression declines. The results from observational studies further indicate that cardiovascular diseases and associated risk factors play a limited role in the expression of depression in older age, and secondary analyses of randomized trials designed to manage hypertension, hyperlipidemia and high

plasma homocysteine found that treatment does not reduce the frequency of clinically significant depressive symptoms. These findings do not mean that cardiovascular diseases play no role at all in the pathogenesis of depression, but strongly suggest that they are not the sole or, perhaps, even the most important factors in predisposing, precipitating and perpetuating depression later in life.

Clinicians and researchers can now use modern imaging techniques to "see vascular lesions" in the brains of older people with depression. We can count those lesions, accurately measure their volume and determine their precise location. We can use sophisticated statistical analyses to determine how those lesions correlate with various measures of mental function and cardiovascular risk factors, and feel reassured when some of our numerous tests confirm our predictions that vascular lesions are associated with depression. We can also measure patients' blood pressure, check their hearts and arteries, and even successfully manage risk factors such as diabetes, hypertension and hyperlipidemia. We have been empowered! But, after 10 years, has the vascular hypothesis truly improved our understanding and management of depression in later life?

In his acceptance speech on being awarded the 2005 Nobel Prize in Physiology or Medicine, Barry Marshall reminded us that "the greatest obstacle to knowledge is not ignorance; it is the illusion of knowledge."

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