International Psychogeriatrics, Vol. 15, Suppl. 1, 2003, pp. 7-10

Guest Editorial

Vascular Burden of the Brain

This supplementary issue of *International Psychogeriatrics*, titled "Vascular Burden of the Brain," is the product of a special meeting of the International Psychogeriatric Association (IPA), with involvement from Alzheimer's Disease International, the World Federation of Neurology Dementia Study Group, the United States Food and Drug Administration (FDA), and the European Commission for Pharmaceutical and Medicinal Compounds (CPMP). The meeting was held in Madrid in November 2001 and was a closed gathering of many leading international experts on various aspects of vascular brain disease. Attendees included basic scientists, psychiatrists, neurologists, epidemiologists, and neuroradiologists. This wealth of expertise, both from clinicians and scientists, emphasized the necessity for interdisciplinary research into vascular disorders of the brain that affect cognition and behavior. One aim of the meeting was to produce a position paper that summarized the current situation in this field, both highlighting recent advances and identifying important areas where further progress is required. This paper, entitled "Vascular Cognitive Impairment," has been published in *Lancet Neurology* (O'Brien et al., *Lancet Neurology*, February 2003, *2*, 11-20). This issue of *International Psychogeriatrics* contains the individual articles submitted by participants in the special IPA meeting in November 2001.

One of the main difficulties in this area, which is reflected in the title of this supplement, is current lack of consensus regarding the most appropriate terminology and diagnostic criteria to adopt. At the heart of this lies the still uncertain nature of the role that cerebrovascular pathology has, not only in the cognitive and noncognitive features seen in "classic" vascular dementia (VaD) and after stroke, but also the increasing role it is recognized to play in other areas, including "normal" aging, neurodegenerative disease, and hereditary vascular diseases. After much deliberation, and in order to avoid any a priori preconceptions that might limit progress or discussion, the term "Vascular Burden of the Brain" was adopted for the meeting. This recognized both the need to move forward from traditional, narrow views of VaD and sought to encompass the wider influence of vascular disease on cognition and to include cognitive impairments that fell short of meeting the criteria for dementia.

The content of the meeting included historical background and current concepts on diagnosis, pathophysiology, epidemiology, clinical phenomenology, and treatment. It was a sign of the huge strides that have been recently made in the treatment of dementia in general and vascular disease in particular that a significant part of the meeting was concerned with treatment. This included primary prevention, secondary prevention, symptomatic treatments, and therapies designed to slow progression. There was extensive discussion on trial design and regulatory issues, reflecting topics that would be extremely important in making further progress towards effective management of this patient group.

There was agreement that cerebrovascular disease is the second most common cause of acquired cognitive impairment and dementia. Historically, concepts of VaD were largely based on the infarct model, with the view that multiple cortical infarcts were needed to produce vascular ("multi-infarct") dementia. However, in recent years, the full spectrum of vascular pathologies has been acknowledged, most particularly the very important contribution of small-vessel disease and subcortical pathology and the influence of vascular pathology on other disease; for example, the known modifying effects of vascular pathology on the clinical expression of AD. The meeting advocated use of the term "vascular cognitive impairment" (VCI) as a way of broadening the concept and also recognizing that many cases of cognitive impairment due to cerebrovascular disease do not fulfill currently accepted definitions for dementia which, being heavily based on the Alzheimer's model, require deficits in memory as a prerequisite. The term "vascular dementia" was reserved for VCI cases that met traditional criteria for dementia, and the term "vascular mild cognitive impairment" (vMCI) for those with mild cognitive impairment with a presumed vascular basis.

Currently proposed diagnostic criteria for VaD were recognized as being an advance on previous formulations, though the currently proposed criteria are clearly not interchangeable. Criteria such as the National Institute of Neurological Disorders and Stroke and the Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS/AIREN) criteria for probable and possible VaD and the proposed criteria for subcortical ischemic vascular disease and dementia (SIVD) are appropriate for research studies, including clinical trials, but they require further validation. One major shortcoming of all current criteria is that they do not acknowledge mixed dementias, arguably the most common forms seen in the general population. There are no accepted criteria for cases of VCI which fall short of dementia. Important subtypes of VCI identified included post-stroke dementia, subcortical ischemic vascular disease and dementia, single and multi-infarct dementia, and hereditary vascular dementias. Increasing overlap between VCI and AD was illustrated by the many risk factors that are now known to be common to both (hypertension, atherosclerosis, ischemic heart disease, raised homocysteine levels, smoking, diabetes mellitus, hypercholesterolemia) and the additive effects of both pathologies on the clinical expression of cognitive impairment. The characteristic cognitive profile of VCI was identified, involving relatively preserved memory with predominant

impairments in attention, psychomotor speed, and executive functioning. Despite the term VCI, the great importance of noncognitive features was highlighted, particularly depression, apathy, and psychosis. There is also a wider relationship between vascular disease and depression, as illustrated by the concept of "vascular depression," which requires further study.

Although little is known about primary prevention in regard to VCI, there is clearly a wealth of knowledge about primary prevention of VaD in general. Secondary prevention (e.g., of subsequent cognitive decline after stroke) may be practical, as there have been major advances in acute stroke therapy with the advent of early thrombolysis, aspirin therapy, and specialist stroke services; these offer real advances over previous management. There are several well-established treatments for recurrent stroke prevention, including treatments for lowering the blood pressure, antiplatelet agents, warfarin (if indicated), and carotid endarterectomy (if indicated). Little, however, is known about therapies that may help slow the progression of vascular cognitive impairment (for example, modifying progression of white-matter changes). Early studies of symptomatic treatments in VaD were disappointing, but propentofylline and memantine have shown promising evidence of efficacy. Recently, evidence has become available that the cholinesterase inhibitors galantamine and donepezil may also be useful in those with VaD and mixed vascular dementia and AD; further studies are awaited with interest.

There was wide debate about future trial design and appropriate groups to target. It is important to note that trial designs and endpoints that have been developed for studies of AD are not necessarily applicable to various forms of VCI because of differences in cognitive profile, variability of rates of progression, and heterogeneity of underlying pathology. Target trials in VCI should ideally consist of homogeneous subgroups. The difficulty of assessing disease progression in those with VCI that falls short of dementia was an important issue, because such subjects are likely to be the focus of future clinical trials. An endpoint of "conversion" to VaD, paralleling the conversion to AD endpoint adopted for MCI studies, may be particularly inappropriate because of the uncertain and variable involvement of memory, as discussed earlier. Rates of progression of cognitive impairment may be more appropriate until validated surrogate markers (e.g., change in volumes of infarcts, white-matter lesions, or whole brain) are available for VCI. Outcomes should include cognitive and global function measures as well as activities of daily living (ADL) and assessment of noncognitive symptoms. Cognitive evaluations should focus on deficits known to be associated with VCI, and, to this end, the development of a vascular equivalent to the Alzheimer's Disease Assessment Scale–Cognitive subscale (ADAS-cog) (namely, VADAS-cog) has been an advance. In studies, it might be appropriate to include measures of declarative memory and other types of assessment (for example, hippocampal volume on MRI) to try to determine the presence and effect of concurrent Alzheimer pathology. A special consideration in trials of VCI includes accounting for the effect of comorbid disabilities on factors such as ADL (e.g., motor or sensory loss). While further validation of categories of vascular cognitive impairment

is undertaken, regulatory bodies such as FDA and CPMP currently accept the use of NINDS-AIREN criteria for the diagnosis of VaD for the purpose of trials addressing symptomatic treatment. Other defined populations likely to be recognized include subcortical ischemic vascular disease and dementia, and mixed Alzheimer and cerebrovascular disease.

In regard to AD, in recent years, it is clear that considerable advances have been made in terms of refining and validating diagnostic criteria, determining natural history, examining etiological factors, and undertaking rigorous clinical trials that, together, have led to effective therapies now being available and improved awareness of the disorder. From the evidence of the articles in this issue, it will be apparent that considerable research strides have been made along this path in regard to VCI, but it is also apparent that there is much more that needs to be done. That is the challenge for everyone working in the field of the Vascular Burden of the Brain.

John O'Brien
Professor of Old Age Psychiatry
Institute for Ageing and Health
Wolfson Research Centre
Newcastle General Hospital
Newcastle upon Tyne, UK

Barry Reisberg
William and Sylvia Silberstein Aging
and Dementia Research Center
NYU School of Medicine
New York, NY, US

Timo Erkinjuntti
Department of Neurology
University of Helsinki
Helsinki, Finland