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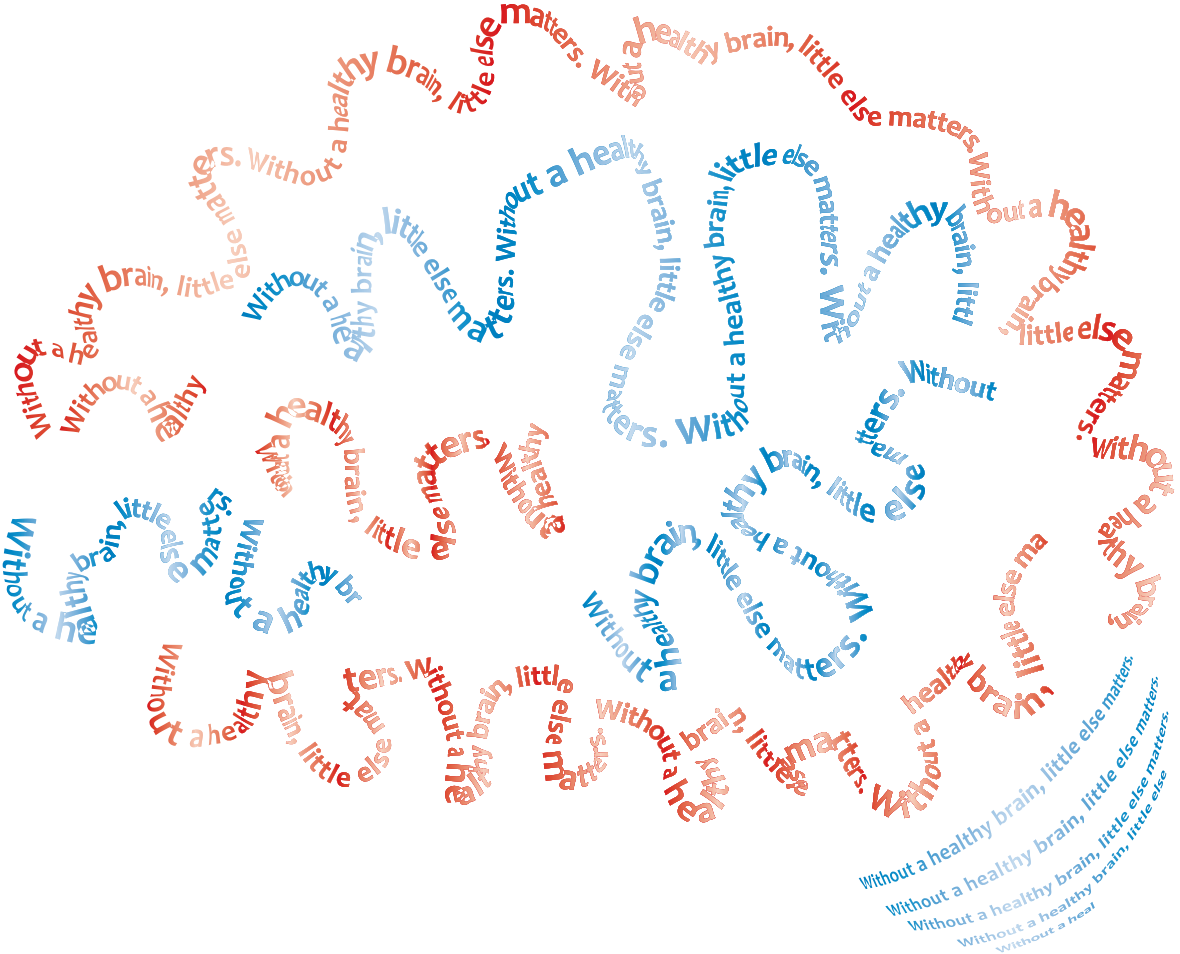
The Long Fuse:
silent strokes and insidious Alzheimer disease

VLADIMIR HACHINSKI



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Short Biography

Vladimir Hachinski, CM, MD, FRCPC, DSc, is Distinguished University Professor of Neurology and past Richard and Beryl Ivey Chair of the Department of Clinical Neurological Sciences, University of Western Ontario, London, Canada. He graduated with an MD from the University of Toronto and trained in internal medicine and neurology in Montreal and Toronto and in research in London, U.K., and Copenhagen, Denmark.

Dr. Hachinski's contributions include discovering the key role of the insula of the brain in cardiac complications of stroke including sudden death, crystallizing the concepts and coining the terms multi-infarct dementia, leuko-araiosis, vascular cognitive impairment and brain attack and devising the ischemic score that bears his name. He was the principal neurological investigator of the Canadian American Ticlopidine Study, the EC/IC Bypass Study and the North American Symptomatic Carotid Endarterectomy Trial. He was the Editor-in-Chief of the journal STROKE, the leading publication of this field from 2000-2010. He introduced 9 international editions and began a unique mentorship program for authors of developing countries. He received the Mihara Award of the International Stroke Society and the Willis Lecture Award of the American Heart Association. In 2008 he was named

to the Order of Canada, the country's highest award. In 2010 he received the Ontario Premier's Discovery Award in the Life Sciences for "ground breaking research on the relationship between stroke and Alzheimer disease" and most recently he was awarded the 2010 BIAL Merit Award in Medical Sciences for a monograph on "The Long Fuse: silent strokes and insidious Alzheimer disease".

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This monograph builds on the work of many colleagues, collaborators and students who are acknowledged by the co-authorship of papers and books. But many more have contributed, the indispensable people who make our hospitals, clinics and research laboratories function, and above all, our patients, inspirers, collaborators and ultimate beneficiaries of anything that we can achieve. I thank in particular, those with whom I have disagreed. They have made me think and work harder. In medicine we are very aware of Einstein's admonition; what we do not know is so much greater than what we know, that in the search for knowledge, we are more or less equally ignorant. So we must work collegially. Together we can do better.

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I Summary

One in three of us will end up with a stroke, dementia or both, unless we improve diagnosis, treatment and prevention.

Silent strokes are the commonest form of cerebrovascular disease and silent lesions, the most prevalent form of Alzheimer disease. When individuals with these "silent" lesions are examined, however, they often show subtle cognitive and physical deficits. Thus, "subclinical" may better describe this state. Since stroke and Alzheimer disease commonly occur together, share similar vascular risk factors and can interact, they can be best considered, treated and prevented together.

Risk factors have **momentum**, their extent multiplied by their duration. We need to discover the **pivotal points** at which risk translates into disease and discover when the processes become irreversible. We cannot simply move the diagnosis of Alzheimer disease to an earlier stage, i.e. mild cognitive impairment and hope that we can avert it. We must find out by studies the point of no return. We cannot afford the price of delay.

Lesions in the brain do not add up, they multiply. Vascular lesions decrease the threshold for Alzheimer disease. We can prevent strokes and should be able to delay Alzheimer disease. Moreover, our newly discovered amyloid connection between stroke and Alzheimer disease, gives hope that existing anti-amyloid and anti-inflammatory treatment given at pivotal points can slow or prevent Alzheimer disease.

If we are to succeed in stemming the anticipated tsunami of devastated brains, we need to act early, in an integrated and leveraged approach, focusing on vascular risk factors and preventing subclinical and overt strokes at the individual, community and population levels. If we do, available data suggest that we could prevent the majority of strokes and delay Alzheimer disease. Most strokes and Alzheimer disease have a long fuse. Let us find the burning fuse and extinguish it, before it harms the brain.

II The present and future danger

Without a healthy brain, little else matters.

The worst fate may not be death, but a faltering brain. And yet, one in three of us will suffer a stroke, dementia, or both[1] unless prevention improves. Among brain diseases, stroke and Alzheimer disease account for 67% of the world's[2] DALY's (disability adjusted life years) a combined measure of preventable death and disability. (Fig. 1)

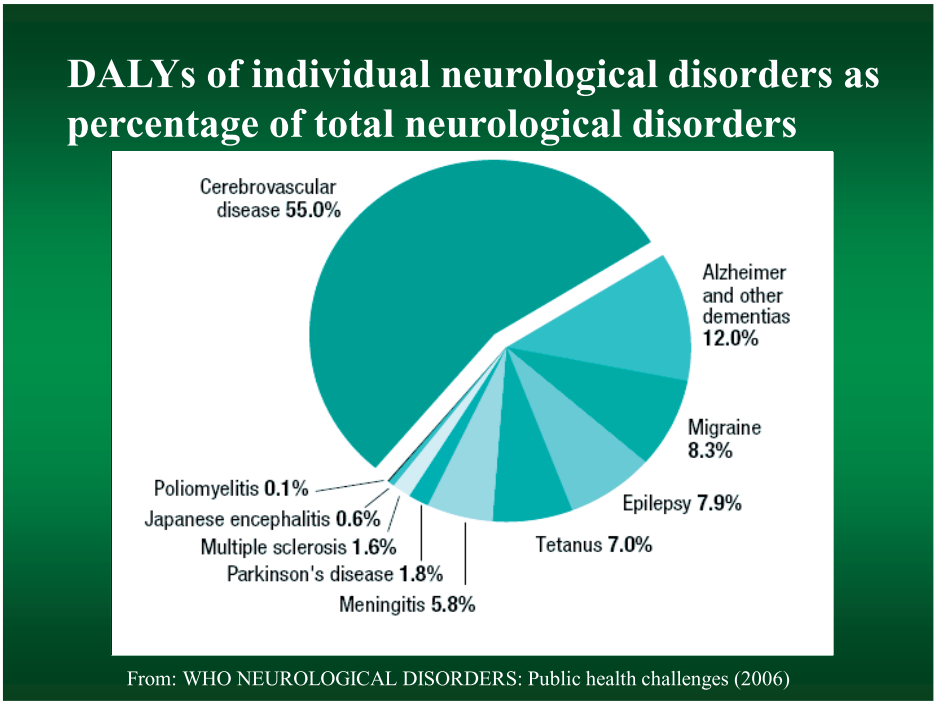

Figure 1: Two thirds of DALY's due to neurological disorders are attributable to cerebrovascular and Alzheimer disease

The human toll is immeasurable. We need more effective approaches if we are to stem the anticipated tsunami of devastated brains.[3,4]

Stroke and dementia often occur together, but are managed apart. 8% of Canadians over the age of 65 years have dementia and 8% have had a stroke. Among individuals having a stroke, 64% have some cognitive impairment

and among individuals with some cognitive impairment 25% have had a stroke. Moreover, for each individual with a stroke or dementia, two have some cognitive impairment short of dementia, (i.e. 17%).[5]

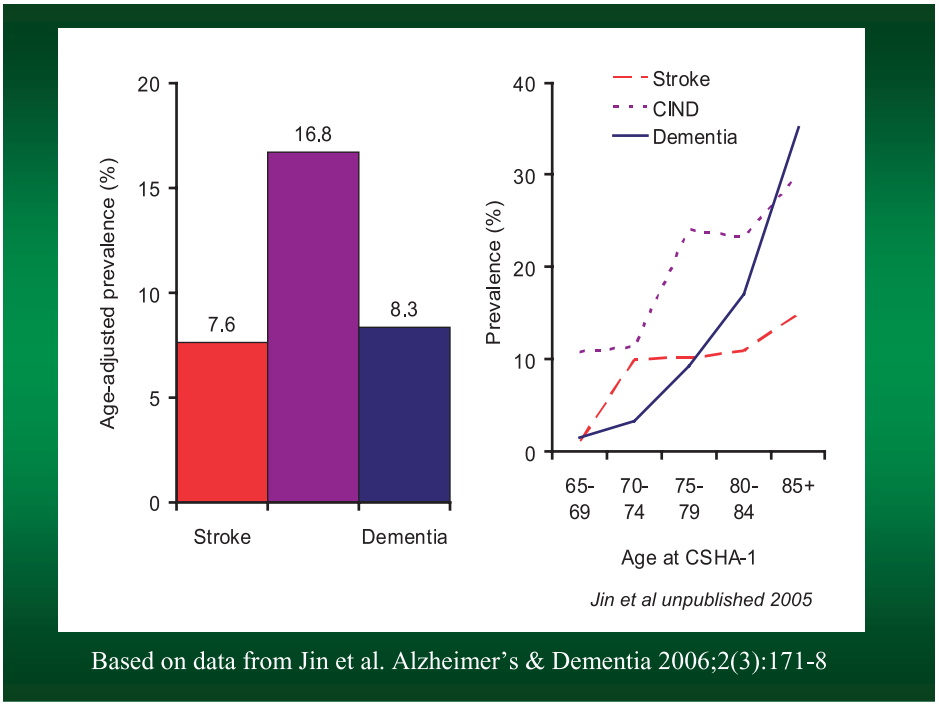

Figure 2: Prevalence of stroke, dementia and cognitive impairment no dementia (CIND) in subjects aged 65 years and older

Regretfully, stroke and Alzheimer disease are mainly studied, diagnosed and managed at the advanced stages. Only 12% of individuals who have a first stroke get a warning in the form of a transient ischemic attack[6] (Fig. 3) and by the time that the diagnosis of Alzheimer disease becomes certain, it may be too late to reverse its relentless and fatal progression.[7]

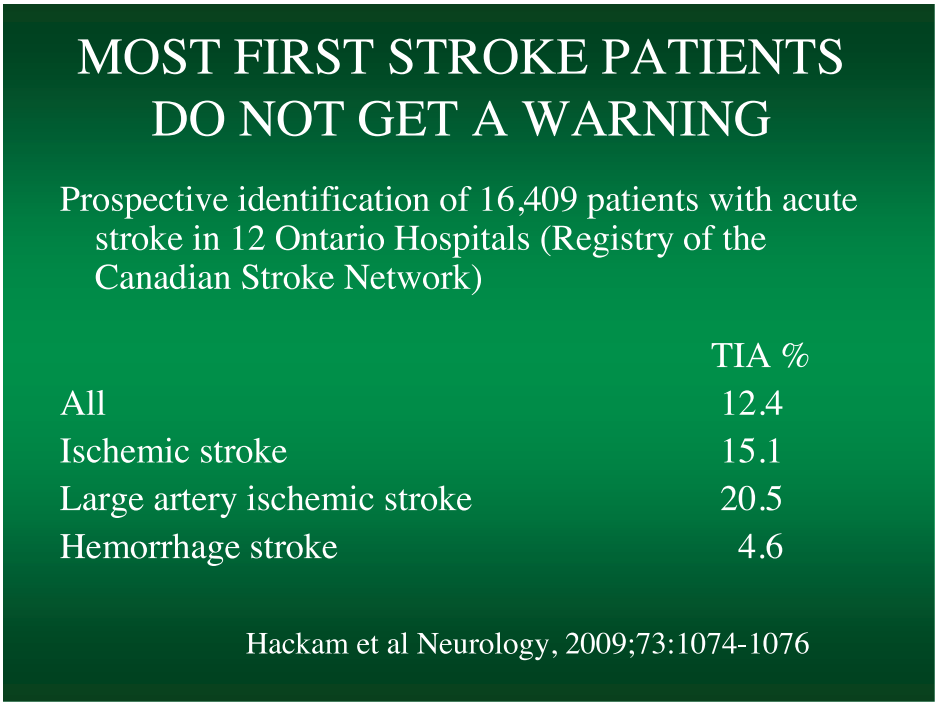

Figure 3: Percentage of first stroke patients experiencing a warning in the form of a transient ischemic attack (TIA)

We must learn to identify patients at risk much earlier and "resist beginnings, before disease has gained strength", as the Roman poet Ovid advocated.

III Stroke and Alzheimer Disease: Preludes, Concomitance and Interactions

Silent strokes represent the commonest type of cerebrovascular disease. Leary and Saver[8] estimated that in 1998 770,000 patients suffered a clinical stroke in the United States. At the same time 9 million silent infarcts and 2 million silent hemorrhages occurred. Silent strokes love company. Individuals who suffer a silent stroke, become more prone to develop others, as well as clinical strokes. Silent infarcts and hemorrhages are associated with subtle cognitive and physical changes.[9,10] The best opportunity to prevent a stroke is early, and no later than at the time of the appearance of silent infarcts and microhemorrhages.

Similar to cerebrovascular disease, Alzheimer disease begins decades before any symptoms appear. Some individuals who later develop Alzheimer disease, may show changes in their neuropsychological testing 22 years before any clinical manifestations appear.[11] Since cerebrovascular and Alzheimer disease start silently, we must intervene at the pre-symptomatic, what we have called the "brain at risk" stage.[12]

The role and contributions of cerebrovascular disease to cognitive impairment have been grossly underestimated.[13] Vascular damage is neither necessarily progressive nor lethal. Unlike Alzheimer, an evolving and ultimately fatal disease, silent strokes may not cause enough damage to produce symptoms that come to medical attention. The Mini-Mental State Examination (MMSE) is the most widely used screening instrument for epidemiological and clinical studies. This test is sensitive to memory disorders, the commonest manifestation of Alzheimer disease, but insensitive to executive function, the most common type of cognitive disorder associated with vascular disease.[14] Patients with cognitive disorders are usually identified by using dementia criteria, which only capture individuals with such severe impairment that it interferes with their daily life. Patients with pure vascular cognitive impairment seldom have memory deficits and hence are not identified by the diagnostic criteria.

We have proposed the concept of "vascular cognitive impairment"[15] as an alternative to "vascular dementia". (Fig. 4)

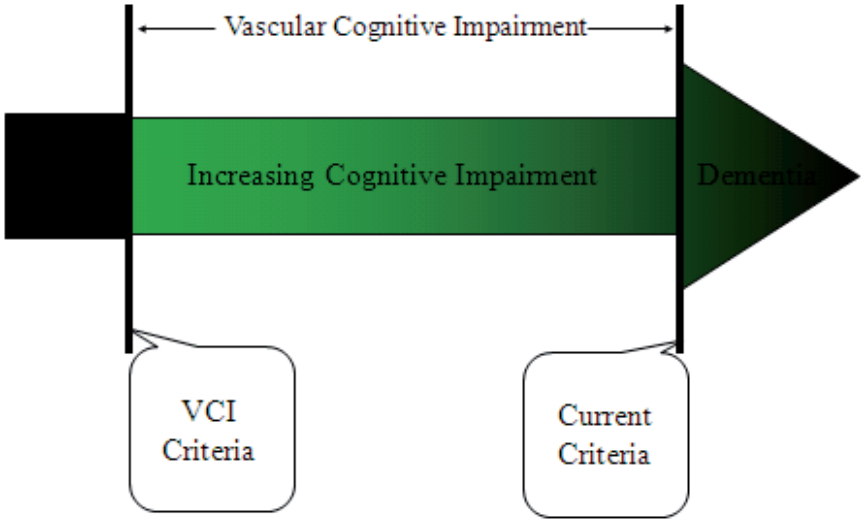

Figure 4: The spectrum of cognitive impairment (Bowler JV, Hachinski VC, eds. Vascular Cognitive Impairment. Oxford and New York: Oxford University Press; 2003)

It includes the whole spectrum of any cognitive impairment caused or associated with vascular factors, including individuals with subclinical or early Alzheimer disease and vascular risk factors or subclinical or manifest stroke.

Dementia criteria are a late and inaccurate method of ascertaining cognitive impairment. In one study, by using [5] different criteria for dementia on the same set of 1879 patients identified as being demented by consensus, showed a tenfold variance! Using ICD 10 criteria 3·1% of the Canadian population over the age of 65 years were considered demented, and if DSM-III were used, then 29·1% were deemed demented.[16]

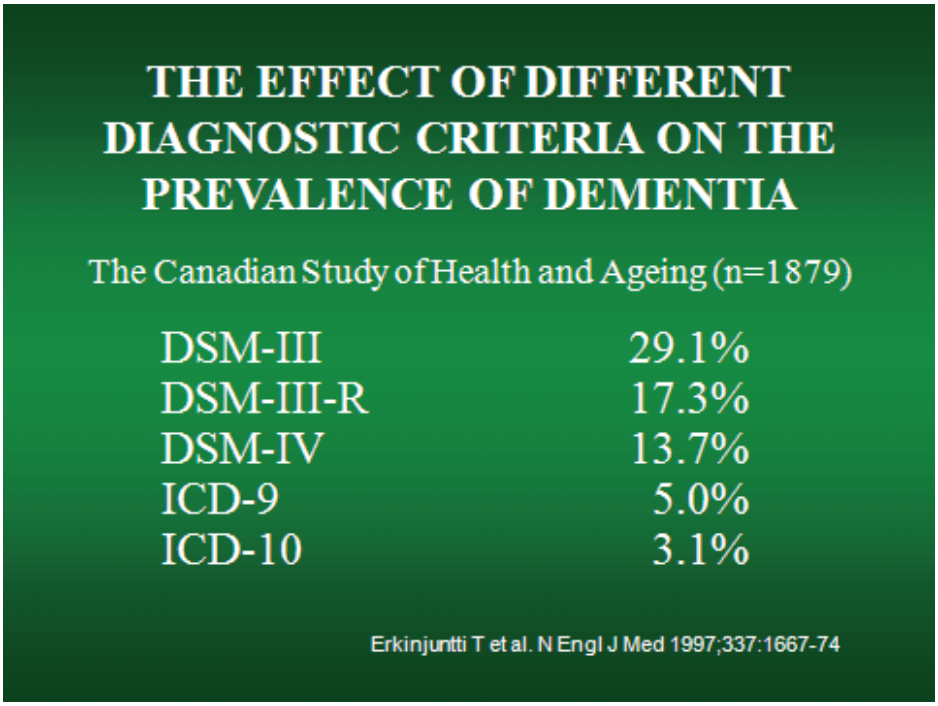

Figure 5: Great variability in the number of patients identified as demented depending on the criteria used

A test giving one result at one laboratory and a value 10 times greater at another would never be used. And yet, we carry on with our dangerously obsolete panoply of dementia criteria.

Criteria for so-called "vascular dementia" are no better. In the Cardiovascular Health Study, none of the criteria identified the same group of subjects.[17] The criteria used in this study have a specificity of 89% but a sensitivity of only 50%.[18] The Hachinski Ischemic Scale,[19] with a sensitivity of 89% and a specificity of 89%[18] was not used.

A further source of bias is that most investigators dealing with dementia work in memory clinics and Alzheimer centers. The persons most likely to go to a memory clinic or an Alzheimer center are those with a memory problem and underlying Alzheimer disease. Consequently, a large literature of clinical pathologic series over reports Alzheimer disease. Only patients who deteriorate and die, make it into the series. However, about 22% of patients

initially diagnosed with Alzheimer disease do not progress.[20] Their brains are not examined and are seldom accounted for. If they are, the accuracy of an initial diagnosis of Alzheimer disease becomes lamentably less than claimed in the literature. The positive predictive value is 81% in the presence of other brain pathology and 44% for pure Alzheimer disease.[20]

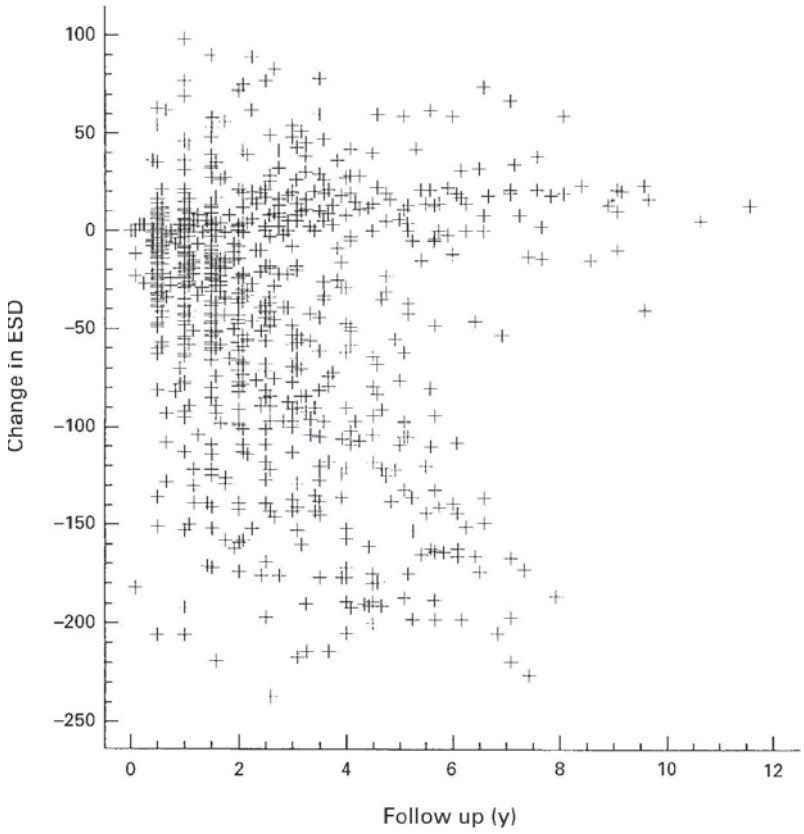

Figure 6: Follow-up of patients initially diagnosed as having Alzheimer disease clinically, but neuropsychological testing and brain imaging

In contrast to the literature arising from Alzheimer's centers, clinical pathological series from community studies show that vascular and Alzheimer lesions occur with similar frequency, and that the commonest

type of cognitive impairment in the elderly arises from the combination of vascular and Alzheimer lesions.[21] Moreover, an overlap exists between neurodegenerative and vascular factors in the pathogenesis of dementia.[22]

Cerebrovascular and Alzheimer disease may not only coexist, but interact.[5] The Nun Study showed that among women with a pathological diagnosis of Alzheimer disease, only 57% had any cognitive difficulties in life. If they additionally had a cortical infarct, then 75% of them did. If they had small basal ganglia, thalamic or white matter infarcts, then 93% of them did, suggesting an interaction between cerebral infarcts and Alzheimer disease.[23] We have modeled this interaction experimentally. Animals rendered Alzheimer-like by the injection of an A-ß amyloid fragment had difficulty learning and remembering a task, both problems becoming worse with time. A small unilateral striatal infarct in rats had no significant impact on learning or remembering. However, the addition of a striatal infarct to the injection of A-ß amyloid, multiplied the pathological effect and cognitive deficits of the A-ß amyloid. It resulted in enhanced amyloid and tau protein deposits and activated microglia in the brain, especially in the hippocampi bilaterally, particularly in the CA3 region and the dentate gyrus, the areas most involved in learning and remembering.[24] The volume of experimental cerebral infarcts decrease and the peri-infarct inflammation subsides over time. By contrast, infarcts in the presence of amyloid are larger and grow, and show greater and intensifying inflammation.[25]

These findings may have important clinical implications. Amyloid deposits occur commonly in the brains of the elderly.[26] Thus cerebral infarcts in a milieu of amyloid may be and grow larger and set up inflammatory reactions that may result in further amyloid deposition, inflammation, brain damage and cognitive impairment.

IV The Matter of White Matter

With the advent of brain imaging, white matter changes in the elderly were reported with rising and troubling frequency. Labels such as "Binswager's disease", "subcortical ischemia" and "subcortical arteriosclerotic encephalopathy" were applied with profligate ease. However, Binswager's disease is neither Binswager's nor a disease[27] in that white matter changes arise from many causes. We suggested the term "leukoaraiosis" (LA) i.e. white matter rarefaction, as a neutral, descriptive term "exact enough to define white matter changes…and demanding enough to require precise clinical and imaging descriptions."[28] Since then, the literature has grown enormously, but our understanding much more slowly. Leukoaraiosis can be associated with cognitive changes, gait impairment, small deep infarcts, and increased likelihood of depression, dementia, stroke and intracerebral bleeding with anticoagulation or tPA treatment.[29] However, work lags on the causes and mechanisms of LA. Ignorance is as ubiquitous as white matter changes. Harm is often inflicted by interpretating even trivial white matter changes as "ischemic", particularly on MRI.

Brain imaging shows us much more than we understand. The most important aspect in assessing a patient is the history, examination and supplementary evaluation. Extensive LA can be a prognostic marker, but the primary consideration remains to treat the patient, not the image.

V Silent Strokes and Insidious Alzheimer Disease

Since silent strokes and asymptomatic Alzheimer lesions often occur together, it makes sense to consider them together. However, "silent" is not an appropriate adjective for the strokes detected on imaging.[9,10] If elderly subjects are examined, they often have subtle deficits. About a third of cognitively normal elderly have lacunar infarcts, their number correlating with executive dysfunction.[30] Also subcortical ischemic lesions occur more frequently in severely demented patients with early onset sporadic AD.[31] Individuals who eventually develop Alzheimer disease also show neuropsychological changes years before becoming clinically symptomatic.[11] Thus "silent" is also an inappropriate term for asymptomatic Alzheimer lesions, because cognitive[11], brain imaging and biomarker changes[32] can occur before symptoms do.

Risk momentum and Pivotal Points

The presence of vascular risk factors in middle age, best predict the risk for stroke and dementia in old age.[33]

Main Proposed Risk and Protective Factors Common for Stroke and Dementia

Non-modifiable risk factors	Modifiable factors	
	Risk factors	Protective factors
Advanced age	Cerebrovascular disease/stroke	High education
Genetic factors	Cardiovascular diseases	Physical activity
e.g. ApoE ε4	Hypertension	Active lifestyle
Family history	Hypercholesterolaemia	Alcohol consumption
	Obesity	Antioxidants
	Diabetes	Fish oils
	Smoking	Antihypertensives
	Homocysteine	Statins
	Psychosocial stress/depression	

Kivipelto and Solomon J of Nutr Health & Aging 2008;12:89S-95S

Figure 7: Common risk factors for stroke and Alzheimer disease

Momentum in physics is defined as velocity multiplied by mass. Risk factors also have momentum, not only their extent, but their duration matter. At what point does risk translate into disease? We know very little about this with respect to the brain. For example, the guidelines for treating hypertension have been largely developed on the basis of the risk of heart disease and to a lesser degree, stroke, but growing evidence suggests that the optimal blood pressure levels for brain protection are considerably lower than current guidelines. In terms of stroke prevention, the lower the blood pressure the better. No lower limit has yet been established.[34] We need to fill the gap between epidemiological risk and pathological outcomes by pathophysiological studies along the spectrum of vascular risk. What are the pivotal points at which different processes become pathological? What are the points of no return?

Such an approach is even more urgent for Alzheimer disease. At long last, we have come to realize that by the time that the condition is manifest, there is little that we can offer, except symptomatic and compassionate care. Experts have developed new criteria for mild cognitive impairment (MCI)[35] and biomarkers[32] to detect the early stages of the disease. This may allow diagnoses a bit earlier. Given that the molecular mischief of Alzheimer disease begins decades before any clinical manifestations, how do we know that even by the stage of MCI it is not too late? Should we not be doing more research on discovering the pivotal point(s) at which the Alzheimer process becomes irreversible?

Lesions in the brain do not add, they multiply. Arresting one pathological process may slow the evolution of another. Education has long been established as a protective factor for developing Alzheimer disease, presumably on the basis of increasing brain reserve.[36]

Brain reserves may be a real phenomenon, but so is the concommittance of Alzheimer lesions and cerebrovascular lesions. Vascular lesions decrease the threshold at which AD will manifest clinically including hemispheric infarcts.[37]

VI Current Approaches

Although about 30% of stroke patients will have significant cognitive impairment at 3 months,[38] cognition is not routinely measured in acute stroke patients. Stroke physicians seldom have expertise in assessing cognition and Alzheimer's physicians rarely have experience in treating and preventing cerebrovascular disease.

Although stroke and Alzheimer disease share similar vascular risk factors,[39] little is being done to provide an integrated approach to prevention. Risk factors are poorly controlled. Hypertension, affecting almost 30% of the U.S. adult population[40] is controlled in only 30% of individuals.[41] The premise is that once well informed, individuals will change their lifestyle. Reality belies this. Understanding and good intentions are not enough. Witness the litany of broken New Year resolutions most of us have tried. Risk must be individualized and prevention focused. In addition to information, individuals need motivation and the means of implementation. Prevention goes beyond individuals and extends to their working and living environments, their ability to be physically active, eat healthy and maintain good habits. We live in "a metabolically toxic environment".[42]

VII An Early, Integrated and Leveraged Approach

Early. What you do not know could hurt you. Risk for stroke and cognitive impairment needs to be individualized. People differ by risk, and their motivation to act with varies with its type and degree. Physicians are more likely to act, as are patients, if they have a measure of the risk.[43]

Risk factors act in cumulative fashion, diminishing capacity of the brain to repair itself. The earlier we can show the effect of risk factors, the greater the postponement of reaching a clinical threshold. (Fig. 4) From a practical viewpoint, a healthy environment and lifestyle should prevail, beginning with mother and child health and be continued for a lifetime. Lifetime habits are formed in childhood, thus it is particularly important that a healthy diet and environment be provided by integrating efforts of the family, schools and communities. Such changes at the societal level would have tremendous health, quality of life and economic benefits. Despite this, at some stage individuals will develop diseases, it becomes important to know the optimal time for intervention. The question as to the cost effectiveness of screening and intervention needs to be a subject of study. Almost certainly our current approach of waiting until the symptomatic stage is costly and counterproductive.

Integrated. We are witnessing an unprecedented growth and fragmentation knowledge. Integration of such knowledge is long overdue.[44] One great obstacle has been the lack of a commonly, agreed, precise methods for identifying and describing individuals with cognitive impairment. Recently we have published minimum standards for describing vascular cognitive impairment and identifying individuals with underlying Alzheimer disease.[45]

The National Institute of Neurological Disorders and Stroke (Ninds)/ Canadian Stroke Network (Csn) Vascular Cognitive Impairment (Vci) Harmonization Standards

Recommendations

1. Clinical/Epidemiology
   a) Demographics
   b) Informant (if available and determined relevant)
   c) Family history
   d) Health history
   e) Evaluation
   f) Abbreviated clinical evaluation
2. Neuropsychology
   a) 60 minute protocol
   b) 30 minute protocol
   c) 5 minute protocol
   Montreal Cognitive Assessment (MoCA) Subtests
   5 – Word Memory Task (registration, recall, recognition)
   6 – Item Orientation
   Letter Phonemic Fluency
3. Neuroimaging
   a) MRI
   b) CT
   c) Area for further research
4. Neuropathology
   a) Optimal brain handling and processing of autopsy
   b) Data to be collected
   c) What information should the neuropathologist provide?
5. Experimental models
   a) Current models
   b) Cognitive testing
   c) What general principle can be made from animal models?
6. Biomarkers
   a) The blood-brain-barrier of VCI
   b) Recommendations for researchers
7. Genetics
   a) Monogenic disorder associated with VCI
   b) Genetic risk factor for VCI
   d) Standards
8. Clinical Trials
   All clinical trials should include cognitive assessments

Adapted from Hachinski et al. Stroke 2006;37:2220-2241

The use of common standards will allow the cross comparison of different studies and the simultaneous prospective validation of different criteria. If everyone agrees on the same minimum set of data points, several provisional criteria could be devised and tested simultaneously against meaningful outcomes on the same set of individuals. By this approach, criteria can be built on data instead of consensus, which ineluctably incorporates and formalizes areas of ignorance or misinformation.

Leveraged. Databases from several longitudinal studies already exist. If they were to be made compatible, hypotheses generated in one dataset could be validated on another. Moreover, if the databases common standards and data points, and a semantic web were developed, whereby not only words but meaning would be captured, many of the questions that are now being posed could already be answered with existing data. One successful example of this approach in another realm has been the identification of the five key biochemical pathways in addiction.[46] We need to move from segmented, fragmented and sequential studies to a simultaneous, comprehensive and integrated approach from epidemiology, clinical experience and administrative studies (Fig. 8).

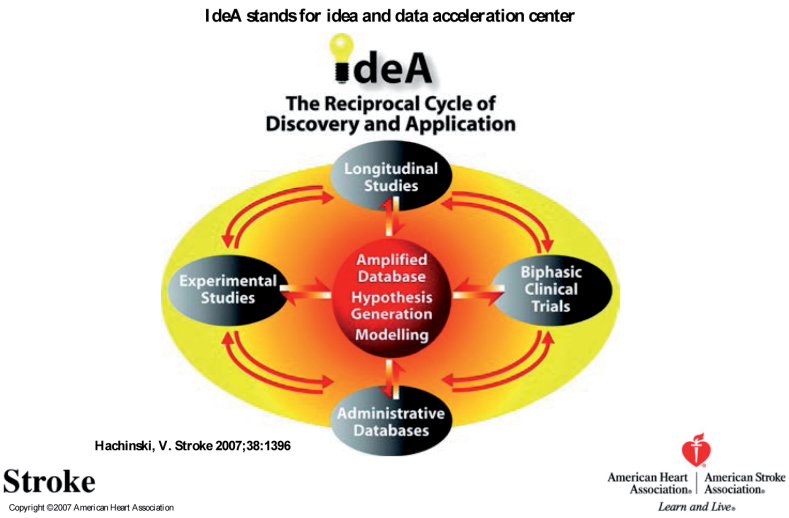

Figure 8: A model of the reciprocal enhancement of discovery and application

At the moment, typically a hypothesis is generated, the data to prove or disprove it obtained, and then the next hypothesis is tested. By having common data elements and having more than one population available, several hypotheses could be tested simultaneously across comparable populations. A number of chronic diseases show the same risk factors. There are trends towards addressing global vascular risk, for organizations to work together and for developing global strategies for tackling jointly the leading chronic diseases.

Stroke is preventable and recently a prioritized world stroke agenda has been developed with the support of all the major international organizations dealing with stroke[47].

The recommendations include:

1. *Stroke prevention:* (1) Establish a global chronic disease prevention initiative with stroke as a major focus. (2) Recognize not only abrupt clinical stroke, but subtle subclinical stroke, the commonest type of cerebrovascular disease, leading to impairments of executive function. (3) Develop, implement and evaluate a population approach for stroke prevention. (4) Develop public health communication strategies using traditional and novel (eg. Social media/marketing) techniques.
2. Education and energize professional, patients, the public and policy makers by using a "Brain Health" concept that enables promotion of preventive measures.
3. Systematic integration of knowledge into programs with coupled with careful evaluation can speed the pace of progress.

Regretfully, the Alzheimer field continues to concentrate on the end stages of the Alzheimer process, namely mild cognitive impairment and clinical Alzheimer disease and largely ignores the many treatable risk factors that it should with stroke.[48]

VIII Practical Implications: Cognition, the Early Warning System

Memory changes are the earliest manifestations of Alzheimer disease[35] and changes in executive function the earliest warnings of cerebrovascular disease.[13] The latter is a particularly important point since only 12% of first stroke patients ever get a warning in the form of a transient ischemic attack (TIA).[6]

On the other hand, executive dysfunction is highly prevalent among TIA and stroke patients.[14] The cognitive changes are probably largely due to subclinical strokes, which are 5-10 times more common than clinical strokes[9] and highly prevalent. Among community living subjects of the Framingham offspring cohort with a mean age of 63 years, one in ten, already had a silent infarcts.[49]

Practical Approach

History and Examination: This remains the mainstay of any approach. Some questions may appear highly sensitive in eliciting a change in cognitive function. For example:

1) How is your memory compared to a year ago?
2) Has there been any changes in your ability to handle money in the past year?
3) Has there been any change in your ability to play games in the past year? e.g. cards, chess, dominoes, bingo etc.

The functional enquiry should focus on determining risk factors, particularly treatable ones. In the elderly, atrial fibrillation has become a rising menace for stroke and cognitive impairment.[50,51,52] The examination should always include a blood pressure measurement.

Cognitive Screen

The Montreal Cognitive Assessment (MoCA) has proven to be sensitive not only to memory changes but executive function, proving useful in Alzheimer disease, cerebrovascular disease, Parkinson's disease, brain injury, disease, epilepsy, motor neuron disease and multiple sclerosis.

It has been translated into 35 languages and validated in 17 languages[53] . (please see Appendix I). If the screen is positive a 30 or 60 minute battery is recommended.[45]

Identifying a Vascular Component

At the moment, the vascular component of cognitive impairment is the only one that is potentially treatable and preventable.

If cognitive impairment is detected, the Hachinski Ischemic Score (please see Appendix II) can be applied. It was originally developed to differentiate multi-infarct dementia from primary degenerative dementia. Although it distinguishes well between pure AD and MID, it does not discriminate between pure MID and mixed vascular and Alzheimer pathology. It is best considered as a sensitive (89%) and specific (89%)[18] identifier of a vascular component.

Investigators

These will be dictated by the history and examination. Ruling out vitamin B12 and folic acid deficiences, neurosyphilis, hypothyroidism and other treatable conditions, will be appropriate for specific patients.

If imaging and other investigations are warranted, it is recommended that they follow the VCI Harmonization Standards.[45]

What can be expected?

We already know that strokes can be prevented. (Fig. 10 and 11) We have also reason to believe that treatment of risk factors can prevent progression of cognitive impairment in selected cases.

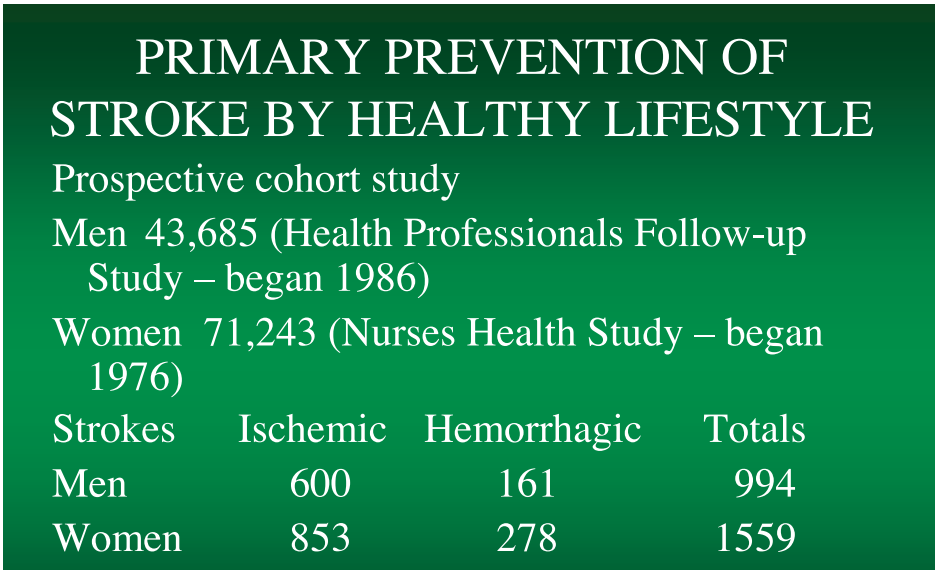

Figure 10: Primary prevention of stroke – cohorts and outcomes. Chiuve et al. Circulation 2008;118:947-954

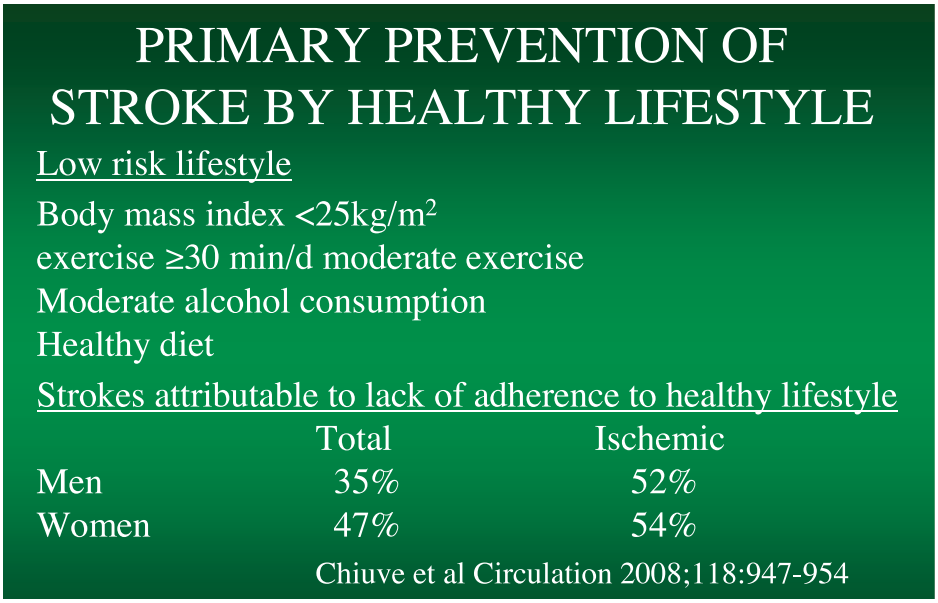

Figure 11: Primary prevention of stroke - outcomes

Hypertension, Executive Dysfunction and Progression to Dementia

We studied 990 subjects with a mean age of 83.06 years having cognitive impairment but no dementia.[54] These were followed up for 5 years in the Canadian Study of Health and Aging. Among subjects with executive dysfunction alone, 57.7% having hypertension progressed to dementia compared with 28.0% having normal blood pressures.

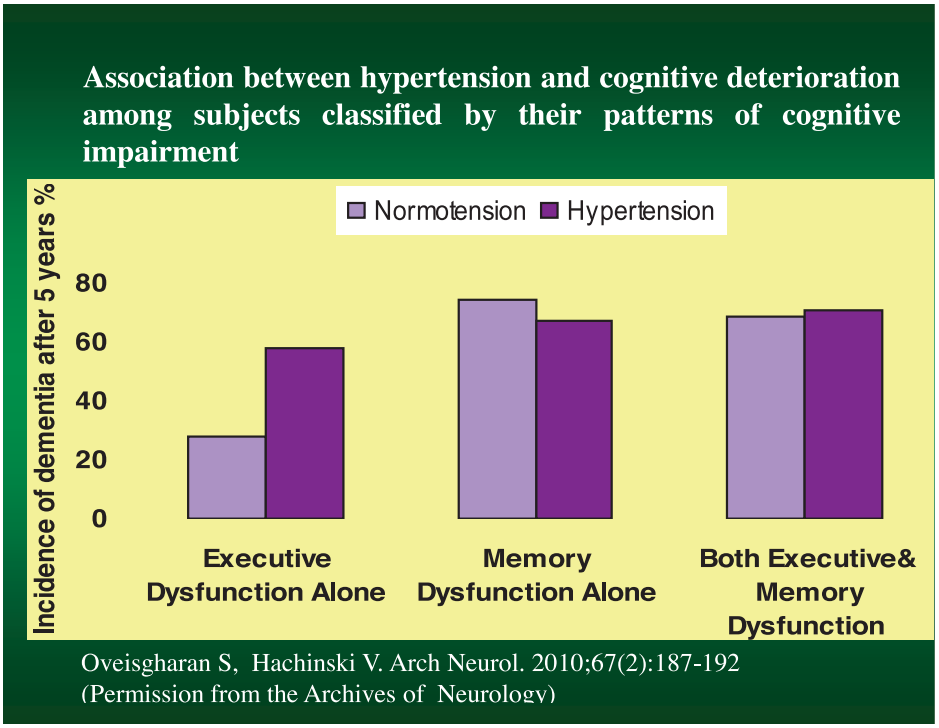

Figure 12: Hypertension and cognitive deterioration

Hypertension predicts progression to dementia in older subjects with executive potentially dysfunction but not memory dysfunction, consequently control of hypertension could prevent progression to dementia in half of subjects with executive impairment.

If the onset of dementia could be delayed by 5 years, prevalence would fall

to half.[55] Control of risk factors prevents stroke. Consequently, management of hypertension and perhaps other risk factors probably could if not prevent, but delay Alzheimer disease. Blood pressure control could not only delay, but perhaps prevent cognitive impairment, including Alzheimer disease.[56] A parallel already exists in regard to congestive heart failure. In the 1950's the mean age of onset was 57 years, by the 1980's it became 76 years.[57] Imagine the lives spared, the health care costs saved, the productivity maintained and the quality of life enjoyed! The onset of heart failure has been delayed, brain failure can also be delayed, let's do it!

IX Conclusion

The worst fate is a sick brain, because we are our brains. If the risk for stroke or dementia gets identified early, and measures taken, cerebrovascular and Alzheimer disease can probably be delayed, and perhaps prevented. But if we are to achieve this, we will have to intervene early, in an integrated and leveraged approach, with realistic expectations, a feasible agenda and the resources to bring this about. We can and should do it. Our brains depend on it.

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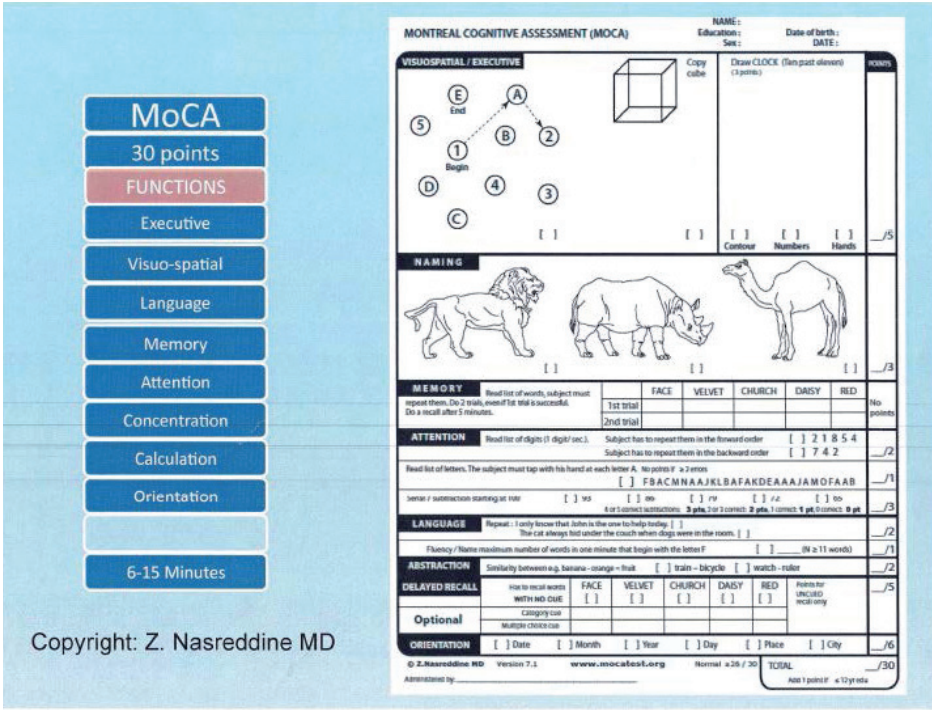
Appendix

Appendix I



(Nasreddine ZS, Phillips NA, Bedirian V, Charbonneau S, Whitehead V, Collin I, Cummings JL, Chertkow H. The Montreal cognitive assessment, moca: A brief screening tool for mild cognitive impairment. J Am Geriatr Soc. 2005; 53: 695–699 http://www.mocatest.org)

Appendix II

The Ischemic Scale (Hachinski V et al. 1975)

Feature	Value
Abrupt onset	2
Stepwise deterioration	1
Fluctuating course	2
Nocturnal confusion	1
Relative preservation of personality	1
Depression	1
Somatic complaints	1
Emotional incontinence	1
History/presence of hypertension	1
History of strokes	2
Evidence of associated atherosclerosis	1
Focal neurologic symptoms	2
Focal neurologic signs	2
	Total score

Scores >7 suggest a vascular aetiology for dementia,
whereas scores up to 4 do not support a vascular aetiology.

Appendix III

Declaration

Neuro
epidemiology

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Declaration of San Antonio, Texas

San Antonio, Tex., July 14, 2007

Members of the International Society for Vascular Behavioral and Cognitive Disorders (Vas-Cog), representing 41 countries, met in San Antonio, Tex., USA, for the Third Vas-Cog International Congress (July 11–14, 2007). The Vas-Cog society members express hereby their concern with the worldwide declining support and lack of interest of Public Health services, scientific funding agencies, and pharmaceutical industry on the brain at risk from vascular factors and stroke.

- Despite the fact that prevention and early treatment of vascular disease are widely available at reasonable cost, almost all countries face the more expensive option of paying the expenses of hospitalization, nursing home, and loss of labor and life resulting from stroke, heart disease and dementia as a consequence of untreated vascular risk factors.
- Despite evidence of successful prevention of dementia by treatment with antihypertensive medications, no current trials have addressed this obviously cost-effective approach of major importance in health economics.
- Despite advances in the treatment of hypertension, diabetes, hyperlipidemia and other causes of stroke and heart disease, almost no recent studies have addressed the effects of these treatments on the prevention of vascular cognitive impairment and vascular dementia.
- Despite the fact that cerebrovascular disease and cardiovascular disease are the most common contributors to cognitive decline in older persons, and despite evidence that the combination of cerebrovascular disease and Alzheimer's disease is the most common pathological finding in dementia, there has been only limited research on the interaction of these two disease processes as a cause of dementia.
- Despite the fact that one in three stroke survivors are left incapacitated with vascular dementia and that as many as two thirds have behavioral and cognitive changes such as depression, apathy and intellectual decline, few stroke trials include cognitive and behavioral endpoints in the evaluation of new treatments for stroke.
- Despite the fact that vascular dementia is the second-most common form of dementia in the elderly after Alzheimer's disease, very few trials are being conducted on the use of existing and developing therapies for this devastating condition.

Therefore, it is the hope of the members of this international scientific society that Governments around the world, scientific funding agencies, and the pharmaceutical industry will recognize the importance of this problem and implement Public Health and research programs for the prevention and treatment of the deleterious consequences of vascular injury to the brain.

By the Executive Committee of Vas-Cog on behalf of the General Assembly

Vladimir Hachinski, MD, FRCPC, MSc, DSc, Hon. Dr. med. (Professor of Neurology, University of Western Ontario, London, Ont., Canada), Chairman

Ingmar Skoog, MD, PhD (Professor of Neuropsychiatric Epidemiology, Neuropsykiatri SU/Mölndal, Sweden), Secretary General

Philip Scheltens, MD, PhD (Professor of Cognitive Neurology and Director of the Alzheimer Center, Vrije Universiteit Medical Center, Amsterdam, The Netherlands), Treasurer

Anders Wallin, MD, PhD (Professor of Neurology and Geriatric Neuropsychiatry, Göteborg University and Sahlgrenska University Hospital, Göteborg, Sweden), Vice-Secretary

Timo Erkinjuntti, MD, PhD (Professor of Neurology and Director of the Memory Research Unit, University of Helsinki and Helsinki University Central Hospital, Finland), Coordinator Working Groups

Ken Nagata, MD, PhD (Director of Neurology, Research Institute for Brain and Blood Vessels, Akita, Japan), Coordinator Vas-Cog Asia

Florence Pasquier, MD, PhD (Professor of Neurology and Head of the Memory Clinic, Lille University Hospital, Lille, France), Chair Membership Committee

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Rajesh N. Kalaria, PhD, FRCPath. (Professor of Neuropathology, Institute for Ageing and Health, Wolfson Research Centre (Neuropathology), Newcastle General Hospital, Newcastle upon Tyne, UK), Chair Scientific Committee San Antonio, Tex. 2007 and Singapore 2009

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Gustavo C. Román, MD, FACP, FRSM (Lond.) (Professor of Medicine/Neurology and Director of the Memory Clinic, University of Texas Health Science Center and the Geriatric Research Center, Veterans Administration Hospital, San Antonio, Texas, USA), Local Organizer Vas-Cog 2007 San Antonio, Tex., USA

Countries Represented

Argentina, Australia, Austria, Bolivia, Brazil, Canada, Chile, China, Colombia, Croatia, Denmark, Finland, France, Germany, Hong Kong, India, Indonesia, Israel, Italy, Japan, Republic of Korea, Mexico, Netherlands, New Zealand, Nigeria, Norway, Poland, Portugal, Russian Federation, Serbia and Montenegro, Singapore, Spain, Sri Lanka, Sweden, Switzerland, Taiwan, Thailand, Trinidad and Tobago, United Kingdom, United States, Venezuela.

Grande Prémio Bial de Medicina 2010

Instituído em 1984, o PRÉMIO BIAL tem vindo a premiar conceituados profissionais de saúde de vários países, reconhecendo e distinguindo a investigação básica e clínica na área da medicina. Promovido pela FUNDAÇÃO BIAL, com periodicidade bienal, é considerado um dos maiores prémios na área da Saúde em toda a Europa.

O júri da edição PRÉMIO BIAL 2010 foi constituído por Nuno Sousa, que presidiu, e por Agostinho Almeida Santos, Henrique Barros, José Manuel Calheiros, António Sousa Guerreiro, Carlos Lopes, Joana Palha e Leonor Parreira.

A obra "The long fuse: silent strokes and insidious Alzheimer disease" de autoria de Vladimir Hachinski, Professor de Neurologia na Universidade Western Ontario, Canadá, foi galardoada com o GRANDE PRÉMIO BIAL DE MEDICINA.

Na décima quarta edição do PRÉMIO BIAL foram também distinguidas quatro obras com Menções Honrosas.

O PRÉMIO BIAL conta com os altos patrocínios do Senhor Presidente da República, do Conselho de Reitores das Universidades Portuguesas e da Ordem dos Médicos.

Com o objetivo de continuar a divulgar obras de grande repercussão na pesquisa médica e acompanhar a evolução da investigação na área da medicina, a FUNDAÇÃO BIAL vai organizar a edição do PRÉMIO BIAL 2012 envolvendo o GRANDE PRÉMIO BIAL DE MEDICINA, o PRÉMIO BIAL DE MEDICINA CLÍNICA e ainda quatro Menções Honrosas.