

# **DRUGS AND METHODS IN C.V.D.**

**Proceedings of the International  
Symposium on Experimental  
and Clinical Methodologies<sup>1</sup>  
for Study of Acute and Chronic  
Cerebrovascular Diseases**

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## Preface

S.I.R., Scientific International Research is a private Research Organisation born in France to carry out basic research in the fields of cerebrovascular disease, cardiovascular disease, neuropsychopharmacology, drugs metabolism, skin, vessels and some other forecoming topics. Under its care, S.I.R., Scientific International Research must organize symposia in the fields where contradictory opinions stand. In the past, S.I.R., Scientific International Research has carried out this activity by organizing International Symposia such as « the pathopharmacology of the cerebrovascular diseases » (Reims, July 1978), or « the pathogeny of cerebrovascular diseases » (December 13th, 1978) and by sponsoring the Beaune Conference on « Acute cerebro-vascular diseases » (1979-1980). In order to form a continuity in the publication, S.I.R. has decided to publish a series of volumes based on its Symposia through Pergamon Press. The present volume is the first of this series and its subject is : « the Experimental and Clinical Methods for the Study of acute and chronic cerebrovascular diseases ». This first publication of S.I.R. was selected as a topic of high clinical and pharmacological interest. Both sociologists and pharmacologists will benefit from this informative reference sources for the biochemical, metabolic, behavioural and clinical pharmacological aspects of such diseases. The most fascinating aspect of this Symposia was the semantic and clinical opposition and sometimes clash between some American neurologists and some Europeans but surprisingly from all the discussions, finally came out some conclusive remarks, in a few words : the aging of the brain is not a disease but a factor of risk. With the first brain injury starts the chronic brain. The main feature of the meeting was the friendship which allowed people to say freely what they had to say. This possibility to give scientists the right to speak and to write is, above all, the aim of S.I.R., Scientific International Research.

*S.I.R., Scientific International Research*  
*January 1981*

Jean Cahn  
*President*

*Certains le liront pour apprendre  
Et d'autres pour le critiquer  
Il sera facile de l'étendre  
Mais difficile de l'imiter*

**Ronsard**

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**PART ONE**

**CHRONIC CEREBROVASCULAR DISEASES (C.C.V.D.)  
AND CEREBRAL AGING  
(EXCEPT DEMENTIA)**



## WHAT IS CHRONIC CEREBRAL VASCULAR DISEASE ? CLINICAL CONSIDERATIONS

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**key-words** - aging - TIA - Alzheimer-senile dementia - post-stroke syndromes

With admirable courage, the organizers of this S.I.R. conference have taken the first step in an attempt to come to terms with a health problem that faces many countries in today's world. In all of Western Europe and most of North and South America, public health statistics say that more and more people are living longer and longer. In the United States in 1950, only about 8 % of persons, a total of 12.3 million, were older than 65 years. By 1978, the fraction had risen to 11 % and numbered 22 millions. Demographic predictions say that when our youngest grand-children reach ripe maturity in the year 2030, America will contain more than 51 millions persons aged 65 years or more, equal to a full 20 % of her population (Figure 1).

In many ways, medicine can take deserved pride in these documentations of increased longevity. They partly reflect a remarkable reduction in infant mortality by improved public health. Even more, perhaps, they show the direct effects of many fundamental medical research discoveries as well as the development of new therapeutic agents and technics since the end of World War II (Beeson P.B., 1980).

For many of the elderly, however, mere longevity has proved to be a disenchanting gift. About 10 % of our present older population occupy nursing homes and many more suffer from feelings of loneliness, neglect, fear of the unknown, and a variety of symptoms which reflect the presence of more or less serious functional or organic disease of the nervous system. The cost of caring for these unfortunate persons represents a substantial national expenditure. The Institute of Aging of the USPHS National Institutes of Health estimates that the present annual cost of caring for patients with chronic dementia equals about

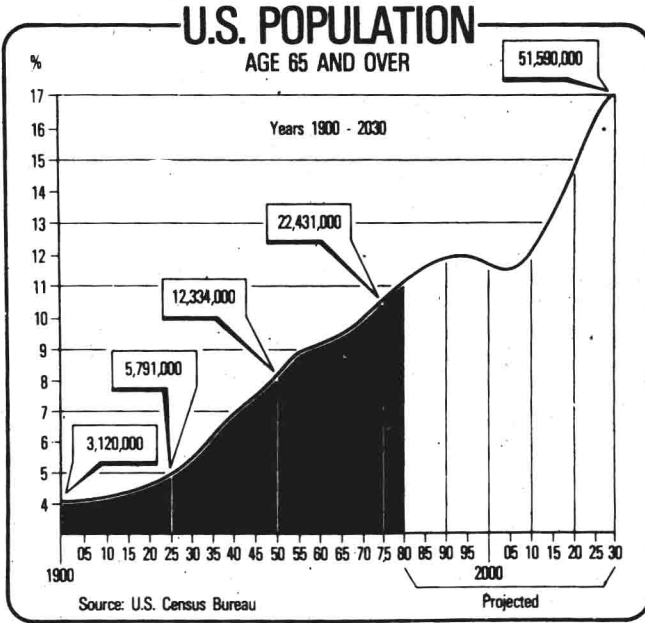


Fig. 1 Chart showing the percentage of the U.S. population aged 65 years and older from 1900 to 1975, with predictions for 1980 to 2030. (Reprinted from *Nature* 279, 372-373. With permission of Macmillan Journals Ltd.

12 billion dollars and that these persons represent 50 % of our chronic nursing home and institutional population. No one has even provided an informed guess at the cost of care for those elderly with less severe neurological or psychiatric symptoms. Estimates of future health care cost for this group of patients rise alarmingly. Conservative projections are that by the year 2030, if we continue on our present course, the U.S. will be spending 30 billion of 1978-value dollars for the care of patients with chronic neurological and psychiatric infirmities. This sum far exceeds our present or projected allocations for all health care research and threatens to place a major burden on a proportionately smaller working-age population. Only effective present research directed at prevention of the medical and social effects of aging on the nervous system can reduce this potential economic threat (Plum, 1979).

Before one can aim one's research guns or initiate clinical trials to evaluate any purported form of specific prevention or treatment for the neurological disorders of the senium, the target must be precisely delineated. A major question in front of us at this meeting is, does an entity of Chronic Cerebral Vascular Disease (CCVD)

exist as an important specific cause of morbidity in the aged? The answer to that question must be sought by defining in the most rigorous terms possible, the clinical, physiological, and pathological criteria of what we already know about neurological or psychiatric disease in the elderly.

As a clinical neurologist, I can identify among my elderly patients four relatively well-defined clinical disorders that are accompanied by prominent symptoms implying nervous system dysfunction. The fact that the headings are limited to four does not necessarily imply that no more exist, only that they are less clearly delineated at the present time. These four conditions include :

- 1) neurasthenic-depressive reactions of aging,
- 2) cerebrovascular transient ischemic attacks,
- 3) Alzheimer-senile dementia,
- 4) post-stroke syndrome and multi-infarct dementia.

Since these conditions are not always clearly demarcated from one another in discussions on the symptoms or treatment of the elderly, it may be useful to do so at this point.

### **Neurasthenic-Depressive Responses in Older Persons**

This is an extremely common problem, which in the USA probably represents the largest cause of complaints that take the aged to physicians. The root origins of the disorder undoubtedly are heavily determined by social factors, but at the present time we have almost no knowledge of whether an underlying physiological-pathological abnormality in the brain is required as well. Nor do we yet know whether or not the social-psychological responses can cause cerebral physiological abnormalities. Such physiological mechanisms and responses seem likely, but are unproved.

Symptoms in the neurasthenic depressive response appear to represent a compounding of physiological and emotional insufficiency. On the physiological, side one observes very real deteriorations in coordination and fine skills in all four extremities. No matter what else one observes in their intellectual powers, few subjects fail to lose a certain degree of memory for names once the fifth decade has passed. General body health declines. Whatever the cause, the patients suffer from a fairly consistent syndrome of insomnia, fatigue, a sense of intracranial giddiness coupled with a loss of sure-footedness, a loss of interest in the environment, and at least a mild loss of attention, abstract thinking and drive. The most immediate effect of these inner troubles tends to express itself in a querulous, demanding dependency on family, acquaintances and physicians.

Abnormal neurological signs among such patients usually are limited to a mild decline in testable intellectual qualities, consistent with age and disinterest, and perhaps a widening and unsteadiness of the gait, coupled with some generalized bodily akinesia and the well known cervical-thoracic lordosis. I have never been able to find any other consistent neurological abnormalities either by physical examination, chemical laboratory tests, CT scans, or physiologically oriented tests



such as EEG's evoked responses, test of labyrinthine function, etc... Any or all of these measures can contain some small abnormality or another, but none occur sufficiently regular to suggest a physiological common denominator for the symptoms. Accompanying these physical limitations is a sense of loneliness and rejection that often affects those retired from social and vocational occupations. Perhaps related is the fact that even during their most vigorous years, many citizens of our present Western world feel unable to cope with rapidly changing times and the routine burdens of their everyday living. In the U.S., at least, physicians have difficulty in giving patients with the above complaints the advice that since they lack a consistent physiological explanation for their symptoms, no drug can bring specific relief. As a result, many agents are tried, most of which one suspects are pharmacologically no more than placebos. Our favorites in the U.S. seem to be tranquilizers and antidepressants while conversations with physicians at this conference suggests that European physicians use vasoactive drugs much more frequently than do Americans. Whatever recourse, the combined expenses for this pharmacological blind-shooting must run very high for the patient and society.

### Transient Ischemic Attacks

As the audience well knows, cerebral transient ischemic (TIA's) are relatively brief episodes of neurological insufficiency producing signs and symptoms consistent with the specific territorial distribution of one or more of the branches of the internal carotid or vertebral-basilar arterial systems. Although experts in the field officially allow the definition to include episodes where neurological deficits last up to 24 hours before disappearing, most TIA's last less than 10 minutes, whereafter they depart without leaving a trace. To my mind, TIA's are the cerebral circulation's equivalent of the angina pectoris of coronary artery disease. Most patients with cerebral transient ischemic attacks have demonstrable disease of the cervical arteries, and arteriograms show that many have incipient intracranial vascular disease as well. Both focal and general reductions of cerebral blood flow have been found by different investigators (Skinhøj *et al.*, 1970; Rees *et al.*, 1970). Therapy for patients with transient ischemic attacks is well defined and reasonably successful in controlling the symptoms. Despite their objectively verified vascular disease, most such patients lack the symptoms that characterize the elderly neurasthenic depressive syndrome.

### Alzheimer-Senile Dementia (ASD)

Pathologists have recognized the morphological identity of these conditions for decades. Recent years have seen epidemiologists and clinicians also agree that senile plaques, neurofibrillary tangles and granulo-vacuolar degeneration characterize a single disease that can affect persons of almost any age, but becomes