GERIATRICS SYMPOSIUM ON DEMENTIA AND BRAIN ISCHAEMIA

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Introduction to the pathogenetic mechanisms of senile dementia and its therapeutic approaches

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Ageing is not a disease in its narrow sense because although it is accompanied by a series of morphological and biochemical changes, it stays within the limits of the functional reserve capacity of the body, in particular the brain. However, if this functional reserve is exhausted by ischaemia or by traumatic or toxic brain lesions, a normal ageing brain may shift into a psychoorganic defect syndrome, or senile dementia (Fig. 1). Unlike presenile dementia, such as Alzheimer's disease and Pick's disease, hereditary factors are not considered to have an important role.

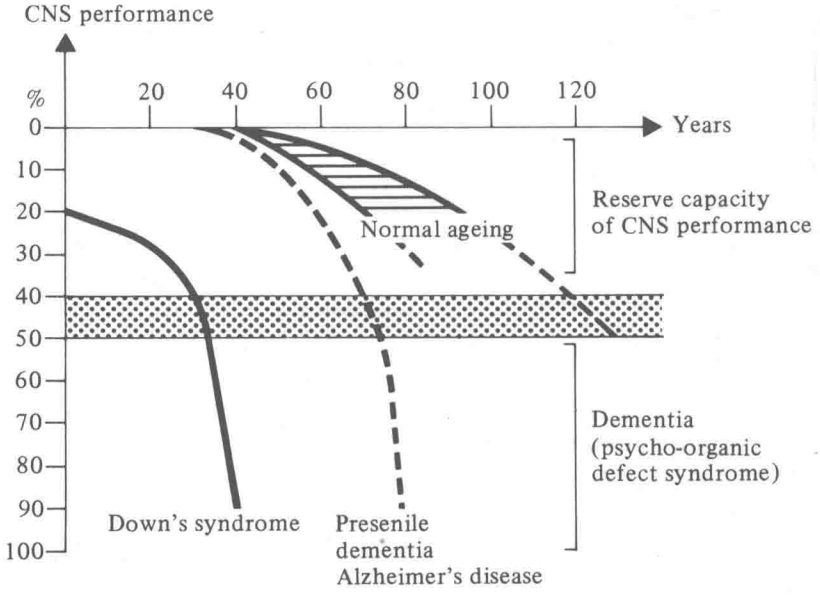

Fig. 1. CNS performance in normal and pathological brain ageing.

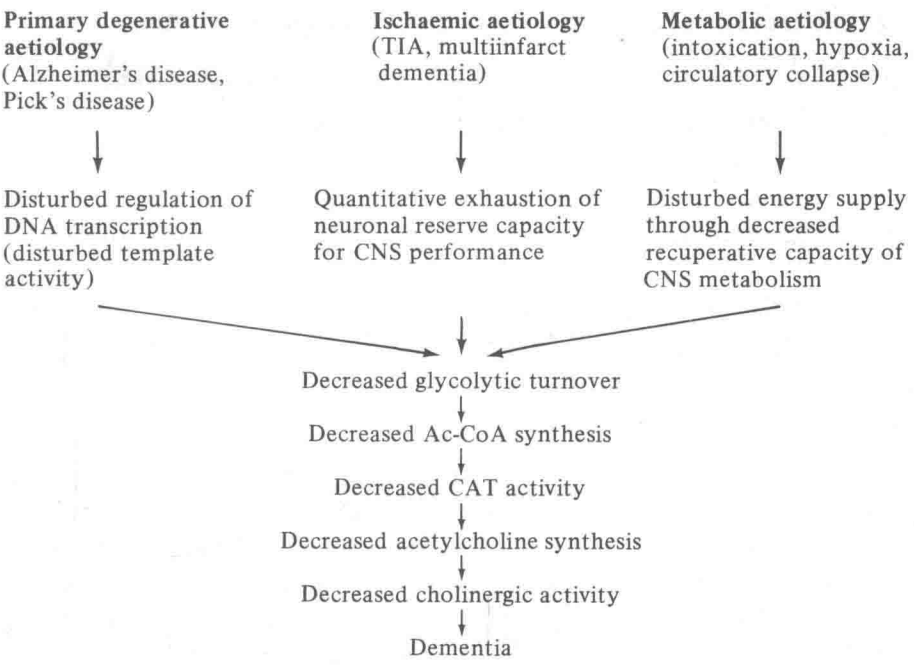

Fig. 2. Pathogenesis of senile dementia.

KEY PROCESSES

Since the brain uses glucose as its main or even sole source of energy, changes in glycolytic turnover might be expected to have serious consequences as far as the energy-requiring synthetic processes are concerned (Fig. 2). A decrease in the glycolytic turnover capacity lowers pyruvate, for example, and subsequently acetylcoenzyme A, which is necessary for the synthesis of acetylcholine. Alzheimer's disease is characterized by a significant decrease in choline acetyltransferase activity in the brain cortex and hippocampus, resulting in decreased cholinergic activity; therefore senile dementia can be described as a cholinergic deficit disease of the brain. Perry et al.[1] observed that the extent of the decrease in choline acetyltransferase is directly correlated with a decline in mental test scores or intellectual activity and an increase in the number of senile plaques (Fig. 3).

The decrease in choline acetyltransferase activity in the demented brain is observed on the presynaptic side of the nerve cells, while the number of muscarinic receptors on the post-synaptic side remains unchanged. In addition, we have been able to prove by stereologic investigations that in the different cortex layers in senile dementia –

compared with age-matched controls – a significant atrophy of neuronal perikarya occurs. In Alzheimer's disease, the shrinkage of the nerve cells is in the range of 51 ± 4% (Fig. 4).[2] In normal ageing brains of people more than 85 years old, a significant decline of nerve cell size (on average, 35 ± 6%) can be demonstrated.[3]

To understand metabolic changes in senile dementia, we must study them in the normal ageing brain. In normal people over 71, a significant decrease in turnover of the glycolytic key enzymes, hexokinase, phosphofructokinase, aldolase and phosphoglycerate mutase is observed (Fig. 5). These metabolic changes in the glycolytic pathway are seen 10–15 years earlier than shrinkage phenomena of the nerve cells. This reduction in energy-producing capacity probably has a significant adverse effect on the ability of the neurons to meet increased demands.

CHARACTERISTIC METABOLIC CHANGES

Decreased cholinergic activity in senile dementia indicates that the key pathogenetic mechanism is the disturbance of the cholinergic system.

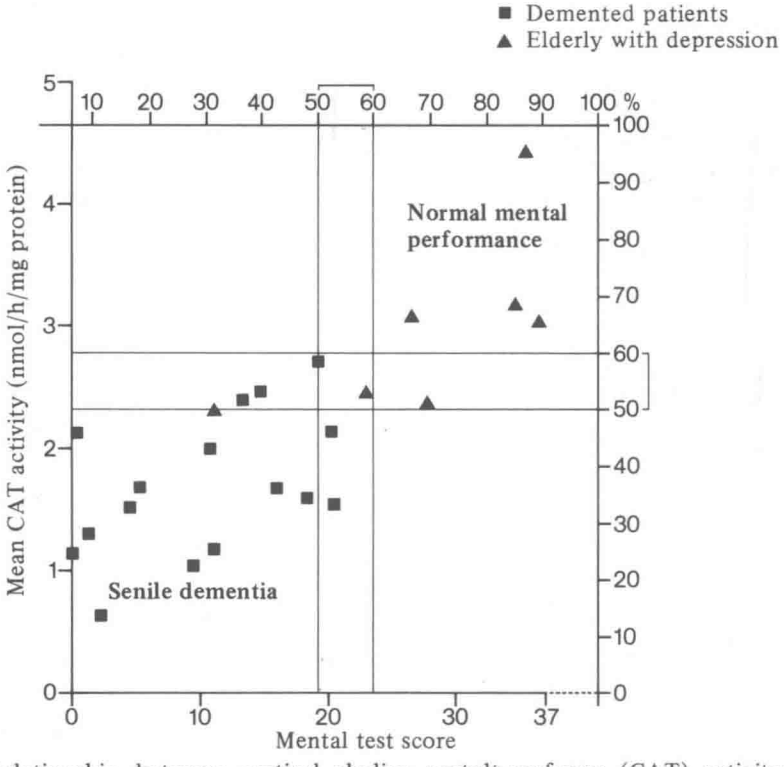

Fig. 3. Relationship between cortical choline acetyltransferase (CAT) activity and mental test score.[1]

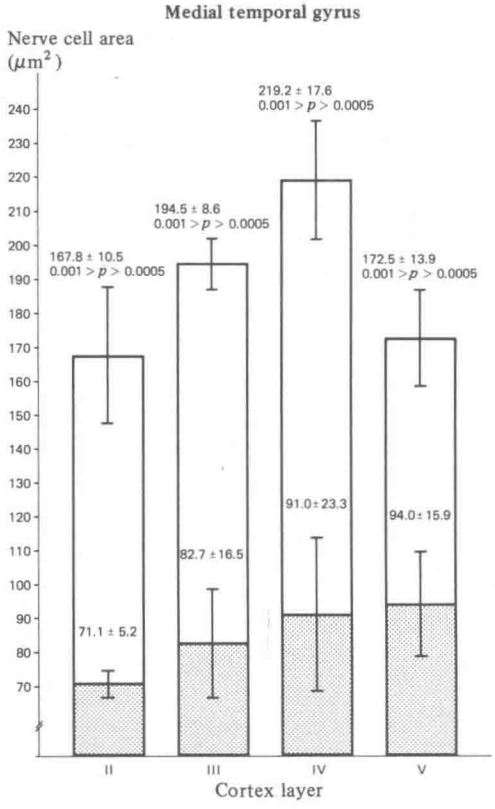

Fig. 4. Stereologic nerve cell measurements in the medial frontal gyrus in senile dementia (85–95 years, n = 14) in comparison to age-matched controls (85–95 years, n = 12). This demonstrates a significant decrease in nerve cell size.[2]

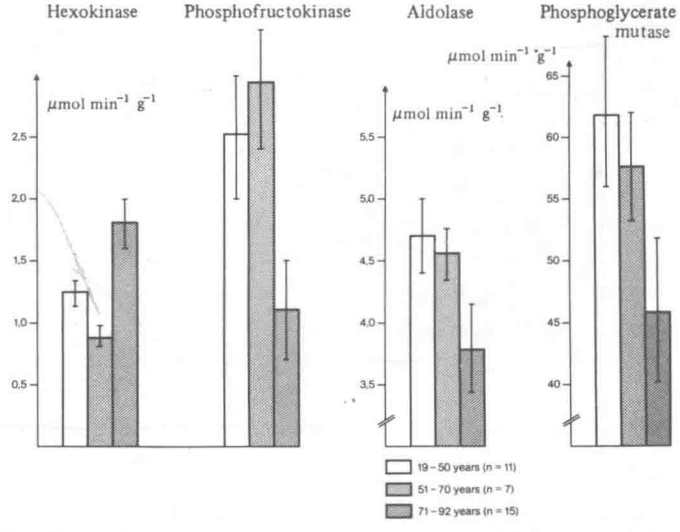

Fig. 5. Age-dependent changes in glycolytic enzymes of the human brain cortex.

Gibson and Blass,[4] Siesjö and Rehncrona[5] and others have also shown that the cholinergic system is highly dependent on intact energy formation. Recovery of acetylcholine synthesis after energy deprivation is much slower than the recovery of energy-rich phosphates or catecholamines. Neurochemical investigations of patients with Alzheimer's and Pick's disease, but also those with senile dementia of the Alzheimer type, reveal, in comparison with normal ageing, greatly decreased phosphofructokinase activity (Fig. 6). In addition, a significant decrease of phosphoglycerate mutase, aldolase, phosphoglucose isomerase and triosephosphate isomerase activity is observed.

The difference in glycolytic turnover between normal ageing and senile dementia is characterized by quantitative but not by fundamental qualitative differences. In the normal ageing brain, the decline of brain metabolism and function stays within the range of the reserve capacity or redundancy of normal brain performance. In senile dementia, however, the functional reserve capacity and metabolic turnover rates are exhausted.

TREATMENT OF DEMENTING BRAIN DISEASE

In the light of the neurochemical changes occurring in senile dementia,

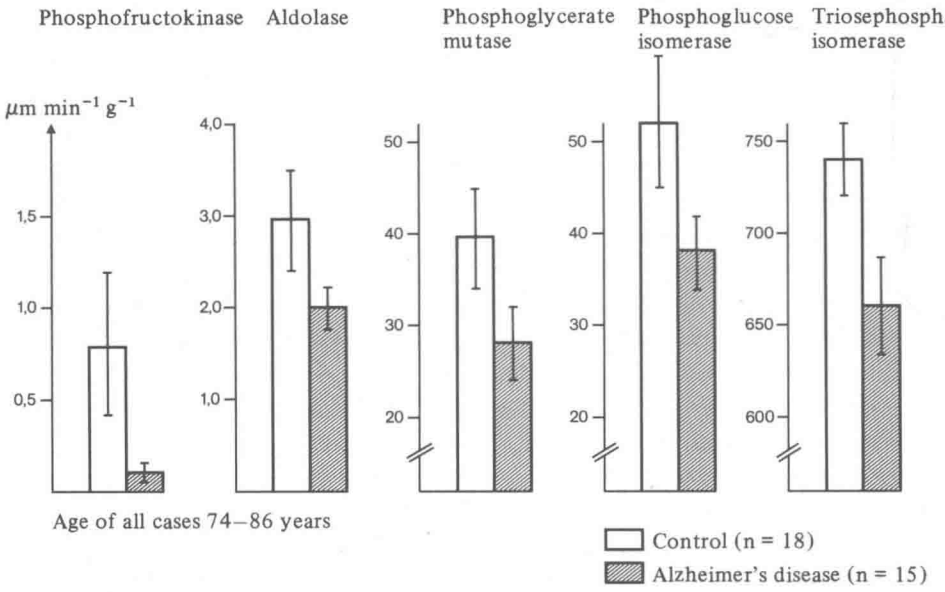

Fig. 6. Changes of glycolytic enzymes in Alzheimer's disease.

two pharmacological approaches are promising. They are: a pathogenetic approach, aiming to enhance cholinergic activity; and an aetiological approach, aimed at an enhancement of glycolysis and energy formation, or a balancing of the cerebral energy-producing processes. Since age-related cerebral changes have been shown to be primarily metabolic, there is no longer any rationale for the administration of vasodilators or any attempt to improve cerebral blood flow or oxygen supply to the brain.

Early forms of a dementing brain disease may be manageable by nootropic and psychotropic drugs. The serious neurochemical and irreversible morphological alterations in senile dementia, however, do not allow – nor will they in the future – any effective treatment. We can only compensate for some of the cognitive dysfunctions of senile mental decline. The most important groups of drugs are: psychostimulants, such as amphetamine; vasodilators, such as papaverine and isoxsuprine; analeptics, such as pentetrazol; and nootropics, such as co-dergocrine mesylate. However, of those, only the nootropic substances have a proven efficacy in senile mental decline. They improve cognitive function, vigilance and mood. An improvement in memory can also be expected, particularly if the compound is given in combination with a cognitive training. These drugs also alleviate dizziness and decrease fatigue. In contrast, analeptics only stimulate respiration and the vasomotor centre; they increase blood flow and stimulate non-specifically the central nervous system. Psychostimulants have similar effects in that they increase blood pressure and pulse frequency, while smooth muscle tone, appetite, fatigue and depressed mood are decreased. Vasodilators have lost their psychogeriatric indication in many countries.

The number of nootropic drugs used in psychogeriatric therapy is remarkably high and it is often hard for the practitioner to decide which drug to prescribe. However, the number of prescriptions written gives an idea of how physicians view the different drugs (Table 1).

Co-dergocrine mesylate (Hydergin®) was the first drug registered in the USA to be effective in the psychogeriatric indication of senile mental decline (registered by the FDA in 1974). In a review commissioned by the German drug authorities (BGA) in 1985 of drugs used in treatment of brain dysfunction in the elderly, only Hydergin® and pyritinol HCl (Encephabol) were approved as being effective.[6] In the same year, the Swiss drug authorities reviewed psychogeriatric drugs and evaluated the use of vasodilators, cerebral activation and metabolic enhancing drugs. The drugs assessed were categorized according to apparent clinical efficacy. Only Hydergin® was placed in the top category A as having its "clinical efficacy demonstrated". Naftidrofuryl

TABLE 1

Prescription profile of nootropic drugs in psychogeriatric therapy (number of prescriptions, according to IMS-MIDAS, 1985)

Millions of prescriptions	Drug name (generic form)
22.2	Hydergin (co-dergocrine mesylate)
14.3	Trental (pentoxifylline)
8.0	Hopate (calcium hopantenate)
6.1	Praxilene (naftidrofuryl)
4.9	Nootropil (piracetam)
4.9	Sermion (nicergoline)
4.7	Sibelium (flunarizine)
4.5	Nicholine (citicoline)

(Praxilene) was rated in category B, as "probably clinically effective" and pentoxifylline (Trental) was in category C.[7] These ratings by national drug authorities must not be overvalued. Clinical efficacy is the only parameter of importance to the physician and the clinical results and varied pharmacological activities of co-dergocrine mesylate appear to be appropriate for its indication in conditions of senile mental decline. It is accepted as the most thoroughly investigated drug in psychogeriatric medicine, both from the pharmacological and from the clinical standpoint. Double-blind studies conducted over a period of 12 months have shown that senility symptoms steadily improve in the course of treatment.[8-10]

A controlled three-year study in healthy retired people demonstrated that co-dergocrine mesylate appreciably retards the development of symptoms of senility.[11] The efficacy of co-dergocrine mesylate in early forms of senile dementia has been confirmed elsewhere.[12, 13] It improves cerebral metabolism, normalizes the age-related depression of glucose utilization and corrects the transmitter imbalance associated with senile dementia. Secondary symptoms of senile mental decline may need additional treatment with anxiolytics, antidepressants and antipsychotics. In general, however, they are not used as a first choice in drug therapy.

It must be kept in mind that only the early symptoms of senile dementia are amenable to treatment, for once it has run its course, dementia represents a terminal state characterized by verifiable neuropathological lesions which are irreversible. We are, at present, far from able to correct all the symptoms of early senile dementia by drug therapy alone. Nevertheless, Yesavage et al.[13] have shown that a combination of drug therapy and cognitive training yields the best results. This brings home the fact that drug therapy can at best create

the preconditions for better mental performance which can only be consolidated in real and lasting improvement by continuous cognitive training. The treatment of the symptoms of senility and early senile dementia thus calls for an appropriate training programme in addition to drug therapy. This programme should not be the sole concern of the patient and the psychologist, but should also involve the family.

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Geriatrics, a growing challenge in health care

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Only in the past few decades has attention on a national and worldwide scale been drawn to social, economic, political and scientific questions raised by the phenomenon of ageing on a massive scale. Previously, although some individuals have lived into advanced stages of life, their numbers and their proportion in the total population were not high. In many parts of the world, however, the twentieth century has witnessed, among other changes, the control of perinatal and infant mortality, a decline in birth rate, improvements in nutrition and basic health care and the control of many infectious diseases. This combination of factors has resulted in more people surviving into advanced life as a greater proportion of the general population.

The problems of old age concern all of us. They now have a socio-economic and political dimension as well as a health care one, the two being interrelated. The twentieth century has also witnessed the very rapid development of technology and industrialization, in which social norms, traditions, religions and attitudes have been slowly changing towards individualism and materialism, loosening human bonds and threatening old people (Fig. 1).[1]

In 1982, Halfdan Mahler, Director General of the World Health Organization, made the following statement on ageing:

"Ageing is . . . a vulnerable phase of life. Older people are at greater risk of mental and social disruption than are other adults, and are physically more vulnerable than any other age group apart from infants. A lifetime of exposure to hostile elements in the environment, the ticking down or the irregular ticking of the biological clock, make them particularly vulnerable. Therefore, ageing people require a wide range of preventive, curative and rehabilitative care. They have special needs in nutrition, in hygiene, in exercise and in immunization. Housing, transport and personal security should be adapted to their particular needs, and in some places already are. Research in all these

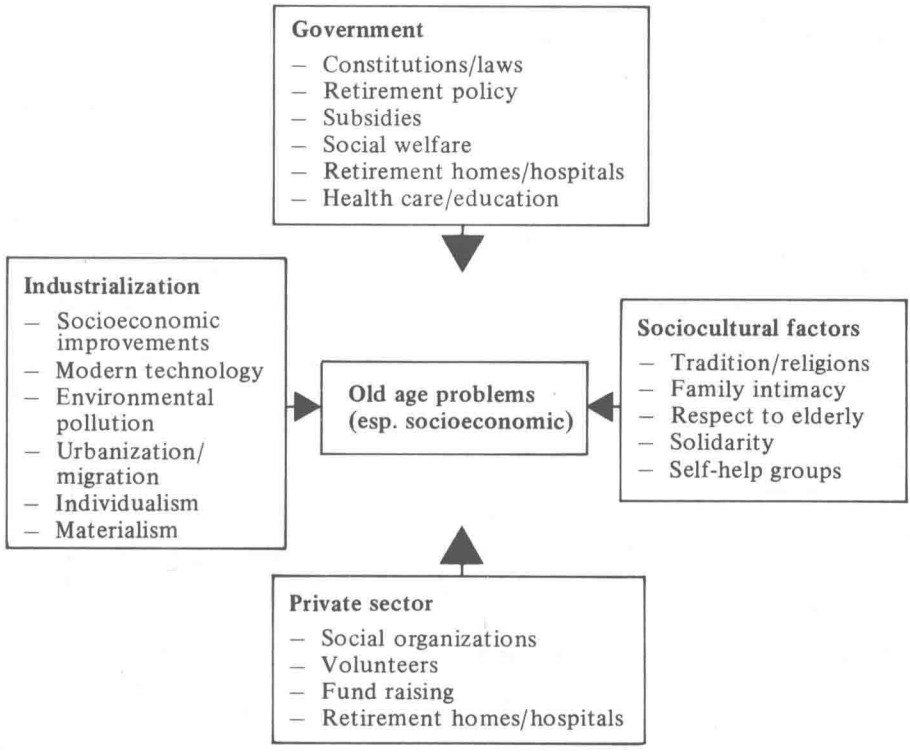

Fig. 1. Important factors influencing problems of old age.[1]

areas and into the whole social and biological process of ageing should receive new impetus.

The situation in many developing countries is somewhat different from that in countries where industrialization and urbanization took place many years ago. Today, in many developing countries, there are still living customs which incorporate the elderly into the life of the community, and these should be maintained. In fact, in these countries, wisdom is still equated with age and the elderly are often considered to be the natural statesmen of the community.

However, nowhere in our world is the situation static, and developing countries are undergoing rapid change as they industrialize and large portions of their population move into urban centres. In such situations, there is a real danger that the mistake, made elsewhere, of excluding the aged from the life of the community will be repeated. Just when the most industrialized countries are rediscovering the human worth of the aged and trying to allow them to live within the community and outside of institutions, whenever possible, it would be tragically ironic if developing nations were to discard their own traditions which accord a place of honour to the aged."[2]

HEALTH CARE

Health care, including medical care, should now take into account gerontology and geriatrics and particularly one of its branches, neurogeriatrics. It is a mistake to think that the scope of geriatrics, even of neurogeriatrics, only consists of dementia and brain ischaemia; on the contrary, its scope is much wider. Health is a state of complete physical, mental and social well-being, not merely the absence of disease or infirmity. Implicit in this is the concept of adding life to years as well as adding years to life. Health care means promotive and preventive, curative and rehabilitative care throughout all periods of the human life cycle, including geriatric health care.

The health of people in South-east Asian countries has less to do with doctors, hospitals, drugs or technology than with sufficient nourishing food, clean water, good sanitation, adequate housing, safe rural or industrial working conditions, maternal health and family planning. Halfdan Mahler has said that "tap water availability is a better indicator of the standard of health in developing countries than the number of hospital beds".

In many South-east Asian countries, the major cause of death is still infectious disease. However, the scourges of industrialized nations, such as heart diseases, cerebrovascular diseases and cancer, are rising rapidly. Thus, while it is still suffering from diseases of want, diseases of plenty are already increasing in South-east Asia. The problems of ageing are also beginning to increase and can be predicted to become more and more common.

GERONTOLOGY, GERIATRICS AND NEUROGERIATRICS

Gerontology is the science of ageing as it affects all aspects of human life. Gerontology is concerned with health rather than with prevention of ageing, while geriatrics is the study of the peculiarities in development, diagnosis, treatment and prevention of diseases in the ageing organism and the question of how to prevent premature ageing. Neurogeriatrics embraces all the points where geriatrics and neurology interact. Its clinical dimensions include the diagnosis and treatment of neurological conditions specifically associated with old age and the processes of ageing.

In general, neurological diseases found in the young can also affect elderly people; however, some neurological diseases are more common in elderly people, in whom the clinical picture may differ from that found in younger age groups. There are no known neurological disorders affecting only elderly people but neurological disturbances are

the most common cause of disability in the elderly. Certain neurological diseases or certain sets of neurological signs and symptoms, e.g. dizziness, falls, gait disorders, mental deterioration and stroke, become more frequent, more obvious or more severe with age.

Stroke

Stroke is a neurological disorder more common in older people since its incidence doubles every decade above the age of 40. Hypertension is known to be associated with increased incidence of stroke but the role of heart disease, diabetes and hyperlipidaemia is less well-defined, except in a clear example such as embolism in valvular heart disease. The vast majority of stroke syndromes are managed medically and conservatively. Indications for surgical management of the thromboembolic state are still not completely agreed upon, although certain general principles seem to apply. Medical management is determined by the presence or absence of associated disease conditions that may contribute to the total disability of the stroke patient.

Dementia in the elderly

Dementia is a global impairment of the cognitive function; it is usually progressive and interferes with normal social and occupational activities. The core of cognitive impairment is characterized by deficits in memory and/or impaired directed or abstract thinking, judgement and intellectual performance. There are two types of dementia: the primary or irreversible type and the secondary or reversible type. Secondary dementia, left undiagnosed and untreated, can also lead to irreversible dementia.

Evaluating dementia patients referred to a neurologist, Albert[3] found that half showed cortical degenerative processes. Multiinfarct dementia, depressive pseudodementia and the effects of alcohol were the next three most common diagnoses. Normal pressure hydrocephalus (NPH) is the most common potentially reversible neurological disorder.

Treatment of dementia

There is still no treatment for primary dementia but secondary dementia can be managed in a number of ways. The first is to treat the underlying cause, such as antibiotics for an infection, removal of a tumour, shunting operations or the correction of metabolic encephalopathies. CNS stimulants (psychostimulants) and metabolic enhancers can be used but the former, including amphetamines, methylphenidate

and magnesium pemoline, may have adverse effects. In animal studies, metabolic enhancers such as piracetam and centrophenoxine typically reduce the effects of experimentally-induced anoxia and improve learning and memory. Some metabolic enhancers alter cerebral blood flow and oxygen utilization. Ergotamine derivatives (co-dergocrine mesylate) are the most widely used and studied all over the world, acting both as vasodilator agents and metabolic enhancers. These drugs are known to increase the activity of certain enzymes of intermediary metabolism in ganglion cells, alter glucose stores in astrocytes, increase cerebral oxygen utilization and increase EEG amplitudes. The changes in EEG activity have been attributed to increased catecholamine reuptake and increased activity of cyclic AMP and ATP.

In 1975, Meyer[4] concluded that the use of effective vasodilator drugs on a long-term basis in patients with atherosclerotic cerebral diseases offers the possibility of improving neuronal function by maintaining cerebral perfusion and by improving neuronal viability and function. This was supported by controlled clinical trials showing improvement of neurological and psychological status. In his 1984 study and review, however, he concluded that "arteriosclerosis is not the sole cause, nor is it necessarily the main cause of the progressive atrophy of the brain. The brain can be expected to age and atrophy regardless of the state of cerebral vasculature, but the appearance of concomitant cerebrovascular disease enhances, accelerates and compounds its ageing process".[5]

While neurotropic agents such as pyritinol cannot arrest the process of ageing, they may at least slow it down. Pyritinol activates anabolic cerebral processes, influences the passage of certain substrates across the blood-brain barrier and increases the glucose supply to the brain tissue. Flunarizine, a calcium channel blocker, is now being tried for vascular dementia.

Brain tumours

Brain tumours may be primary or metastatic. Most primary brain tumours in the geriatric population are glioblastomas and astrocytomas, and they almost always occur above the tentorium cerebelli within the substance of the cerebral hemispheres. By contrast, tumours metastatic to the CNS are found below the tentorium within the brainstem and cerebellum. Malignancies in the lungs of men or in the breasts of women are most likely to metastasize to the CNS in the general population, but CNS secondary tumours from malignancies of the gastrointestinal and urinary system are found more often in people over 65 years of age. Treatment is by surgery.