MEETING REPORT

The Fourteenth International Summer School of Brain Research: Aging of the Brain and Senile Dementia

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THE 14th International Summer School of Brain Research on Aging of the Brain and Senile Dementia took place from August 26–30, 1985, in Amsterdam, The Netherlands. The Summer School was organized by the Netherlands Institute for Brain Research and the University of Amsterdam at the "Trippenhuis," seat of the Royal Netherlands Academy of Sciences. The School was attended by some 170 participants from various disciplines; over 30 papers and 36 posters were presented. During the first four days of the Summer School the following topics were discussed: (1) Diagnosis, (2) Alterations in the Brain and Etiological Factors and (3) Animal Models. The final day of the Summer School, which took place at the Academic Medical Center near the new quarters of the Netherlands Institute for Brain Research, was devoted to the topic (4) Therapeutic Strategies.

I. DIAGNOSIS

The first session was opened by Dr. H. Van Creveld (Amsterdam, The Netherlands), who presented a rational, clinical approach towards the diagnostic problem in the individual patient. This approach emphasized, first of all, an attempt to differentiate between dementia on the one hand, and depression, focal neurological disorders, confusional states and normal aging on the other hand. Once dementia has been established, neurological signs (pupillary abnormalities, pseudobulbar signs and gait disturbances) may provide clues towards the etiology of the dementia. It was pointed out that ancillary investigations (blood and cerebrospinal fluid (CSF) tests, electroencephalogram (EEG) and computerized tomography (CT)) should not be used indiscriminately. Van Creveld stressed the need for follow-up investigations.

In the next paper, Dr. J. Jolles (Utrecht, The Netherlands) reviewed the behavioral, emotional and cognitive deficits in aging and Alzheimer's disease. As people grow older, one usually observes a decrease in nearly all cognitive functions which can be measured: the average aging subject is characterised by a decrease in intellectual functioning, memory, language functions, problem solving and perception. In addition to cognitive deficits, older people also are more likely to develop specific personality characteristics such as a tendency towards inflexibility, cautiousness and a conservative attitude. Evidence has not been found thus far to suggest that the pattern of cognitive deficits in Alzheimer's disease is different from that seen in "normal" aging, although on the average, Alzheimer's disease patients perform significantly worse compared to age-matched controls on all cognitive functions tested. It was stressed that neuropsychologically, the degree of clinical signs in Alzheimer's disease parallels behaviorally similar stages in neuropathological degeneration. For a "definitive" diagnosis of Alzheimer's disease, neuropathological investigation is mandatory.

Dr. R. D. Terry (San Diego, USA) compared neuropathological changes in the aging brain with similar changes in Alzheimer's disease. With normal aging, there is some shrinkage of the brain, while a few tangles or plaques are found. The number of glia cells increases with age. In Alzheimer's disease, these neuropathological lesions are found in larger numbers, while the proportion of fibrous astrocytes is increased without a difference in the total number of neocortical glia. Cell loss is seen in hippocampus, basal nucleus and locus coeruleus. Hirano bodies and granulovacuolar bodies are found in hippocampus, substantia innominata and regional neuropil, and high concentrations of these lesions correlate with the severity of the disease.

The relationship between Down's syndrome and Alzheimer's disease was discussed by Dr. R. S. Williams (Waltham, USA). In Down's syndrome, precocious age-related degenerative changes occur in most organs, and virtually all cases develop neuropathological changes characteristic of Alzheimer's disease by age 40. The neuropathological changes in older individuals with Down's syndrome are identical to those of Alzheimer's disease by conventional criteria. In contrast, relatively few individuals with Down's syndrome autopsied after age 40 exhibit unequivocal clinical signs of Alzheimer's disease and those who do are usually over age 55. The hiatus of several decades in Down's syndrome between the presumed appearance of neuropathological changes in the 4th decade and clinically manifest Alzheimer's disease in the 6th decade or later is not understood at present, but may indicate the presence of an "incubation" period of Alzheimer's disease in the general population.
Dr. R. S. J. Frackowiak (London, United Kingdom) presented a paper on modern imaging techniques. Computerized tomography (CT) scanning and nuclear magnetic resonance (NMR) scanning reveal changes in brain structure, while positron emission tomography (PET) is concerned with the measurement of metabolic, biochemical or pharmacological processes. The latter technique allows for visualization, e.g., of energy metabolism, blood flow and pH by using a variety of ligands. CT, NMR and PET scanning are complementary techniques in the investigation of structural and functional abnormalities of the human brain.

Recent developments in electrophysiology relevant for aging and Alzheimer’s disease were presented by Dr. E. Donchin (Champaign, USA). The latency of the P300 component of the event-related brain potential (ERP) seems to be a promising tool in the study of cognitive deficits in aging and Alzheimer’s disease. A subset of individuals aged 60–85 appeared to have ERP’s without a P300 component, which appeared to be related with a specific psychophysiological profile. Further investigation is needed before definite conclusions can be drawn regarding the value of the P300 in the diagnosis of Alzheimer’s disease.

II. ALTERATIONS IN THE BRAIN

Alterations in the brain during aging and in Alzheimer’s disease were discussed in the second session. Dr. J. M. Candy (Newcastle upon Tyne, United Kingdom), Dr. C. G. Gottfries (Hisingen Backa, Sweden) and Dr. E. Fliers (Amsterdam, The Netherlands) reviewed changes in the various neurotransmitter systems. With respect to acetylcholine, Dr. Candy focused on the nucleus basalis of Meynert, the major source of cortical cholinergic input. This nucleus is severely affected in cognitively impaired cases of Parkinson’s disease, while a moderate neuron loss is found in Alzheimer’s disease. Candy therefore suggested that the cortical cholinergic abnormalities in Parkinson’s disease reflect the primary degeneration of neurons in the nucleus basalis of Meynert, whereas the neuropathological changes in the cortex in Alzheimer’s disease may lead to a secondary retrograde degeneration of cholinergic neurons. The latter hypothesis was supported by animal experimental data as presented by Dr. M. V. Sofroniew (Baltimore, USA), who showed degeneration of immunocytochemically identified cholinergic neurons in the basal forebrain of the rat after mechanical or chemical lesions of the alio- or neocortex. This observation again raised the question whether or not the primary lesion in Alzheimer’s disease might be located in the neocortex. In addition, the cholinergic system is only one of the neurotransmitter systems showing changes in Alzheimer’s disease. Dr. Gottfries showed that the metabolism of dopamine, noradrenaline and 5-hydroxytryptamine might also be disturbed in Alzheimer’s disease. It was proposed, based on changes in their metabolites, that amineergic neurons compensate for cell loss by increased activity in the remaining cells. Moreover, evidence was presented for myelin changes in white matter. The possibility was raised that the latter changes might be of primary pathogenetic significance. Changes in neuropeptidergic systems were discussed by Dr. Fliers. Research on vasopressin and oxytocin neurons has shown that peptidergic neurons undergo differential changes with aging and in Alzheimer’s disease and is dependent on the brain area and cell type studied. Vasopressin cells in the suprachiasmatic nucleus (a hypothalamic structure which is essential for the regulation of circadian rhythms) were found to degenerate to a large extent in senescence and in Alzheimer’s disease, while the “classical” neurosecretory vasopressin cells in the supraoptic and paraventricular nuclei showed signs of increased activity in the same subjects without concommitant cell loss. Fliers concluded on the basis of these observations that normalization of neuropeptide concentrations by supplementation therapy therefore is a difficult, if not an impossible, task to accomplish.

Changes in the suprachiasmatic nucleus may be causally related to changes in circadian rhythms observed in senescence and in Alzheimer’s disease, as evidenced in the temporal patterning of sleep and wakefulness. Therefore, Dr. W. A. Van Gool (Amsterdam, The Netherlands) stressed the necessity of taking into account time-of-day effects rather than referring to static, “normal” young values in gerontological research. A possibly causal relationship was hypothesized between changed biorhythms and changes in performance which accompany aging and Alzheimer’s disease.

Dr. A. J. Cross (Manchester, United Kingdom) presented data on neurotransmitter receptors in aging and Alzheimer’s disease. A specific loss of the S2 serotonin receptor subtype was found to be an early phenomenon in Alzheimer’s disease, which may reflect the loss of a subset of cortical neurons. Furthermore, an increase was observed in several lysosomal enzymes, possibly reflecting an active degenerative process in the cortex.

Dr. H. Braak (Frankfurt, West Germany), used Nissl preparations counterstained for lipofuscin pigment to characterize cortical neuronal types and showed a decrease in the ratio of local circuit neurons to projection cells in the prefrontal cortex with normal aging. In Alzheimer’s disease this decrease occurred at an earlier age.

Dr. R. S. Sohal (Dallas, USA) presented evidence to suggest that the rate of lipofuscin accumulation is governed by the metabolic rate of experimental animals. On the basis of existing knowledge, Sohal suggested that rates of metabolism, lipofuscin accumulation and aging process are interrelated. Oxygen free radicals may be involved in the genesis of certain lipofuscin components.

Dr. J. Korf (Groningen, The Netherlands) discussed two hypotheses proposed to explain crucial events leading to irreversible cell damage. Some have suggested a pathogenetic role for calcium and other cations, while others have identified such a role for the excitotoxins, including glutamate and kainate. Neurochemical data from post-mortem brain material relevant to these hypotheses were presented.

Dr. W. H. Gispen (Utrecht, The Netherlands) discussed age-related alterations in neuronal membrane-fluidity in relation to changes in signal transduction. Ultrastructural studies have shown age-related changes in hippocampal terminals containing the neuron-specific protein B50, which by its degree of phosphorylation modulates synaptic membrane function. Gispen hypothesized that signal transduction may be affected by these alterations in presynaptic hippocampal membranes resulting in a loss of synaptic plasticity in certain hippocampal neuronal circuits with increasing age.

Elegant morphometrical research on changes in the dentritic tree of cortical neurons in senescence and Alzheimer’s disease was presented by Dr. P. D. Coleman (Rochester, USA). Dendrites in the aging brain may exhibit not only net stability or regression but even proliferation depending on region or species studied and events in the immediately surrounding tissue. Dendritic proliferation was found in brain regions that lose closely neighboring neurons, perhaps as a
compensatory mechanism. This mechanism, Coleman proposed, might ultimately fail in Alzheimer’s disease.

Dr. K. Iqbal (New York, USA) presented recent developments in the study of the classical neuropathological hallmarks of Alzheimer’s disease, e.g., neurofibrillary tangles and neuritic plaques. Tangles are composed of paired helical filaments (PHF) which are also found in plaques. PHF are made up of polypeptides and differ both ultrastructurally and biochemically from amyloid and from normal neurofibrils. However, they do share some antigenic determinants with neurofilaments and microtubule-associated proteins.

III. ETIOLOGICAL FACTORS AND ANIMAL MODELS

The third session of the Summer School focused on etiological factors and animal models in the study of Alzheimer’s disease. Dr. C. Kidson (Brisbane, Australia) lectured on DNA damage, DNA repair and the genetic basis of Alzheimer’s disease. Interestingly, Kidson showed a marked, but not complete association between Alzheimer’s disease and genetic susceptibility to DNA damaging agents such as ionizing radiation, which is compatible with mutations in genes regulating DNA repair.

Dr. C. A. Marotta (Belmont, USA) showed changes in mRNA in post-mortem specimens of Alzheimer’s disease brain. Decreased brain proteins and enzymatic activities in Alzheimer’s disease were proposed to be due to a proliferation of astrocytes and a reduction in protein synthesis on the basis of increased cortical RNA-ase activity in Alzheimer’s disease.

Dr. J. Goudsmidt (Amsterdam, The Netherlands) reviewed research on slow virus in relation to various forms of dementia. Scrapie-associated fibers (SAF) have been isolated from the brains of patients with Creutzfeldt-Jakob disease and have been associated with infectivity. These glycosylated proteins show structural similarities with amyloid and paired helical filaments (PHF) found in Alzheimer’s disease. It is questionable, though, whether this may re-open the discussion on possible involvement of infectious agents in Alzheimer’s disease, since experiments concerning the possible infectivity of Alzheimer’s disease brain material have not produced positive results. The possible involvement of aluminum in brain aging and Alzheimer’s disease was discussed by Dr. D. R. Crapper McLachlan (Toronto, Canada). Among the neurotoxic effects of aluminum of possible importance in the pathogenesis of Alzheimer’s disease are a disturbance of calcium homeostasis, in vitro accumulation of 10 nm filaments and increased binding of human linker histones to DNA. The Parkinson/dementia cases of Guam have high density of neurofibrillary degeneration, while the neurons contain high concentrations of aluminum. Although the primary pathogenetic role of aluminum in Alzheimer’s disease remains to be proven, the many toxic effects of the metal to neural tissue to not allow it to be excluded as a causal factor.

Dr. G. W. Van Hoesen (Iowa City, USA) presented evidence for specific neuropsychological lesions in structures that in rhesus monkeys have been shown to link the hippocampal formation and the association cortices, the mammillary bodies and anterior thalamus. These changes, Van Hoesen suggested, might disconnect the hippocampus from other parts of the hemisphere and thus produce memory disturbances.

Dr. C. F. Hollander (Rijswijk, The Netherlands) discussed the many methodological pitfalls in aging research with experimental animals. Several species should be employed in attempts to develop animal models for Alzheimer’s disease, each species contributing in a particular way to a particular problem, since no known animal model mimics all the behavioral and neuropathological defects of Alzheimer’s disease. Hollander suggested that the research method (i.e., longitudinal or cross-sectional) should depend upon both the nature of the experiment and the lifespan of the species to be studied.

Dr. R. T. Bartus (Pearl River, USA) presented a paper describing attempts to assess behavioral and biochemical effects of lesions of cholinergic neurons in the rat basal forebrain (NBM). Lesioned animals showed selective deficits on several memory tests, but following months of elaborate behavioral testing, complete functional recovery was eventually observed. Since post-mortem investigation revealed the expected damage to the cholinergic system without any signs of compensation, a specific and isolated degeneration of the cholinergic system is not likely to be the only important pathogenetic factor in Alzheimer’s disease.

IV. THERAPEUTIC STRATEGIES

The last session dealt with therapeutic strategies in aging and Alzheimer’s disease. Dr. D. F. Swaab (Amsterdam, The Netherlands) pointed out that pharmacological therapies during the last century have not been specific for Alzheimer’s disease, but rather have followed new developments and fashions in neurobiological research in general. Examples were given of strategies derived from endocrinological (transplantation of testicular tissue), vascular and metabolic hypotheses and neurotransmitter research. Even though various explanatory hypotheses have proven to be invalid, some treatments, including environmental manipulation, have resulted in modest improvements in Alzheimer’s disease patients.

Dr. J. M. Palacios (Basle, Switzerland) discussed pharmacological and clinical properties of muscarinic cholinergic agonists. Although clinical trials with direct muscarinic agonists are still limited in number, the compound RS 86 produced memory improvement in a subgroup of Alzheimer’s disease patients. However, Palacios stressed that the feasibility of a cholinergic substitution therapy in Alzheimer’s disease is still doubtful.

The role of neuropeptides in the treatment of cognitive deficits in senescence and Alzheimer’s disease was reviewed by Dr. J. Jolles (Utrecht, The Netherlands). ACTH- and vasopressin-related peptides have been used in clinical studies. ACTH influenced attention and/or motivation upon subchronic administration to patients with minor brain degeneration but did not influence memory processes. Vasopressin-likpeptides were found to have effects on performance in verbal learning tasks, on speed parameters and vitality. The effects of peptides were larger in patients who were less affected by the disease.

Dr. M. Mirmiran (Amsterdam, The Netherlands) presented data on environmental stimulation as a means to influence aging and possibly Alzheimer’s disease. Since environmental complexity appears to enhance brain development in rodents, it was proposed that it might also counteract some of the functional effects of aging. Experiments in old rats are consistent with this notion: housing old rats in an enriched environment influences the sleep-wakefulness pattern in a way similar to that seen in young rats. However, neither the age-related change in circadian organization of sleep-wake behavior nor the deficiency in radial maze performance were corrected. Therefore, environmental stimu-
lation may improve only specific functional changes in old age.

Another "non-pharmacological" approach was presented by Dr. H. R. Lieberman (Cambridge, USA), who related changes in neurotransmitter systems during aging to plasma concentrations of their dietary precursors. Dietary administration of tryptophan, tyrosine, choline and lecithin can influence synthesis of neurotransmitters which show a decrease in the senescent brain. These findings may lead to further research on precursor treatment as a therapeutic strategy in Alzheimer's disease.

Dr. G. S. Roth (Baltimore, USA) discussed the observed age-related decline in dopaminergic regulation of certain motor functions, neurotransmitter release and cyclic nucleotide metabolism, especially in the nigrostriatal system. Recent studies have shown a preferential age-related loss of the D2 receptor subtype, which is most closely linked to control of motor function. Dietary restriction retards the loss of D2 receptors and prevents to a large extent the decrease in psychomotor responsiveness, as well as inducing an increase in mean life span by about 40%. Restoration of responsiveness, according to Roth, is associated with an elevation in striatal receptor levels.

A non-pharmacological approach towards functional recovery of the aged brain was presented by Dr. A. Björklund (Lund, Sweden) who discussed the possibility of nervous tissue transplantation. The possibility that age-dependent deficits in selected behaviors are related to regionally selective degeneration in an anatomically defined systems, has resulted in attempts to improve function by grafting of nervous tissue. Grafts of fetal dopaminergic neurons and cholinergic neurons into the caudate-putamen and hippocampal formation, respectively, were shown to improve motor coordination and spatial learning in aged recipient rats.