KEY TOPICS IN BRAIN RESEARCH

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**Early Diagnosis and
Preventive Therapy in
Parkinson's Disease**

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Preface

Recent studies show an age-dependence of a variety of neurotransmitters, their metabolites and the receptor systems. Similar research strategies are in line with the suggestion that Parkinson's disease cannot be regarded as a simple pronunciation of aging. Rather the underlying pathophysiology is independent of or superimposed to normal aging processes. It has thus been hitherto assumed that Parkinson's disease, if diagnosed early, could be treated in such a way that any progression could be halted or at least minimized. This idea prompted us to organize a workshop dedicated to the question of an early diagnosis and possible therapeutic strategies. A variety of methodological possibilities are available. However, uncertainty exists about the specificity and sensitivity of such methods. In fact, our current knowledge and today's availability of circumscribed methods of different origin do not put us in a position to be able to come to a conclusive diagnosis of Parkinson's disease by the use of only one of these strategies. On the contrary, a high rate of diagnostic accuracy can be achieved only by the use of several methods including imaging techniques, biochemical, electrophysiological and clinical assessments.

A second item concerned the possible therapeutic strategies of early Parkinson's disease. Here, overall agreement was achieved between all participants: a patient with early signs of Parkinson's disease should be treated from the outset. Furthermore, it became evident that not all MPTP-antagonizing substances are of therapeutic value in Parkinson's disease. It also transpired that a variety of animal species are more useful for simulating the early phase of Parkinson's disease (e.g. rats, mice) while others are more suitable for covering the symptoms of advanced phases (e.g. monkeys).

These proceedings give a survey of the most recent aspects of early diagnosis and preventive therapeutical strategies. By including the most important parts of the discussions, we hope to give the reader a lively insight into the problems behind these important new vistas and stimulate the scientific community into developing methods and diagnostic possibilities to help prolong both the life-

expectancy and the quality of life of those rendered susceptible to Parkinson's disease.

This workshop would not have been possible without the financial support of Hoffmann-La Roche, Grenzach-Wyhlen. In particular, we would like to thank Mr. J. Wanzlik for his help in organizing this meeting.

Furthermore we are grateful to Dr. K. Blau who improved the english style of a number of manuscripts and the "Discussions". The secretarial help by Mrs. J. Philipp, Mrs. H. Bigge, Mrs. I. Riederer, and Dr. R. Steinberg is gratefully acknowledged.

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October 1988

H. Przuntek and P. Riederer

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Welcome and introduction

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Ladies and Gentlemen,

It gives me great pleasure to welcome you to the Symposium on "Early Diagnosis and Preventive Therapy in Parkinson's Disease".

The Neurological Clinic of Würzburg University is the oldest Neurological clinic in Bavaria, and right from its foundation the investigation and treatment of extrapyramidal disease has been a significant aspect of its work, starting with Professor Schaltenbrandt. In this connection we may recall his stereotactic atlas, which even today is still in regular use in the stereotactic department.

The early diagnosis of extrapyramidal disease seemed in the first place to be of particular value in genetically determined diseases, since it offered the best chance of discovering and treating affected patients in the families afflicted with the disease. Thus in the seventies our attention in Würzburg was above all focussed on the early diagnosis and treatment of Wilson's disease.

After we had established the possibility of early diagnosis of Wilson's disease, and the resulting early treatment, we turned increasingly to attempts at an early diagnosis of Huntington's chorea, where psychometric measurements, biochemical determinations and gene probes found their application. It turned out that the psychometric procedures as well as attention to fine motor performance showed clear evidence of the disease before it became evident through its clinical manifestations.

It was precisely the results of these investigations which led us to suspect that it might be possible that Parkinson's disease too might be detectable at an earlier stage than that at which the diagnosis becomes evident from the clinical signs. In contrast to the genetically determined diseases, however, the early diagnosis of Parkinson's disease represents a much more difficult problem, since, as was the case earlier with tuberculosis, there was no way of avoiding serial investigations.

If we start out from the fact that the disease manifests itself sub-clinically for years before frank clinical symptoms appear, then it should ideally be possible to recognise it by a carefully directed early diagnostic methodology. And if animal experiments with the MPTP-model (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) were to come up with drugs that were prophylactically effective it might then be possible to investigate such drugs for their effectiveness in preventing the progression of the disease in Parkinsonian patients.

It therefore seems particularly important to investigate whether psychometric procedures might not be suited, as in Huntington's chorea, to provide evidence of the presence of Parkinson's disease. Various studies indicated that the pre-morbid personality in Parkinson's disease was characterised by depression, introversion, rigidity and inflexibility. These findings were confirmed in twin studies, from which it became evident that the twin who developed Parkinson's disease was less extroverted, more introverted and more depressive than the unaffected twin. In more detailed experiments this was shown by higher perseverance-scores e.g. in the Wisconsin card-sorting test. It remains to be established whether such disturbances are ascribable to the degeneration of the mesocortico-limbic system.

Poewe and Gerstenbrand in particular noted early on that the relatives of patients who subsequently developed Parkinson's disease observed distinct early personality changes, so we have to ask ourselves whether such changes might be quantifiable and could be made more specific by suitably designed additional investigations. We also need to enquire whether dementia is a typical feature of Parkinson's disease or whether it is rather occurring within the framework of a multi-infarct syndrome or a dementia of the Alzheimer type.

Patients with Parkinson's disease very early on complain of subjective and autonomic disturbances, which tend to be ignored because they are overshadowed by the more prominent motor disturbances. These subjective symptoms generally take the form of deafness, paresthesia, crawling of the skin, and aches and pains. While it may be difficult to quantify such subjective disturbances, it might be relatively simple to measure autonomic disturbances that manifest themselves by defects in temperature regulation and by seborrhoea.

In Huntington's chorea a pathological posture is seen early on, before other hyperkinetic signs appear which then generally raise the suspicion of a choreatic hyperkinesia. In Parkinson's disease we ought perhaps to consider the possibility that video-recordings might help us early on to document deviations from the patient's normal state. In particular this approach should enable us to make early recordings and to detect and evaluate changes in the patient's postural reflexes.

One of the things one notices is that stress or emotional tension can provoke tremor in Parkinsonian patients. It might be worth seeing whether it is possible, analogous to the effect of curare in myasthenia, by using a stress-inducing substance e. g. β -carboline prematurely to elicit a resting tremor, or by administering a short-acting dopamine agonist perhaps to discover some kind of threshold dose at which a healthy person would not show any movement deficit but a Parkinson patient would respond by showing akinesia and rigor.

Any attempts at early diagnosis procedures must in the first place be based on early-diagnostic procedures which are simple and which can eventually be applied routinely by medical ancillary personnel. For this reason we should use batteries of tests which focus on motor performance so that any noticeable deviations from normal can be followed by diagnostic procedures specific for Parkinson's disease. Because it is the complex motor performance which is affected in Parkinson's disease it should be possible, by refining the testing procedures currently available, to detect motor disturbances earlier than is possible at present. We might, for example, submit patients who have come to our notice because of defects in fine motor performance to some investigation like positron-emission tomography ("PET-scanning"), although it is at this point in time not clear at what clinical stage quantifiable PET-scan results would appear, and what kind of band-width we might expect from age-correlated investigations.

Since we must assume that the pathological changes in Parkinson's disease are not restricted only to the central nervous system, we may expect that beyond psychometric, kinesiological, electrophysiological and pictorial-recording modalities we may find detectable effects in clinical chemical investigations, perhaps on blood cell receptors or changes in enzyme activities. Whether we should extend these to studies on urinary excretion or cerebrospinal fluid changes will be discussed during the symposium.

Parkinson's disease has indeed become a paradigm of the way the pathogenesis and therapy of a neurological disease should be investigated. The last few years particularly have seen us pass a number of important new milestones with regard to our understanding of factors affecting motor function: there has been the MPTP-model, the development of transplantation techniques and the study of Lewy-bodies, as well as the biochemical investigation of tyrosine hydroxylase, of iron metabolism and of the investigation of neuropeptides. There have been fresh insights into the function of the differentiated dopamine-receptors and the reciprocal GABA-ergic and dopaminergic innervation. These are all factors which cannot fail to influence

the treatment of Parkinson's disease. We have to take a fresh look at the treatment approaches used hitherto particularly from the viewpoint of preventive treatment: for example we should look for an answer to the problem, bearing in mind that monoamine oxidase B is not found in the dopaminergic nerve-endings of the striatum, just how MPTP-antagonists might be suited to the provision of a preventive therapy. Further, we have to ask ourselves whether our present pharmacokinetic strategies, particularly with oral administration, where only a fraction of the drug (less than 1% as a rule) reaches the brain following intermittent administration, are not vastly inferior to alternative methods by which the drugs are continuously instilled into the brain. It is my wish for this symposium that a substantial number of these and other questions will find answer or the beginnings of answers. I also sincerely hope that this symposium will be the occasion for closer collaboration between the European researchers active in studies on Parkinson's disease and their counterparts in the friendly neighbouring countries.

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