understanding of the reflex basis of bradycardia is in procedures used for terminating bouts of supraventricular tachycardia. Since breathing inhibits the reflexes that evoke bradycardia all attempts to increase vagal tone—whether by carotid sinus massage, pressure on the eyes, or applying water to the face—should be attempted while the patient voluntarily holds his breath.¹ The obligatory holding of the breath when the face is completely immersed gives the method a physiological advantage over carotid sinus massage or eye pressure¹⁰ unless the patient voluntarily holds his breath during those procedures. Ideally, breath holding should occur in the end-expiratory phase. But as reflex inhibition from intrapulmonary receptors is phasic, and lasts only a few seconds when the lungs are held inflated,³ breath holding in the inspiratory position should carry no great disadvantage.

On the other hand, where bradycardia becomes excessive, as in simple vasovagal faints or during manipulations in ophthalmic and nasopharyngeal surgery,¹¹ it should be preventable by voluntarily increased breathing or by increasing the frequency and amplitude of imposed lung inflations. Even the glass of water given to someone who feels faint makes good physiological sense, for swallowing is known to be associated with intense bursts of firing in central inspiratory neurones, and this central inspiratory activity inhibits vagal excitation and relieves bradycardia.¹

¹ Gandevia, S C, McCloskey, D I, and Potter, E K, *Journal of Physiology*, 1978, **276**, 383.

² Davis, A L, McCloskey, D I, and Potter, E K, *Journal of Physiology*, 1977, **272**, 691.

³ Gandevia, S C, McCloskey, D I, and Potter, E K, *Journal of Physiology*, 1978, **276**, 369.

⁴ Koepchen, H P, Wagner, P H, and Lux, H D, *Pflügers Archiv für die gesamte Physiologie des Menschen und der Tiere*, 1961, **273**, 443.

⁵ Haymet, B T, and McCloskey, D I, *Journal of Physiology*, 1975, **245**, 699.

⁶ Neil, E, and Palmer, J F, *Journal of Physiology*, 1975, **247**, 16P.

⁷ Daly, M B, and James, J E A, *The Peripheral Arterial Chemoreceptors*, ed M J Purves, p 387. Cambridge University Press, 1975.

⁸ Dawes, G S, *et al*, *Journal of Physiology*, 1972, **220**, 119.

⁹ Bystrzycka, E, Nail, B S, and Purves, M J, *Respiration Physiology*, 1975, **25**, 199.

¹⁰ Wayne, J, *Journal of the American College of Emergency Physicians*, 1976, **5**, 434.

¹¹ Katz, R L, and Bigger, J T, *Anesthesiology*, 1970, **33**, 193.

Ciba symposia

How far the mind can be seen as distinct from other functions of the brain is a problem that has challenged neurobiologists, psychiatrists, and philosophers. Last week an invited group of 26 research workers in these and related subjects had a rare opportunity to meet to discuss current concepts on brain and mind at a three-day symposium arranged by the Ciba Foundation.

The meeting was the 200th in a series stretching back to 1950. The published proceedings of Ciba symposia have proved influential in moulding medical opinion on topics such as organ transplantation, artificial insemination, and the medical care of prisoners, as well as providing readers with high-quality reviews of growing points in academic research. Much of the credit for the continued success of the symposia belongs to Sir Gordon Wolstenholme, who is now retiring as director of the Ciba Foundation after 30 years of service. His splendid achievement is plain to see on the shelves of every good medical library.

Regular Review

Aetiology and natural history of Parkinson's disease

A Parkinsonian syndrome may arise from several causes,¹ which should be defined clinically and aetiologically. The common ones are idiopathic paralysis agitans, encephalitis, and the effects of drugs; more rarely, cerebral atrophy or tumour, severe cerebral trauma, carbon monoxide and manganese poisoning, and neurosyphilis may give rise to Parkinsonism.

Drugs may produce Parkinsonism by preventing the action of dopamine in the brain. Phenothiazines and butyrophenones (haloperidol, droperidol) block the postsynaptic dopamine receptor; the ensuing syndrome improves if we stop the drug and give anticholinergic treatment, but it is resistant to dopamine replacement. Reserpine and tetrabenazine produce a similar syndrome but by the different mechanism of preventing dopamine release from the presynaptic neurone; this does respond to levodopa treatment—and withdrawal of the drug.

Parkinsonism was one of the common sequelae of the epidemic of encephalitis lethargica of 1918-26, but the prevalence of this type has declined. Oculogyric crises, dyskinesias, and an early age of onset are characteristic features. The other cerebral disorders that may give rise to

Parkinson's syndrome include progressive supranuclear palsy, the Shy-Drager syndrome, olivopontocerebellar degeneration, the rigid juvenile form of Huntington's chorea, and Wilson's disease. In these conditions the Parkinsonism progresses rapidly with little response to levodopa treatment; and protean physical signs indicate that the Parkinsonian syndrome is only one aspect of a more widespread cerebral disorder. Similarly, Parkinsonian features occur in a variety of diseases causing widespread brain atrophy. Mild signs are particularly characteristic of Alzheimer's disease and senile dementia,² and more rarely complicate severe head injury, cerebral anoxia, and cytotoxic poisoning. Dementia, epilepsy, and corticospinal tract signs are present in varying combinations in these patients. Rarely, the syndrome may be due to a tumour of the basal ganglia, corpus callosum, or thalamus, or to a convexity meningioma. The clinical features and neuro-radiological investigations differentiate these from idiopathic disease.

Parkinson's disease is increasingly common with age. The overall prevalence is about one in 1000, rising steeply over the age of 50 to one in 100. Parkinsonian signs are relatively

common in the geriatric population, in whom the disease often causes little disability and may progress more slowly than in patients with an earlier onset. Some 5-10% of patients have a family history of the disorder, and there exist rare but well-documented cases occurring in several generations. These can be explained if there is a dominant gene with manifestation of the disease in 25% of carriers.³

The most constant pathological finding is a loss of pigmented neurones in the pars compacta of the substantia nigra.⁴ Similar changes are seen in the locus coeruleus and in the dorsal motor nucleus of the vagus. Less often there is a depletion of small nerve cells in the globus pallidus. Lewy bodies are characteristically seen in these areas but are not specific. Some generalised cerebral atrophy, greater than the patient's age would suggest, is common in advanced cases, and recent studies have shown a high prevalence of neurofibrillary tangles, senile plaques, and cerebral atrophy in disproportionate quantity.⁵ Thus there is both clinical and pathological overlap between Parkinsonism and Alzheimer's disease.

Although dopamine deficiency is the most important and constant biochemical lesion in Parkinson's disease, it is not the whole explanation of the clinical features, far less the cause of the disease. The value of anticholinergic substances suggests that one feature of the disease is a relative excess of cholinergic neurotransmission. More important, however, is the evidence of a constant deficiency in striatal dopamine.⁶ Patients excrete less dopamine in the urine than do normal people. Pathologically, the nigrostriatal pathway shows a deficiency of dopamine and homovanillic acid as well as the biosynthetic enzymes tyrosine hydroxylase and dopadecarboxylase. Serotonin, another neurotransmitter, is less strikingly decreased than dopamine. The severity of akinesia is correlated significantly with the degree of dopamine deficiency found in the caudate nucleus; and in patients with predominantly unilateral signs the dopamine deficiency is greater in the contralateral striatum. Drugs that block transmission of dopamine produce a Parkinsonian syndrome; while levodopa, which is converted to dopamine, relieves the symptoms, with dopamine agonists such as apomorphine and bromocriptine producing similar effects both in man and in experimental models.

Although the deficiency of dopamine in the substantia nigra results from destruction of dopaminergic neurones by diverse agents, all the manifestations of Parkinson's disease are unlikely to be caused in this way. Some patients show no response to repletion of dopamine while many who show a good early response have symptoms that are not totally abolished and gradually re-emerge despite prolonged treatment. The disease process is unaltered by dopamine replacement. Another feature is a progressive loss of dopamine receptors in the caudate nucleus, which may explain the decreasing response to levodopa and also indicate that changes of chronic denervation lead to hypersensitivity at the receptor site—clinically apparent as levodopa-induced dyskinesia. This is frequent in patients treated for over a year, and is especially manifest in elderly patients whose brains show diffuse atrophy.

According to one hypothesis, as dopaminergic neurones fail and abandon the receptors in the striatum, cholinergic neurones sprout and innervate these vacant sites.⁷ This leads to an increase in the cholinergic system by a postulated aberrant regeneration, well recognised in the peripheral nervous system.

In considering basic mechanisms we ignore at our peril the

fact that some neuroleptic drugs can diminish the dyskinesia caused by dopamine agonists without increasing the rigidity or akinesia of the disease. Certain drugs can cause acute dyskinesias and neither block therapeutic dopamine nor cause Parkinsonism: metoclopramide is an example. Thus spontaneous and drug-induced dyskinesias probably arise from a population of dopaminergic nerve cells distinct from those affected in Parkinson's disease. This concept of several populations of dopamine receptors is important for treatment.⁸

The roles of other neurotransmitters are described in an excellent paper by Rinne.⁹

Acetylcholine.—In postmortem brain samples acetylcholine esterase activity is decreased in extrapyramidal nuclei and also in the cerebrum and cerebellum. There is an increased ratio of acetylcholine esterase to dopamine in the brains of Parkinsonian patients, which confirms the functional dominance of the cholinergic system.

GABA (gamma-aminobutyric acid).—The main GABA pathways are from the corpus striatum to the substantia nigra, where GABA inhibits dopaminergic nerve cells. The concentration of GABA and its synthesising enzyme (glutamic acid decarboxylase) is reduced by half in patients dying of Parkinson's disease.¹⁰ Deficiency of GABA, which is an inhibitory neurotransmitter, might be expected to release the positive phenomenon of tremor; it has also been held responsible for rigidity.¹¹ In recent trials sodium valproate, which increases GABA concentrations in the brain, had no effect on the Parkinsonism, though it may have produced a minor improvement in levodopa-induced dyskinesia.¹² This is consistent with the fact that increasing GABA concentrations in the pallidum and nucleus accumbens in animals produces akinesia, and diminishes the hyperkinesia induced by dopaminergic drugs.¹³ Baclofen (lioresal) is a GABA analogue and discovery of its value in pyramidal spasticity was followed by trials in Huntington's chorea, tardive dyskinesia, and most recently Parkinsonism.¹⁴ Unfortunately it made the patients worse, and we can only conclude that correcting GABA deficiency in Parkinson's disease is useless. Depletion of GABA is thus likely to be a secondary effect of the disease and of no importance in its causation.

Noradrenaline.—There is a widespread reduction of noradrenaline in brains from patients with Parkinsonism, especially in the mesencephalon and hypothalamus. The decrease is greater than that of its metabolites, suggesting an increased turnover of noradrenaline in the remaining neurones. Its role in extrapyramidal disease, however, remains uncertain.

Serotonin is important in involuntary movements, particularly myoclonus. It is greatly diminished in Parkinsonian brains. Serotonergic neurones may contribute functionally, together with the dopaminergic and noradrenergic systems, in controlling motor behaviour. But serotonin-augmenting agents (for example, fenfluramine) have not produced clinical improvement, nor has L-tryptophan¹⁵ (its precursor) altered extrapyramidal signs.

Peptidergic neurones.—Neural peptides have a probable role in perception of pain, and are widely distributed throughout the nervous system. One of them, substance P, has a high concentration in synaptosomes of the substantia nigra. The concentration of this substance is significantly decreased in the substantia nigra in Huntington's chorea, but the part it plays in Parkinson's disease is unknown. A similar depletion of the peptide angiotensin has been found in Huntington's chorea, but the part it plays in Parkinson's disease is also unknown. A similar depletion of the peptide angiotensin has also been found in Huntington's chorea, but not in Parkinson's disease.

The enkephalins are contained in neurones some of which terminate presynaptically on dopaminergic nerve endings in the striatum. In theory they could modulate the release of dopamine, but how relevant this is clinically we do not know.

Monoamine oxidases.—L-deprenyl potentiates the anti-Parkinsonian effect of levodopa and decreases the on-off phenomenon.¹⁶ This substance is a selective inhibitor of monoamine oxidase type B, and may increase the available dopamine at receptor sites by inhibiting its breakdown.

It has long been known that Parkinson's disease shortens life. In a series of 802 patients in the pre-dopa era (1949-64) there were 340 deaths (43%); the mean duration of illness was 9.7 years, and the mean age of onset was 55.3.¹⁷ Among 241 patients seen within two years of onset and followed up there were almost three times the deaths predicted from life expectancy tables. The course is, however, variable, and we have patients who have survived for 20 years or more. Similarly, Pollock and Hornabrook recorded that nearly a quarter of patients were still alive after 18 years—though this included those with postencephalitic Parkinsonism.¹⁸

In the post-dopa era Barbeau found no evidence that levodopa prolonged the life of akinetic patients, the ratio of observed to expected deaths in his 80 patients being 2.4.¹⁹ The prognosis was worse for women than for men. Other authors, however, have found a significant reduction of death rate during long-term levodopa treatment. In four different series the ratios of observed to expected deaths have been 1.9 (100 patients),²⁰ 1.46 (597),²¹ 1.0 (1160),²² and 1.85 (349).⁹

Levodopa and its analogues not only improve the symptoms but prolong the period during which patients are physically and socially independent. The morbidity and mortality

resulting from chronic inactivity is reduced by symptomatic treatment. In our experience patients dying from true Parkinsonian incapacity, confined to bed and succumbing to bed sores, pneumonia, and venous thromboembolism, are now uncommon. Most deaths are in patients with advanced disease, and result from trauma—for instance, fractures resulting from accidental falls at a stage of the illness when before levodopa they would have been chairbound or bedfast. Increasing survival is also accompanied by increasing death rates from incidental coronary and cerebrovascular occlusions and from malignant disease. Undoubtedly effective treatment delays disability and reduces the number of deaths due to the Parkinsonism itself.

Parkinson's disease poses increasing problems in the aging population, and though the main identifiable abnormality, dopamine deficiency, is amenable to treatment, the prime cause remains unknown. Other neurotransmitters are probably important, though we are still investigating their precise relation to individual symptoms and to the natural progression of the disease. Pharmacological considerations have enabled us to make advances in treatment as shown by the efficacy of dopamine agonists such as bromocriptine²³ and possibly of selected monoamine-oxidase B inhibitors (for example, L-deprenyl).¹⁵ But the associated cerebral atrophy and dementia^{2 5 24} with Alzheimer-like changes indicate a disease that extends diffusely beyond the basal ganglia, and this is the most important limiting factor in treatment.

J M S PEARCE

Consultant Neurologist,
Hull Royal Infirmary

I am indebted to the Parkinson's Disease Society for support of work done in this department.

¹ Pearce, J, Symptomatic Parkinsonism, *Postgraduate Medical Journal*, 1977, **53**, 726.

² Pearce, J, The extrapyramidal disorder of Alzheimer's disease, *European Neurology*, 1974, **12**, 94.

³ Pratt, R T C, *The Genetics of Neurological Disorders*, p 57. London, Oxford University Press, 1967.

⁴ Alvord, E C, et al, The pathology of Parkinsonism, *Advances in Neurology*, 1974, **5**, 175.

⁵ Hakim, A M, and Mathieson, G, Basis of dementia in Parkinson's disease, *Lancet*, 1978, **2**, 729.

⁶ Pletscher, A, Biochemical and pharmacological aspects of Parkinson's syndrome, in *Advances in Parkinsonism*, ed W Birkmayer and O Hornykiewicz, p 21. Basle, Roche, 1976.

⁷ Spehlmann, R, and Stahl, S M, Dopamine acetylcholine imbalance in Parkinson's disease, *Lancet*, 1976, **1**, 724.

⁸ Bédard, P, Parkes, J D, and Marsden, C D, Effect of a new dopamine-blocking agent (oxiperomide) on drug-induced dyskinesias in Parkinson's disease and spontaneous dyskinesias, *British Medical Journal*, 1978, **1**, 954.

⁹ Rinne, U K, Recent advances in research on Parkinsonism, *Acta Neurologica Scandinavica*, 1978, **57**, suppl 67, p 77.

¹⁰ McGeer, P L, McGeer, E G, and Fibiger, H C, Glutamic-acid decarboxylase and choline acetylase in Huntington's chorea and Parkinson's disease, *Lancet*, 1973, **2**, 623.

¹¹ Barbeau, A, GABA and Huntington's chorea, *Lancet*, 1973, **2**, 1499.

¹² Price, P A, Parkes, J D, and Marsden, C D, Sodium valproate in the treatment of levodopa-induced dyskinesia, *Journal of Neurology, Neurosurgery, and Psychiatry*, 1978, **41**, 702.

¹³ Pycok, C J, and Horton, R W, Possible GABA-mediated control of dopamine-dependent behavioural effects from the nucleus accumbens of the rat, *Psychopharmacology*, 1976, **49**, 173.

¹⁴ Lees, A J, Shaw, K M, and Stern, G M, Baclofen in Parkinson's disease, *Journal of Neurology, Neurosurgery, and Psychiatry*, 1978, **41**, 707.

¹⁵ Lees, A J, et al, Deprenyl in Parkinson's disease, *Lancet*, 1977, **2**, 791.

¹⁶ Beasley, B L, Davenport, R W, and Chase, T N, Fenfluramine hydrochloride treatment of Parkinsonism, *Archives of Neurology*, 1977, **34**, 255.

¹⁷ Hoehn, M M, and Yahr, M D, Parkinsonism: onset, progression and mortality, *Neurology (Minneapolis)*, 1967, **17**, 427.

¹⁸ Pollock, M, and Hornabrook, R W, The prevalence, natural history and dementia of Parkinson's disease, *Brain*, 1966, **89**, 429.

¹⁹ Barbeau, A, Six years of high-level levodopa therapy in severely akinetic Parkinsonian patients, *Archives of Neurology*, 1976, **33**, 333.

²⁰ Sweet, R D, and McDowell, F H, Five years treatment of Parkinson's disease with levodopa, *Annals of Internal Medicine*, 1975, **83**, 456.

²¹ Yahr, M D, Evaluation of long-term therapy in Parkinson's disease: mortality and therapeutic efficacy, in *Advances in Parkinsonism*, ed W Birkmayer and O Hornykiewicz, p 435. Basle, Roche, 1976.

²² Zumstein, H, and Siegfried, J, Mortality among Parkinson patients treated with L-dopa combined with a decarboxylase inhibitor, *European Neurology*, 1976, **14**, 321.

²³ Pearce, I, and Pearce, J, Bromocriptine in Parkinsonism, *British Medical Journal*, 1978, **1**, 1402.

²⁴ Pearce, J, Mental changes in Parkinsonism, *British Medical Journal*, 1974, **2**, 445.