Most neuroscientists, I suspect, have two beliefs about tardive dyskinesia. The first is that these involuntary and embarrassing movements result from chronic neuroleptic treatment such as that employed for schizophrenics. The second is that the mechanism for this action of neuroleptics is based on the supersensitivity of post-synaptic dopamine receptors resulting from dopamine receptor blockade. Readers of this new volume edited by Bannet and Belmaker will find both of these beliefs challenged.

One of the major obstacles encountered has been in the occurrence of different forms of dyskinesia which can readily be classified in a purely descriptive sense, but for which the inter-relationships and aetiological conditions remain unestablished. The chapter by Jeste et al. is quite helpful in this respect, distinguishing the phenomenologically similar acute dyskinesia and withdrawal-emergent dyskinesia from tardive dyskinesia in course, prognosis and in pharmacological response. For example, the symptoms of acute dyskinesia respond well to anticholinergic agents whereas those of tardive dyskinesia generally are worsened. It was a pity, however, that no use was made of the more quantitative approaches to classifying movement disorders which, for example, have recently been used to identify three major components, including separate cephalic and combined axial and limb dyskinetic syndromes. In addition, I wonder, in view of the interesting results reported by Casey and Toennies in another contribution, whether the subclassification of reversible and irreversible tardive dyskinesias merely reflects quantitative differences in rates of recovery.

The hypothesis of enhanced dopaminergic receptor supersensitivity, although attractive, is judged inconsistent with many clinical and experimental facts. For example, the increased incidence of these movements in aged subjects does not seem to be consistent with a greater susceptibility to receptor supersensitivity. There is also no convincing evidence of specific dopamine receptor abnormalities specifically in post-mortem tissue of patients presenting with tardive dyskinesia. Furthermore, recent animal models of tardive dyskinesia as reviewed by Goetz, Klawans and Carvey provide quite convincing evidence of spontaneous oral movements following long-term chronic neuroleptic treatment (especially in rats with prefrontal cortical lesions) which are, however, not necessarily accompanied by changes in receptor sensitivity. The complementary review by Domino and Kocsis provides a comprehensive and critical survey of neuroleptic-induced movement disorder in monkeys, some of which appear to resemble closely the clinical phenomenon of tardive dyskinesia.
Other chapters in the book explore the pharmacology of tardive dyskinesia in an attempt to specify causal factors and therapeutic strategies. Thus, there are two chapters (by Hyttel and Christensen, and by Pi and Simpson) discussing the possible development of new neuroleptics with lower potential for inducing tardive dyskinesia, based on advances in understanding the subtypes of dopamine receptor and in the actions of the atypical neuroleptics. Most of the other chapters have tried to capitalize on recent advances in specifying basal ganglia circuitry for identifying possible neurotubulation of dopamine activity. These include dopaminergic pre-synaptic agonism, and cholinergic, gabergic and enkephalinergic mechanisms. Many of these chapters embody fresh new approaches which, however, seem unlikely by themselves to provide the answer to tardive dyskinesia. In particular, the effective use of systemic administration of gabergic agonists would seem likely to be masked by the sometimes opposed effects of activity of the gabergic synapses that would occur at different points in striatal outflow.

Finally, Crow and his colleagues make the provocative suggestion that tardive dyskinesia is not in fact a direct effect of neuroleptic administration, but a part of their type II classification of schizophrenia. This is an interesting suggestion in view of the evidence of cell loss and structural changes in the brain which are postulated to be the underlying pathology in type II schizophrenia. Crow et al. point out that abnormal involuntary movements were described by Kraepelin well before the introduction of neuroleptic drugs and therefore it is unlikely that all involuntary movements in schizophrenics are due to these drugs. It is of course a pity that we can never be sure of the exact similarity of these old clinical descriptions to modern-day tardive dyskinesia. However, Crow’s observations emphasize that neuroleptic drug treatment may be one of several predisposing factors in tardive dyskinesia rather than their only cause. The possibility that the predisposing factors exert their effects by causing structural change and cell loss in the basal ganglia is not the subject of any particular chapter in this present collection which seems an unfortunate, if unavoidable, omission. There is, for example, published evidence of cell loss in ventrolateral striatum following chronic neuroleptic treatment in rats by Nielsen, Lyon and Pakkenberg and the implications of this finding seem sufficiently important to be worthy of further work.

In summary, New Directions in Tardive Dyskinesia Research provides a concise and stimulating review of previous work while also alerting non-specialists to the recent trends in this field. The greater space afforded for discussion of results than is usual for journal articles is probably most welcome to contributors. However, the abiding impression gained from reading these reports is one of mild depression. If a disorder with such easily identified and measured symptoms, and with a large clue about its underlying aetiology, is so resistant to understanding and treatment, what hope is there for our study of the greater complexities of major psychiatric or neurological disorder?

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