DYSKINESIA - AN ANALYSIS OF ABNORMAL INVOLUNTARY MOVEMENT TYPES AMONG WHITE PSYCHIATRIC INMATES OF TOWN HILL HOSPITAL, PIETERMARITZBURG

by

JOHN ANTHONY DUNN

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A B S T R A C T

An overview of the varied clinico-neurological features of dyskinesias in general is presented, and literature on the epidemiology of tardive dyskinesia since the introduction of antipsychotic drugs in 1950, reviewed. Furthermore reasons for the wide variations in previously published prevalence figures have been critically highlighted, and suggestions based upon the current state of clinical and experimental knowledge put forward concerning the pathogenesis of drug induced movement disorders.

The type and prevalence of abnormal or purposeless involuntary movements has been surveyed among a large sample of long term White patients resident in Town Hill Hospital for a period of not less than 4 years, most of whom were either currently receiving or had received neuroleptic medication. This sample comprised 190 men and 98 women whose ages ranged from the third to the ninth decade. Patients manifesting abnormal movements were grouped into 5 general diagnostic categories for analysis viz. schizophrenic disorders, affective disorders, organic brain disorders and syndromes, defective mental development and discrete neurological disorder. The movements were clinically classified in terms of the areas of the body involved and semi quantitatively measured according to a standardised duration rating scale procedure.

Involuntary movements were noted to be present in a total of 83 patients examined, most of which were adjudged to correspond to the syndrome currently termed 'tardive dyskinesia'. Subtype analysis of movement distribution indicated that 27% of cases manifested classical orofacial dyskinesia while 52% showed body dyskinesia of the type designated 'pseudoakathisia'; the balance of the patients presented combinations of the two types.

Schizophrenic disorders constituted the commonest diagnostic category in the dyskinesia group up to the fifth decade. Functionally obtrusive involuntary movements were observed in only some 7% of the patients with dyskinesia. Prevalence overall was equal between the sexes, and no correlations were discerned between age, sex, diagnosis or dyskinesia subtype of cases and the rating scores obtained.

Prevalence rates obtained by this survey are favourably low by comparison with many results of overseas investigators, and are similar in this respect to figures reported in the very few prevalence studies carried out to date in South African institutions.

P R E F A C E

This study represents original work by the author and has not been submitted in any other form to another university. Where use was made of the work of others it has been duly acknowledged in the text.

The research described in this dissertation was carried out in the Department of Psychiatry, University of Natal, under the supervision of Professor W H Wessels.

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C O N T E N T S

CHAPTER 1

INTRODUCTION

1.1 NATURE OF THE PROBLEM

During the 19th century the study of abnormal involuntary body movements engaged the attention of physicians and neurologists who described a variety of symptom clusters emanating from organic brain pathology. Following delineation of mental disorders as discrete clinical entities by Kraepelin and Bleuler in the early years of this century, psychiatric interest focussed on abnormal movements, presumably of functional origin, associated principally with psychotic mental states. Some fifty years later the advent of antipsychotic drugs introduced a neuropharmacological dimension to the problem of abnormal body movements. At present neuroleptics represent the most valuable single therapeutic tool available for treatment of major mental illness but they have been associated with the development of a range of unpleasant clinical sequelae including a potentially irreversible movement disorder.

The clinical value of neuroleptic drugs lies in their ability to induce a state of tranquility without concomitant clouding of consciousness, a quality which has established these compounds as the mainstay of management of acute toxic confusional and psychotic mental states. The

longer term use of neuroleptics has been advocated for the control of chronic schizophrenic thought disorder and the prevention of acute relapses in schizophrenic outpatients (Hogarty and Ulrich,1977). Their widespread therapeutic application was closely associated with neurological side effects which appear to be intimately bound with and indeed may even parallel antipsychotic potency. Within the first few years of clinical usage there were a variety of reports indicating dystonic attacks and parkinsonism as complications presenting in the early phases of treatment, while an involuntary hyperkinesia was recognised as a later phenomenon (Berger and Rexroth,1980). This delayed hyperkinetic syndrome was termed 'tardive dyskinesia' (Faurbye et al,1964) to signify a movement disorder that could manifest itself and persist for years, even after the discontinuation of treatment with the precipitating agent. The name 'tardive dyskinesia' (TD) has become generally accepted and recognised, although other designations have been used in the past to describe this condition including 'terminal extrapyramidal insufficiency syndrome', 'persistent extrapyramidal hyperkinesia' and 'complex dyskinesia' (Gerlach,1979).

As will become evident later, TD thus represents a rather loosely defined clinical entity which is empirically related to usage of drugs which block dopamine receptors in the central nervous system. Some of the abnormal involuntary movements of TD are very like those encountered in other forms of dyskinesia produced by specific disease processes involving the basal ganglia. It is probably for this reason, at least in part, that studies attempting to define predisposing, precipitating and perpetuating factors in relation to TD have yielded inconclusive, varied and often conflicting findings. Currently doubt has been voiced

concerning the use of the term TD to describe involuntary movements of different patterns and unpredictable response to medication (Kidger et al,1980), and there is a body of opinion favouring the view that TD represents a heterogenous group of disorders with a variety of anatomical, neuropathological and pathophysiological bases (Baldessarini et al,1980).

1.2 RATIONALE FOR THE PROJECT

Numerous surveys and studies have been conducted both on hospital residents and outpatient populations to establish the frequency of TD, and to establish parameters such as sex, age and type of underlying psychiatric disease that would have bearing on its appearance in patients exposed to neuroleptics. The results of the work to date are characterised by diversity rather than consensus and frequently the findings of one group of researchers have either not been confirmed, or even contradicted, by the observations of another group.

Over the past four years no research data on the topic of TD have appeared that could be considered as contributing fundamentally new information, or that permit clarification of the many problems relating to its aetiology and epidemiology (Kane et al,1985). Local South African prevalence surveys are sparse, and therefore of particular interest are the findings of 2 studies employing patient samples selected from chronic patients at the Valkenberg psychiatric hospital in Cape Town.

In the first of these, a group of 196 institutionalised patients with

chronic mental illness was studied to determine the prevalence of unrecognised physical disease (Morris et al,1983); the cases examined were all White patients from three randomly selected 'chronic' wards. The authors noted that some 22 (11%) of these individuals manifested dyskinetic movements, some of which 'may have been due to tardive dyskinesia' (sic). The anatomical character, age distribution and severity of the dyskinesias was not defined, and neither the means of clinical assessment nor the clinical diagnoses of the patients manifesting abnormal movements were specified. Noteworthy within the context of the latter point is that 'organic psychosis' comprised some 35 of the total sample, together with a few cases of epilepsy and Huntington's chorea; all but 2 of the 22 dyskinetic patients were females.

More recently published was a survey designed specifically to determine the prevalence and subtype distribution of TD at the same hospital (Holden et al,1984). This later study involved systematic examination of a larger sampling - 278 individuals - of White inpatients drawn also from long term stay wards, and which presumably represents a population overlapping, though not entirely identical with, that reported on previously by Morris. Neurological screening was employed and cases manifesting discrete neurological disorder were excluded; abnormal movements observed were rated on a 4 point severity scale. Prevalence of TD in these patients was estimated to be 17% (25 males and 24 females), a figure which included 7 cases whose dyskinesia might have resulted from spontaneous oral dyskinesia, dental problems and organic brain syndrome - omission of the latter cases lowered the prevalence to some 14%. The mean age of the 49 afflicted patients was 62 years, and 7 were over 80 years.

Classic orolingual symptoms were observed in only 30% (15 cases) of the TD group, the balance being variations of 'peripheral TD' (an orolingual component with permutations and combinations of abnormal movement in limbs and body).

Because of differences in sampling and methodological approach it would be unwarranted to compare the results of these Valkenberg studies too closely, however the findings overall suggest that TD prevalence inclines to be lower than that observed in psychiatric hospitals abroad. Furthermore it would appear that a simple global clinical assessment of TD (as likely employed in the earlier study, which was not instigated with the investigation of abnormal movements as a primary objective) can provide survey results that coincide passably well with those derived from rating assessment.

Computation based on a random sample of 100 Black psychiatric cases drawn from long term inpatients at Ekuhlengeni Sanatorium, Natal, indicates that overall TD prevalence in this racial group approaches 40% (Holden,1985). Although this prevalence was 'corrected' by the author to about 31% after exclusion of patients with no record of antipsychotic drug exposure, the role of race as a possible TD risk factor might be conjectured.

1.3 AIM AND SCOPE OF THE PROJECT

The objective of this survey was to determine the cross sectional prevalence of abnormal involuntary or purposeless movements in chronic institutionalised White patients of both sexes, at the Town Hill hospital

section of the Midlands Hospital Complex in Pietermaritzburg, Natal. This hospital is the only hospital in the province that provides long term residential care for this group of the mentally ill, and as such receives all patients from the entire province, although a few individuals from other parts of the Republic are also accomodated. The geographical drainage of Town Hill therefore covers an area of some 86,967 square kilometres, serving a White population of 560,000 persons (Department of Statistics,Durban:1983).

Such clearcut categorisation in terms of climatic and socio-cultural mileau proffers an excellent potential to expose possible covertly operative environmental risk factors. Furthermore local surveys of this nature published to date are few in number, being restricted to the couple of studies recently conducted at Cape Town's Valkenberg hospital to which reference has already been made. It seemed of no little importance therefore to carry out a demographic study at a second major psychiatric institution in the Republic, especially in view of the widely varying prevalence rates of TD reported in medical publications based on case surveys from other parts of the world over the past 25 years.

The precise relationship of antipsychotic drugs to the phenomenon of movement disorders remains a topic of contentious debate and some investigators have presented evidence suggesting that abnormal movements primarily reflect organic degenerative pathogy in the central nervous system. This study was therefore designed with a view to delineating dyskinesia in terms of the diagnostic categories of patients involved, which hopefully might provide clues as to the pathogenesis of movement disorders in psychiatric patients as well as guidelines for possible

future research.

1.4 HYPOTHETICAL BASE OF THE STUDY

The hypothesis adopted at the outset of this investigation was that TD is a nonspecific clinical entity and represents simply a final common pathway of somatic expression for deteriorated functional integrity of the basal ganglia. It was further suggested that since abnormal involuntary body movements occur spontaneously as part of a natural aging brain process (the neurochemical components of which have not yet been unambiguously defined), neuroleptics might induce an iatrogenic equivalent by disturbing neurotransmitter equilibrium in the central nervous system. The fact that only certain persons develop dyskinesias indicates that degrees of individual neuroplasticity exist permitting buffering of the aforesaid dysequilibrium process, a quality which itself tends to lose flexibilty with age. Further elaboration of these points appears in subsequent chapters of this dissertation, together with mention of some research findings that would support such a speculative viewpoint.

CHAPTER 2

REVIEW OF LITERATURE

2.1 DYSKINESIA - NEUROCLINICAL PERSPECTIVE

2.1.1 Disorders of movement: dyskinesias

Clinically the term 'dyskinesia' is applied to abnormal involuntary reasonably coordinated motor activity manifested in groups of skeletal muscles. Movements of this type should be contrasted with fibrillation, fasciculation and myokymia which represent activity in single muscle fibres or groups of fibres in an individual muscle. The dyskinesias therefore represent pathologically excessive movement (hyperkinesia) arising from functional disturbance of the extrapyramidal nervous system, especially the basal ganglia, by a mechanism known as 'release phenomenon' whereby the spontaneous rhythmic movements initiated by the motor cortex, normally inhibited by the extrapyramidal system, are no longer suppressed. The movements thus 'released' may involve muscles of the head, limbs or trunk and range in amplitude from mild tremors to extremely gross violent jerks.

While the mechanisms, in anatomical and neurophysiological terms, underlying the production of such movement disorders are not always precisely understood, several well described clinical forms have been documented as follows:

I - TREMORS (the main forms include familial or essential, senile, Parkinsonian, cerebellar, Wilson's disease, hepatic disease and toxins).

II - CHOREIFORM MOVEMENTS (coarse, quick, jerky and quasi-purposeful).

III - ATHETOID MOVEMENTS (arrhythmic, slow and sinuous).

IV - MYOCLONUS (abrupt, irregular and spasmodic).

V - BALLISM (sudden, coordinated limb flailing).

VI - TICS or HABIT SPASMS (frequently of psychogenic origin but in some cases an organic component may be present).

2.1.2 Disorders of tone: dystonias

Dysfunction of the extrapyramidal nervous system produces, concomitant with the abnormal movements described above, associated disturbance of muscle tone the commonest being hypertonia. Dystonia usually refers to mobile spasms of the axial and proximal muscles of the extremities, and

dystonic movements tend to involve large portions of the body and have an undulant, sinuous character which may produce grotesque posturing and bizarre writhing movements - the familial disorder of dystonia musculorum deformans (or torsion spasm) represents a particularly disabling example of truncal dystonia. From a functional viewpoint chorea, athetosis and dystonia may be regarded as a series of disturbances which merge into one another. More localised dystonic states not infrequently encountered by psychiatrists include torticollis, retrocollis, oculogyric crisis, blepharospasm and writer's cramp (these latter two entities in particular have been commonly regarded as purely hysterical motor abnormalities, however there is evidence to suggest that psychogenic factors are not solely responsible, and covert brain pathology may in fact be operative). It is important for the psychiatrist to be thoroughly familiar with the characteristic features of neurological disorders with varied or complex manifestations in order not to misdiagnose some of these conditions as tardive dyskinesia (Granacher,1981).

2.1.3 Pathophysiology and aetiology

While the dyskinesia-dystonia disorders constitute reasonably well delineated clinical entities, the mechanisms in anatomical, physiological and biochemical terms are in the majority of cases far from well elucidated. Of such disorders, Parkinson's disease is historically one of the best documented and merits some detailed consideration since the underlying neurochemical disturbance may be viewed as a prototype model for the understanding of movement disorders in general.

The most commonly encountered form of Parkinson's disease is 'idiopathic parkinsonism' or 'paralysis agitans' as described originally by James Parkinson in 1817. The cardinal neurological deficits comprising this condition are tremor, muscular rigidity, hypokinesis and postural abnormality.

A similar constellation of neurological signs was a common aftermath of the pandemic of von Econmo's disease (encephalitis lethargica or epidemic encephalitis) at the close of the Great War. Cases could appear up to 20 years after the original infection which was sometimes extremely mild. The onset of the 'post-encephalitic' variety was usually at an earlier age than the 'idiopathic' type and the former presented clinical features (such as oculogyric crises and abnormal pupillary responses) not encountered in the latter type.

Other conditions that damage the basal ganglia, as well as causing diffuse brain damage, and result in an akinetic-rigid syndrome include repeated head injuries (such as the punch-drunk syndrome), cerebral syphilis, cerebral anoxia, carbon monoxide poisoning and manganese toxicity. Of particular relevance is the fact that a Parkinsonian syndrome can be induced by certain medications, and in addition such a syndrome may appear as part of other degenerative disorders such as Alzheimer's disease, Wilson's disease or cerebral arteriosclerosis. The latter, however, is no longer recognised as a cause of Parkinson's disease *per se* and the category of 'arteriosclerotic parkinsonism' has fallen into disrepute. 'Idiopathic parkinsonism' is usually diagnosed when no evidence can be found from the history and examination for the presence of other diseases which could be aetiologically relevant.

Parkinsonism is associated with lesions in component parts of the extrapyramidal motor system, especially the pigmented nuclei of the brain stem. It is now widely accepted that the substantia nigra of the midbrain is an essential site of origin for the disorder. Histological cellular degeneration affects the globus pallidus, putamen, caudate and associated nuclei and is a constant feature in the zona compacta of the substantia nigra (Greenfield,1963). The melanin-bearing cells of the substantia nigra are particularly affected to a degree that may be visible to the naked eye. In contrast to the cellular changes tract lesions are slight, and scattered nonspecific changes may be found in the diencephalon, brainstem, cord and cerebral cortex. In post-encephalitic parkinsonism the pigmented cells of the substantia nigra and locus coeruleus are similarly lost.

Of major significance in the understanding of the biochemical basis for parkinsonism has been the establishment of a fundamental neurotransmitter disturbance in the affected basal ganglia - the idiopathic disease consequently can be viewed as a specific degeneration affecting one cell system namely the melanin pigmented neurones of the brainstem which synthesise the catecholamine neurotransmitters dopamine and noradrenaline (Parkes and Marsden,1973). Dopamine (DA) is normally found in high concentration in the pigmented cells of the substantia nigra, the nigro-striatal tract and its terminals in the caudate and putamen. DA concentrations are greatly reduced in the brains of most parkinsonian cases, idiopathic and post-encephalitic, sometimes being reduced to 10% of the normal level in the striatum. Such reductions are evidently due to

degeneration of dopaminergic fibres connecting substantia nigra with striatum - the nigro-striatal tract (Hornykiewicz,1971). Available evidence supports the hypothesis that DA and acetylcholine (ACH) act antagonistically in their effects on the striatum and any alteration of the DA-ACH balance which favours cholinergic dominance results in parkinsonism. Further evidence tending to support the concept of DA lack as being fundamental in the genesis of this disorder is the finding of low homovanillic acid levels in the cerebrospinal fluid of untreated patients with parkinsonism - homovanillic acid is the endproduct catabolite of DA metabolism, and its diminution in the cerebrospinal fluid has been cited as a confirmatory test for idiopathic parkinsonism. The successful use of anticholinergic drugs, levodopa and dopamine agonists in the treatment of parkinsonism represents practical exploitation of the biochemical research findings and additional direct confirmation of the postulated neurotransmitter dysfunction.

Research in the field of the other movement disorders has been less decisive in providing biochemical rationale for observed clinical phenomena and in many instances neither the exact aetiology, anatomical location nor the underlying pathophysiology have been established. However in those conditions manifesting gross dystonic or choreo-athetoid features, degeneration of the basal ganglia has been documented at both macroscopic and microscopic levels thus suggesting neurotransmitter imbalance as a final common pathway in the evolution of the total clinical presentation.

Huntington's chorea is characterised by dementia associated with movement disorders of varying severity; not unexpectedly the brain is usually

small and atrophic with morbid changes frequently most emphasised in the frontal lobes. Grossly there is marked dilatation of the ventricular system, especially of the frontal horns, with striking shrinkage of the heads of the caudate nuclei (which instead of bulging into the lateral ventricles atrophy into a rim of tissue along the ventrolateral edge of the dilated anterior horns). Similar neuronal loss is seen in the putamen while the globus pallidus may be spared to a large degree. The microscopic picture is one of cell loss with gliosis in the cortex (especially layers 3, 5 and 6 of the frontal and parietal lobes) with striking small cell disappearance from the caudate and putamen. Less severe changes are sometimes found in the globus pallidus, substantia nigra or cerebellar nuclei. The aetiology of this clearly genetically determined condition is unknown although the dominant inheritance is suggestive of an inborn error of metabolism possibly derived from abnormality in a specific enzyme process controlled by a single gene. Studies on autopsy brain material indicate a reduced gamma aminobutyric acid (GABA) level in the basal ganglia (Perry et al,1973) while a marked reduction of the enzyme responsible for GABA synthesis (glutamic acid decarboxylase) has been noted in the putamen and globus pallidus (Bird and Iverson,1974). GABA is known to be an inhibitory synaptic transmitter and an imbalance between GABA and DA in the striatal and other areas could be the basis of at least the movement disorder component of Huntington's chorea. A more recent review on the role of DA in relation to this condition based upon postmortem brain examination has been provided by Spokes (1979). A further interesting finding is a loss of Substance-P, an undecapeptide, from the substantia nigra and internal segment of the globus pallidus; Substance-P is considered to be an excitatory neurotransmitter in the nervous system (Kanazawa et al,1979).

By contrast with the marked overall brain atrophy of Huntington's chorea, the external appearance of the brain in Wilson's disease is usually normal. On section however the corpus striatum is found to be shrunken and brownish or brick red in colour and the putamen often shows cavitation. Microscopically neuronal loss is evident in the caudate and putamen while the globus pallidus may manifest little pathology. Abnormalities of copper metabolism appear to be fundamental in the development of the cerebral lesions as well as the multinodular cirrhosis which characterises this disease thereby providing the designation hepato-lenticular degeneration. The resulting neurological disorder is confined to the motor system taking the form of extrapyramidal disturbance with rigidity, tremor, athetoid writhing movements and abnormal dystonic postures of the limbs. From the psychiatric aspect the neurological disturbance in the early stages of the disease may be transient and sensitive to emotional influences leading to an erroneous impression of conversion hysteria. The exact pathogenesis of the disorder remains uncertain but is closely related to an associated deficit of ceruloplasmin (Scheinberg and Gitlin,1952) which is a feature of great diagnostic importance. Both the clinical features and the anatomical location of the brain lesions strongly suggest that the movement disturbances originate from a background neurotransmitter imbalance not dissimilar from that of both parkinsonism and Huntington's chorea, however direct experimental evidence in support of such a postulate is lacking.

Ballism is a movement disorder seldom encountered by the psychiatrist, the clinical features of which differ radically from the disorders

already mentioned. It is a violent species of chorea and the sufferer is afflicted with gross flinging movements of the extremities particularly the arms. The abnormal movement is usually unilateral - hemiballismus - and follows a contralateral lesion in or near the subthalamic nucleus of Luys. The syndrome can be simulated by experimental lesions in primates which can, as in man, be relieved by a secondary lesion in the pallidum, thalamus or upper motor neurone system. Detail of the basic pathophysiological mechanism is unknown.

Lack of knowledge concerning fundamental neuropathology underlying other tremors, tics, habit spasms and dystonias is reflected by the generally disappointing forms of therapy currently employed in their clinical management. As previously mentioned several of these conditions have been considered to be substantially of emotional origin and labelled as hysterical features requiring psychiatric modes of treatment. While psychodynamic factors may indeed represent a not insignificant component of the clinical picture in many instances, an underlying DA neurotransmitter dysfunction can be inferred from the fact that many of the drugs proven in any way therapeutically beneficial are established DA-receptor blocking agents.

2.1.4 Schizophrenic hyperkinesia

Erratic and abnormal movements in the form of stereotypies and mannerisms have been classically presented by schizophrenic patients.

In 1907 Kraepelin described 'a type of convulsive movement, involving the

muscles of eye and speech, which is both characteristic and of frequent occurrence in dementia praecox'. He wrote "These movements remind one of choreic movements and are quite independent of ideas and feelings. There may be associated with them smacking of the lips, clucking the tongue, sudden grunting, sniffing and coughing. Furthermore, in the lips we observe very rapid rhythmical movements. More often there exists a peculiar choreiform movement of the mouth which may be described as an athetoid ataxia" (Kraepelin,1907).

Later, in 1911, Bleuler observed "grimaces of all kinds, peculiar ways of shrugging the shoulder, extraordinary movements of the tongue and lips" (Bleuler,1911).

A more recent thorough study of abnormal motility in a long term hospital population reported mainly repetitive, semivoluntary movements and rituals (Jones and Hunter,1969), although choreiform movements have also been documented as accompanying the classical mannerisms and stereotypies of schizophrenia (Yarden and Di Scipio,1971).

These repetitive actions documented in unmedicated schizophrenic patients may in many respects closely resemble the involuntary movements of the disorders already discussed, however there is no evidence at present to indicate that schizophrenic dyskinesia of this type emanates from organic disturbance of the basal ganglia.

2.1.5 Drug induced hyperkinesias

Until 1968 treatment of parkinsonism relied upon the use of anticholinergic drugs based on atropine derivatives. Within the first few years of the introduction of L-dopa an enormous range of side effects were reported including involuntary movements of choreiform type and every described variety of dyskinesia, akathisia, ballistic, myoclonic and facial movement. Such clinical responses reflect the effect of DA excess at the dopaminergic post-synaptic receptor sites and would be predictable by the proposed neurotransmitter imbalance underlying basal ganglia dysfunction.

A clinical picture identical to Sydenham's chorea has been recognised as being provoked in certain women by the use of birth control pills, and similar features have occasionally resulted from administration of anabolic steroids. Metoclopromide (Maxolon), in popular use for gastrointestinal spasm and flatulence, is a drug of the substituted benzamide group which can produce tremors and parkinsonian features (Indo and Ando,1982) as well as dystonic reactions (Lavy et al,1978) and tardive dyskinesia (Wiholm et al,1984); sulpiride (Eglonyl) is another of this drug group that has recently been reported to produce parkinsonism (Quinn and Marsden,1984). Rarely thyroid hormone may induce hyperkinetic movements (Klawans and Shenker,1972).

Of particular interest and importance to the psychiatrist are the varied movement disorders produced by many psychotherapeutic drugs (Roos and Buruma,1983). Such agents include anticonvulsants (carbamazepine and phenytoin), stimulants (amphetamine and related substances), antidepressants (some weakly 'atropinic' tricyclics), major tranquillisers (especially the phenothiazine, thioxanthene and

butyrophenone derivatives) and drugs used in the control of mania (lithium and reserpine). Reserpine, which is also employed in the treatment of hypertension, causes a parkinsonian syndrome at doses lower than any of the other drugs already mentioned. The neurochemical disturbances underlying the iatrogenic dyskinetic effects produced by some of these substances will be amplified in the following section.

2.2 DYSKINESIA - NEUROCHEMICAL PERSPECTIVE

2.2.1 Neural transmission

The basic functional unit of the nervous system is the nerve cell which transmits electrochemical excitation through its specialised microstructure to other neurones. Structurally the nerve cell comprises a body with two principal extensions viz. numerous dendrites that receive information via receptors, and an axone which transmits messages to the presynaptic terminal. A narrow gap, the synaptic cleft, separates two neurones at a transmission point known as the synapse. Neurotransmitter chemical sustances are released from the presynaptic nerve axone terminal, diffuse along the concentration gradient across the cleft and combine with postsynaptic receptor sites on the dendrites of the postsynaptic neurone. Neurotransmitters are thus chemical moeities which facilitate the transmission of electrical potentials between neurones - such stimuli may be either excitatory or inhibitory in character - and researchers estimate that only some 5% of the brain's neurotransmitters have been identified. Some of these chemical substances may function somewhat differently and are thought to affect neurons in a normone-like

way rather than by transferring the nerve signal from the pre- to the postsynaptic element: the term 'neuromodulator' has been appended to this type of neuroregulator, and the criteria for distiguishing between neuromodulators and neurotransmitters has been given by Barchas (Barchas et al,1978). Of the several neurotransmitters already identified, the biogenic amines are considered to have particular relevance to the clinical problem of movement disorders and have been implicated in the production of psychotic mental disturbance including schizophrenia (Smith and Copolov,1979).

2.2.2 Catecholamines : noradrenaline

Noradrenaline (NA) - also termed norepinephrine - is a principal amine transmitter substance in both the central nervous system and the postganglionic fibres of the peripheral sympathetic nervous system, and is also released from the adrenal medulla.

Most noradrenergic neurones originate in the brainstem from the locus coeruleus and tegmental nuclei of the pons and medulla. This is the zone wherein the cell bodies are located and from which two main neuronal tracts - dorsal and ventral - are derived. The dorsal bundle arising in the pons spreads caudally and terminates diffusely in the neocortex, limbic system, hippocampus, cerebellum, thalamus and dorsal hypothalamus. The ventral tract is of more limited distribution travelling from the pons to the hypothalamus and limbic system.

Receptors for NA are classified as alpha or beta depending on drug

affinity; the postsynaptic or alpha-1 receptor is stimulated by adrenaline, noradrenaline and phenylephrine and blocked by phentolamine; the presynaptic alpha-2 receptor acts in an autoreceptor capacity providing feedback inhibition on the release of NA at the presynaptic terminal; beta receptors are most sensitive to adrenalin and isoproterenol, being blocked by propanolol. The exact biological interrelationships of these receptors has not been completely elucidated.

2.2.3 Catecholamines : dopamine

Neurotransmission via DA occurs principally in the central nervous system although it may also take place at some sites in the autonomic nervous system. Synthesis of this amine follows essentially the same chemical intermediate pathway as for NA, however DA neurones lack the enzyme dopamine hydroxylase which converts DA -> NA.

Within the central nervous system five DA sub-systems, showing a high degree of topographic organisation, have been identified. The main extrapyramidal pathway begins in the substantia nigra of the midbrain and ends in the caudate nucleus and putamen of the basal ganglia; this pathway is specifically involved in control of movement but may have additional cognitive functions. Midbrain to forebrain (from the A10 area medial to the substantia nigra innervating the nucleus accumbens and related nuclei including the olfactory tubercle and an area of frontal cortex) connections of the mesolimbic tracts appear to be involved in memory and emotion; it has been suggested (Crow et al,1977) that the nucleus accumbens is the site of action of antipsychotic drugs. Tracts of

more restricted distribution are the tuberoinfundibular system which connects the hypothalamus to the pituitary for control of the hypothalamic-pituitary endocrine system, the incertohypophyseal tract and the periventricular tract (Bjorklund,1978).

The neuroanatomical organisation of fibre tracts interconnecting the 'pyramidal' and 'extrapyramidal' brain systems is exceedingly intricate and complex, and the striatum itself can be functionally divided into 'ventral' and 'dorsal' or 'limbic' and 'non-limbic' moeities (Scheel-Kruger and Arnt,1985). The pharmacology of the DA receptors found within brain regions innervated by fibres arising in the 'ventral' striatum differs considerably from that of the DA receptors arising in the 'dorsal' striatum - the former receptors are stimulated by apomorphine and inhibited by neuroleptics such as haloperidol (D2 receptors), while the latter mesolimbic receptors are stimulated by clonidine-like drugs and inhibited by agents such as ergometrine and piribedil (Nieuwenhuys and Cools,1983).

Currently DA receptors are classified into D-1 and D-2 types, and functionally into either high and low affinity forms (Seeman,1985). The former receptor is linked to the adenylate cyclase system while the D-2 type is not. Drugs which act as D-1 receptor antagonists include the phenothiazines and piribedil, while pimozide, the phenothiazines, butyrophenones (relatively selective) and substituted benzamides (absolutely selective) act on the latter. It is the D-2 receptor that is implicated in the neuroendocrine control of growth hormone and prolactin, the movement disorder of drug-induced parkinsonism and the antipsychotic action of DA antagonists.

2.3 NEUROLEPTIC DRUGS

2.3.1 Mode of action

The current state of knowledge concerning amine receptors and the effects of antipsychotic medication stems from introduction by Delay and Deniker (Delay et al,1952) in the early fifties of the drug chlorpromazine as a specific treatment for psychotic patients. The antipsychotic application of this compound evolved on purely empirical grounds since the original chemical structure resulted from a systematic search for a phenothiazine with stronger central actions than the antihistamine promethazine, and chlorpromazine was first used in an analgesic mixture; its potentially advantageous application to psychiatry was quickly exploited so that by 1954 the efficacy of this halogenated promazine derivative in the treatment of schizophrenia was well established (Swazey,1974). At about the same time reserpine, an extract of Rauwolfia, had also been demonstrated to have antipsychotic effects but its clinical use was rapidly superseded by chlorpromazine (Miner,1955). Following the therapeutic success of chlorpromazine, other neuroleptics were synthesised by chemical substitutions either of the side chain (position 10) or the ring (position 2) of the basic phenothiazine nucleus. Although their mechanism of action was not understood, it had however been suggested (Deniker,1960) that the antipsychotic effects of neuroleptic drugs was related to the tendency of these drugs to induce extrapyramidal effects. The principal argument against this view was that certain compounds - such as thioridazine - have a lesser incidence of

parkinsonian effects than chlorpromazine (the accepted standard phenothiazine), although nonetheless manifesting unequivocal clincial therapeutic activity. It has subsequently become apparent that extrapyramidal effects of antipsychotics may be inversely proportional to their affinity for central muscarinic receptors, thus a drug such as thioridazine may have enough intrinsic anticholinergic effect to compensate for its disturbance of the extrapyramidal balance between dopamine and acetyl choline (Snyder et al,1974).

The further introduction of antipsychotic drugs, some chemically closely related to phenothiazines (such as the thioxanthenes) and others of quite different structure (such as the butyrophenones), have tended to confirm the conjecture that extramidal and antipsychotic effects are closely related and reflect a basic commonality of pharmacolgical action in these compounds. Recalling the findings of Hornykiewicz (1973) mentioned earlier, viz. lowered brain basal ganglia DA concentrations in patients with Parkinson's disease, it is reasonable to assume that the parkinson-like extrapyramidal manifestations (and even the antipsychotic effects) of neuroleptic drugs are a consequence of functional interference with DA systems in similiar areas of the central nervous system. Whilst, however, in Parkinson's disease there is good evidence to believe that the impairment of dopaminergic neurotransmission is a likely consequence of primary organic degeneration in the nigrostriatal and other pathways with a depletion of DA stores, the effect of antipsychotic drugs is accomplished apparently without quantitative DA loss. In fact antipsychotic medication has been found to actually enhance presynaptic DA turnover and increase dopaminergic neuronal firing (Carlsson and Lindqvist,1963), a finding which has been interpreted as indicating a

feedback response of presynaptic receptors to blockade of the postsynaptic DA receptor sites. Consistent with this view is the fact that these drugs can reverse amphetamine induced abnormal mental states which are dependent upon central DA release (Randrup and Munkvad,1965).

Attention was thus focussed on DA receptors and significant progress was made with the finding of a DA sensitive enzyme, adenylate cyclase, in brain striatal tissue (Kebabian et al,1972). This enzyme is intimately bound with a postsynaptic DA receptor site (specifically the D-1 receptor as already mentioned above) and its activation by DA is selectively antagonised by neuroleptic drugs. Studies of the potencies of a range of neuroleptics in antagonising DA stimulation of this enzyme have demonstrated that activity in this system is in general closely related to antipsychotic potency (Clement-Cormier et al,1974).

Use of ligand-binding techniques has also provided information on the function of DA receptors. Butyrophenone drugs such as haloperidol and spiroperidol bind to striatal tissue *in vitro*; by means of radioactive tritium labels and interactions with other compounds it is possible to identify the component of binding associated with the DA receptor. Ligand binding is inhibited by the presence of other DA antagonists and the relative potencies of various neuroleptics in terms of interaction with the DA receptor; thus defined there appears to be a positive correlation between DA receptor antagonism and clinical potency (Seeman et al,1976).

To summarise, there is a substantial weight of clinical and experimental evidence to indicate that the main action of neuroleptic drugs at the

cellular level is one of postsynaptic DA receptor blockade (Berger et al,1978) - the more efficient the blockade the higher the antipsychotic potency of the drug, and the more likely it is to generate undesirable extrapyramidal side-effects as a consequence of hampered DA neurotransmitter activity. However as Hornykiewicz (1978) has pointed out there are exceptions to this general statement which tend to weaken the hypothesis that neuroleptic antipsychotic activity is solely due to selective blockade of brain DA receptors. While the exact antipsychotic mechanism of these drugs has not been elucidated and remains a focus of debate, there can be no doubt that their clinical administration produces profound DA receptor blockade in the nigrostriatal system (producing extrapyramidal motor disturbances) and in the tuberoinfundibular system (inhibiting growth hormone release and increasing prolactin release by the pituitary). The growing list of drugs manifesting antipsychotic properties - some of which have not been exploited commercially because of excessive toxicity or other unacceptable effects - make it extremely difficult to define some common chemical structure that would explain their pharmacological activity and clinical effects. With regard to chlorpromazine one attractive suggestion was that the molecule might assume a configuration such that a part thereof would fit the stereostructure of DA; this would enable chlorpromazine to attach to and occupy DA receptors with a subsequent blocking action (Horn and Snyder,1971). Although a neat and aesthetically pleasing concept it does not seem likely that the newer non-phenothiazine chemical entities will follow such a specific categorisation, and no one is sure which of several possible configurations any particular molecule will assume.

retrocollis). Occasionally there may be involvement of the respiratory or laryngeal musculature (stridor, dysarthria and foaming), or the limb and axial muscles may be affected producing opisthotonus, tonic flexions of the arms or legs and dystonic posture or gait. The sufferer is fully conscious and acutely distressed by the involuntary muscle spasms. Dystonia of this type develops soon - within hours or the first few days - after excessive initial doses or too rapid increments of medication, although its appearance may partly depend upon individual sensitivity. It reportedly occurs more commonly in men than women and in younger rather than older patients (Ayd,1961), and is readily controlled by intravenous benzodiazepines or anticholinergic drugs.

Such reactions occur in some 2% of patients exposed to neuroleptics and the exact pathophysiology of this drug response is incompletely understood. Similar dystonic effects can be reproduced in animals, and bizarre manifestations typical of the syndrome observed in humans have been reported in baboons treated with haloperidol (Meldrum et al,1977). The findings emanating from experiments on primate models would seem to indicate that acute dystonic reactions are produced as a result of effects on presynaptic DA mechanisms.Such a response possibly occurs *via* a compensatory DA synthesis and release provoked by acute administration of neuroleptic drugs, being a physiological attempt by DA neurones to overcome postsynaptic neuroleptic DA receptor blockade (which *per se* stimulates a heightened postsynaptic DA receptor sensitivity, termed 'super-sensitivity').

2.3.2.2 Akathisia

A significant pharmacological effect of neuroleptics in both animals and man is tranquillisation producing mental quiet and motor immobility. Akathisia therefore represents a distinctly paradoxical sequela of neuroleptic treatment, being a peculiar state of mental and motor restlessness characterised by intense desire to move in order to gain relief from overwhelming feelings of distress.

Akathisia and drug induced parkinsonism commonly co-exist and it has been suggested that the former is a consequence of postsynaptic DA receptor blockade in cerebral DA containing areas other than the corpus striatum. Thus while blockade of receptors in the striatum and such mesolimbic areas as the nucleus accumbens produces inhibition of locomotion in the form of akinesia and catalepsy, the reverse occurs on blockade of mesocortical DA systems. In rodents, destruction of the mesocortical pathways or their terminal projection areas in the mediofrontal and cingulate areas causes locomotor hyperactivity; although entirely speculative it is conceivable that blockade of DA receptors in specific cortical areas of the human brain could produce the physical and mental manifestations of akathisia.

2.3.2.3 Parkinsonism

As previously mentioned iatrogenically induced parkinsonism - also called 'pseudoparkinsonism' or 'Parkinson-like syndrome' - comprises the classic Parkinson triad of hypokinesia, rigidity and tremor which may be accompanied by postural abnormalities and hypersalivation. The 'akinetic

syndrome' consisting of hypokinesia or bradykinesia is the primary and sometimes only symptom, being manifested clinically by a lack of facial expression, micrographia, loss of accessory body movements, monotonous speech and slowness in initiating motor actions; voluntary movement is reduced and the patient may complain of muscular weakness and fatigue.

Drug induced parkinsonism presents some 2 to 4 weeks after instituting therapy and usually spontaneously diminishes in intensity without reduction of medication. It has been reported (Gerlach et al,1977) that after 3 months of neuroleptic treatment at most 25% of the patients require treatment with anticholinergic antiparkinsonian drugs. After withdrawal of neuroleptics the condition remits in the course of a few days or weeks, but in a few cases (Marsden and Jenner,1980) it may persist for several months or even become irreversible. Low dose neuroleptics and perhaps depot preparations in particular are more liable to elicit parkinsonism than high dose neuroleptics, possibly due to the high intrinsic anticholinergic effect of the latter.

Broadly speaking drug induced parkinsonism is a dose dependent phenomenon, however in routine clinical use only some 20%-40% of patients develop overt manifestations and it would appear that an individual susceptibility to antipsychotic medication exists, although the factors determining such susceptibility have not been elucidated. The fact that the age incidence of drug induced parkinsonism parallels that of the idiopathic disease (Ayd,1961) strongly hints that a propensity to the latter may determine the incidence of the former.

From the foregoing statements on the pharmacologic action of neuroleptic

drugs it seems reasonable to conclude that a block of cerebral DA receptors producing the equivalent of brain DA deficiency is responsible for iatrogenic parkinsonism (Hornykiewicz,1975).

2.3.2.4 Chronic tardive dyskinesia

Of all the extrapyramidal complications of neuroleptic treatment the entity today commonly termed tardive dyskinesia (TD) is potentially the most serious since the abnormal hyperkinetic movements may appear only after months or years of drug treatment and are not always remediable. Moreover the clinical onset of TD can supervene for the first time when the offending neuroleptic is stopped and it has been postulated that this complication may be permanent despite drug withdrawal (Crane,1973). Further aspects of this formidable syndrome will be considered at some length in the following section, however it would be appropriate at this point to add that TD is currently believed to result from a gradual disappearance of DA receptor blockade by neuroleptic drugs in the striatum and the emergence of striatal DA receptor supersensitivity, despite continuation of drug intake. That this is undoubtedly an oversimplified concept is borne out by the clinical finding that TD and parkinsonism not infrequently may coexist in the same subject (Gerlach,1977, Mukherjee et al,1982), an observation difficult to explain solely on the basis of DA receptor dysfunction witnout consideration of cholinergic-dopaminergic imbalances. Clinical testing of cholinergic agents and drugs which facilitate or inhibit acetylcholine have shown that only some 50% of patients with TD respond in a fashion fitting the cholinergic-dopaminergic imbalance theory, suggesting that TD is not a

pathophysiologically homogeneous entity (Moore and Bowers,1980). In addition the importance of central noradrenergic mechanisms in the regulation of locomotor activity cannot be ignored, since it has been proposed that NA sets up the sensitivity of the neural systems upon which DA acts and thus controls locomotion (Hornykiewicz,1976). In this context it is worth noting that although 'typical' neuroleptics are generally believed to be specific DA receptor blockers (Hyttel et al,1985), there is evidence to implicate a blockade of beta-noradrenergic receptors as one of the major pharmacologic effects of these drugs (Sternberg et al,1981). Some direct clinical data suggesting adrenergic system involvement has been the recent finding of elevated cerebrospinal fluid NA levels in TD patients (Jeste et al,1984), together with earlier documentation of elevated plasma dopa-beta-hydroxylase and renin activities in a subgroup of TD cases (Jeste et al,1982). Further studies are necessary to clarify the relationship between TD and adrenergic neural systems in the brain.

2.4 TARDIVE DYSKINESIA

2.4.1 Neurological syndromes

The clinical value of neuroleptic drugs lies in their ability to induce a state of tranquility without concomitant clouding of consciousness, a quality which has established these compounds as the mainstay of management of acute toxic confusional and psychotic mental states. The longer term use of neuroleptics has been advocated for the control of chronic schizophrenic thought disorder and the prevention of acute

relapses in schizophrenic outpatients (Hogarty and Ulrich,1977). Their widespread therapeutic application was closely associated with neurological side effects which appear to be intimately bound with and indeed may even parallel antipsychotic potency. Within the first few years of clinical usage there were a variety of reports indicating dystonic attacks and parkinsonism as complications presenting in the early phases of treatment, while an involuntary hyperkinesia was recognised as a later phenomenon (Berger and Rexroth,1980). This delayed hyperkinetic syndrome was termed 'tardive dyskinesia' (Faurbye et al,1964) to signify a movement disorder that could manifest itself and persist for years, even after the discontinuation of treatment with the precipitating agent. The term TD has become generally accepted and recognised, although other designations have been used in the past to describe this condition including 'terminal extrapyramidal insufficiency syndrome', 'persistent extrapyramidal hyperkinesia' and 'complex dyskinesia' (Gerlach,1979). As will become evident later, TD thus represents a rather loosely defined clinical entity which is empirically related to usage of drugs which block DA receptors in the central nervous system. Some of the abnormal involuntary movements of TD are very like those encountered in other forms of dyskinesia produced by specific disease processes involving the basal ganglia already described. It is probably for this reason, at least in part, that studies attempting to define predisposing, precipitating and perpetuating factors in relation to TD have yielded inconclusive, varied and often conflicting findings. Currently doubt has been voiced concerning the use of the term TD to describe involuntary movements of different patterns and unpredictable response to medication (Kidger et al,1980), and there is a body of opinion favouring the view that TD represents a heterogenous group of

disorders with a variety of anatomical, neuropathological and pathophysiological bases (Baldessarini et al,1980).

The original early characterisation of TD was that of involuntary hyperkinetic movements varying in localisation and appearance but occurring with most emphasis in the mouth area, the so-called 'bucco - linguo - masticatory syndrome' triad or 'oral dyskinesia' (Uhrbrand and Faurbye,1960). The circumoral muscles with those of the jaw and tongue were involved producing complex movements, typically sucking, chewing and lateral jaw actions, thrusting and writhing of the tongue, and smacking or pursing of the lips. Tic-like motions of the lips might also spread to involve the eyes and eyebrows resulting in erratic grimacing (an oro-facial syndrome). The pattern of movements differ from individual to individual but tend to show constancy of distribution although varying in intensity at different times. It has been stated that in younger patients the movements frequently consist of regular relatively simple tongue protrusions with synchronous jaw movements, while in older persons the movements are more complex and irregular, the tongue rotating and licking in all directions both inside and outside the mouth. Persistent oral dyskinesia can result in hypertrophy of lip and tongue musculature with coarsening of the features.

As the condition was studied more the mouthing movements were further refined to include puckering, panting, smacking and tongue movements inside the mouth, and the syndrome of TD was broadened from oro-facial dyskinesias to include choreoathetoid movements of the head, neck, trunk and limbs (Table I). Furthermore the clinical picture was complicated in some cases by difficulties of speech and swallowing and by irregular

T A B L E - I

CLINICAL PRESENTATIONS OF TARDIVE DYSKINESIA

OCULAR MUSCULATURE:

Blinking
Blepharospasm

FACIAL MUSCULATURE:

Tics
Grimaces

ORAL MUSCULATURE:

Lip Smacking
Puckering
Sucking
Pouting
Cheek puffing

PHARYNGEAL MUSCULATURE:

Clonic soft palate movements
Involuntary swallowing
Abnormal sounds

LINGUAL MUSCULATURE:

Choreoathetoid myokymic movements
Tongue protrusion

MASTICATORY MUSCULATURE:

Chewing
Lateral jaw movements

LIMB MUSCULATURE:

Choreoathetoid finger movements
'Piano - playing'
Wrist flexion or torsion
Ballistic movements
Ankle flexion or torsion
Toe movement
Foot tapping

TRUNCAL MUSCULATURE:

Shoulder shrugging
Pelvic thrusting or rotation
Rocking
Diaphragmatic movements

NECK MUSCULATURE:

Torticollis
Retrocollis

MISCELLANEOUS SIGNS:

Generalised rigidity
Myoclonic jerks

respiration due to disturbed diaphragmatic action. Thus a wide diversity of abnormalities have been documented under the rubric of TD including axial dystonias, flinging or ballistic-type movements particularly of the arms, movements of fingers and toes, shoulder shrugging, rotatory pelvic movements and lordosis (Marsden et al,1975, Baldessarini and Tarsy,1978, Klawans et al,1980).

In general the movements of TD are exacerbated with anxiety and on distraction of attention, volitional motor activity or with any attempts to voluntarily control the dyskinesia. Relaxation or sedation will tend to decrease the dyskinetic symptoms and the movements disappear during sleep.

The early stereotype of a typical candidate for the development of TD was an old, brain damaged woman who had been hospitalised for a number of years and had received large doses of medication. This depiction is far from accurate and TD is now known to occur with noticeable frequency in younger patients, non-brain-damaged subjects and non-psychotic patients who have received neuroleptics.

2.4.2 Variants

Reported drug induced phenomena include syndromes resembling Huntington's chorea, dystonia musculorum deformans, various tics, and other degenerative diseases of the basal ganglia (Crane,1973). Retrocollis has been described as an irreversible and fatal complication of neuroleptics in old patients (Harenko,1967), while permanent torticollis has been

reported following neuroleptic overdosage (Angle and McIntire,1968) and an entity termed 'psychopharmacotoxic encephalopathy' has also been attributed to drugs (Grahmann,1967). Such neurological disturbances seldom closely mimic the orofacial dyskinetic features of TD. There are no established or universally accepted criteria for the diagnosis of TD and a number of neuromedical disorders producing a similar clinical picture have been described which, if not atypical TD variants, may be incorrectly identified as TD (Berger and Rexroth,1980) and thus require brief attention.

2.4.2.1 Spontaneous orofacial dyskinesia

Alternatively termed 'senile dyskinesia', this entity is clinically indistinguishable from neuroleptic induced TD. It has been difficult to arrive at an accurate assessment of the prevalence of spontaneous dyskinesia, and estimates have been based on studies comparing dyskinesia occurring in treated and untreated patient samples, yielding figures ranging from 0%-36% (Kane and Smith,1982). Some of the highest figures were reported in groups manifesting dementia or 'organic disorder' thus implicating neurological pathology partly as the basis of the dyskinesia. In Kane's pooled data analysis the average prevalence among 19 untreated samples involving 11,000 cases was calculated as 5%.

2.4.2.2 Orofaciocervical dystonia

Another movement disorder frequently involving buccal musculature as well

as causing tremor, chorea and torticollis, is orofaciocervical dystonia or the 'Meige Syndrome' (Tolosa,1979) which was first described in 1910. It is distinguished from other facial spasms or tics by unusually bilaterally symmetrical spasms with a predominantly median focus. Symptoms may occur without specific cause (the idiopathic variety) or in combination with a well defined neurological disorder in patients with levodopa or neuroleptic induced dyskinesias (the symptomatic type). Thorough neurological examination should permit the clinician to distinguish this rare condition from TD.

2.4.2.3 Rabbit syndrome

This late onset neuroleptic induced extrapyramidal syndrome is characterised by rhythmic involuntary movements of the masticatory musculature at the rate of some 5-5.5 per second, which resemble the chewing movements of a rabbit (Villeneuve et al,1973). Unlike TD, the rabbit syndrome responds to anticholinergics, reverses readily following neuroleptic withdrawal and also persists in Stage-I sleep.

2.4.2.4 Pisa syndrome

First documented in 1972 as a complication of butyrophenone administration (Ekbom et al,1972) this unusual condition has received little mention in literature on the side effects of drug treatment, however 2 cases have recently been reported following the use of chlorpromazine and fluphenazine (Yassa,1984). The clinical presentation

consists of a tonic flexion of the trunk to one side, accompanied by its slight rotation, in the absence of other concomitant dystonic features. Since it occurs in patients receiving antipsychotic medication for prolonged periods it may be considered as a manifestation of 'tardive dystonia', in contrast with acute dystonic reactions usually appearing in the early stages of treatment. Unlike the conditions already mentioned, the Pisa Syndrome does not involve the face and so presents no problems in the diagnosis of TD, however the combination of TD and dystonic symptoms has been described and is impossible to differentiate especially when the oromandibular region is affected. The fact that tardive dystonia is late in onset, protracted in duration and refractory to therapy suggests an aetiological and pathophysiological relationship to TD.

2.4.2.5 Brueghel's syndrome

The syndrome of blepharospasm-oromandibular dystonia (Marsden,1976). This entity has many features of the Meige syndrome and is considered by some authorities to be a variant of orofaciocervical dystonia.

2.4.2.6 Tardive Tourette syndrome

This unusual condition was first described in a young woman soon after discontinuation of long term neuroleptic treatment (Klawans et al,1978). The symptoms consisted of multifocal facial tics spreading to shoulders and arms, followed after a few months by vocalisations and barking sounds. After this original report several other cases have been

described, mostly after long term treatment or after diminution of neuroleptic drugs (Mueller and Aminoff,1982).

2.4.2.7 Tardive akathisia and pseudoakathisia

Restless or fidgety movements of the limbs and trunk, termed 'late onset akathisia', have been described as occurring after chronic treatment with neuroleptics (Simpson,1977). Subjective symptoms were less apparent and the condition was regarded difficult to treat being also frequently associated with TD. It has subsequently been suggested (Munetz and Cornes,1982) that there may be a positive association between the occurrence of akathisia and TD, and also that some akathisia may actually be TD, or some form fruste of TD called 'pseudoakathisia'. There could be a progression from true akathisia through pseudoakathisia and finally to clear cut TD.

2.4.3 Prevalence rates

While acute dyskinesia had been recognised early in the usage of neuroleptics, with the exception of two brief reports - one German and the other French - TD was not described during the 1950's, and up to 1965 only three epidemiological studies had appeared in the literature.

The bulk of the epidemiological data appearing in all major scientific publications up to 1980 has been analysed in three comprehensive pooled literature surveys, the period 1967-71 by Crane (1973) and the years

1959-79 and 1960-80 by Kane and Smith (1982) and Jeste and Wyatt (1981) respectively. These critiques merit detailed examination since they provide insights into the rationale for inconsistent findings that have appeared in the journals, and so provide guidelines for design of more reliable clinical investigations. It has become evident that multiple causative factors - of which the definition of the syndrome, the type of patient population, the methods used in obtaining information and the clinical assessment of symptoms, play a major role - contribute variably in many of the discrepancies.

In the reviews mentioned above, TD prevalence figures vary from a low 0.5% to a maximum of 56.4% and sample sizes (N) of individual studies examined range from 30 to 10,000 cases. It is important to note that of 6 studies involving the largest patient samples (N > 1,000 cases), all but 1 reflected TD prevalences of 10% or lower. This latter study is also the only one of the 6 employing severity scale assessment, possibly yielding a more reliable measure of TD. Broadly speaking, higher prevalence rates are a characteristic of those studies employing rated severity scales.

Both Jeste and Kane have provided reasonable statistical evidence suggesting an increase in TD over the two decades since 1960. On the basis of Jeste's figures (combined data from 36 studies) the overall weighted mean prevalence of TD among inpatients rose from some 5% in the 1960-1965 period, 13.6% until 1970, 23.3% until 1975, to 25.7% during the five years 1976 through 1980. Review analysis of 56 studies by Kane yielded an average prevalence of 14.6% for 1960 to 1969, while that for years 1970-1979 was 23.9% (Kane has used several studies rejected by Jeste as being unreliable).

These authors contend that their computations represent real increments in TD prevalence and are not aberrations due to factors such as heightened clinical awareness of the condition, increasing age of patients at risk, or concentration of 'sicker' cases in hospitals over the past 20 years following return of less disabled individuals into the community. Furthermore it is inferred that the positive correlation, over the same period, between an increased number of patients receiving long term neuroleptic treatment and this rise in prevalence of TD reflects an aetiological causal relationship. The conspicuous differences in prevalence rates reported in various papers appear to derive from major methodological diversities, which require brief individual comment.

Diagnostic Criteria - Many studies have not defined the symptom clusters employed in diagnosing TD, and overinclusive data will thus inflate figures of prevalence. As has already been stressed, several neurological disorders may present a clinical picture closely similar to TD and it is perhaps doubtful if symptoms such as tremors, rigidity and akathisia should be identified as TD unless clearly accompanied by the typical bucco - linguo - masticatory triad. Problems of this nature are exaggerated if TD manifests in the company of a second pathology such as paralysis agitans or if cases of senile dyskinesia are not identified.

Symptom Severity - The adoption of rating scale severity assessment has undoubtedly introduced more quantitative and objective appraisal of dyskinetic symptoms. Nonetheless the inclusion of cases of borderline or mild dyskinesia may result in unrealistically high prevalence rates and, conversely, selection of only severe cases would artificially lower the

percentage of patients with dyskinesia. The dramatic effect of this variable is exemplified in a large study (Bell and Smith,1978) showing that the prevalence of TD in a group of more than 1,300 patients would be 12% if only severe cases were included, 26% if moderately severe cases were added and 40% if patients with mild dyskinetic symptoms were included.

Subtypes of Dyskinesia - Studies that treat all TD as a uniform clinical entity for statistical purposes may obscure features of significant clinical subtypes. Discontinuation of medication sometimes triggers the appearance of withdrawal dyskinesia which can ultimately resolve, or in fact herald the onset of true TD. Thus at least two clinical forms of TD have been proposed, persistent and reversible - remission of dyskinetic symptoms within three months of withdrawal of neuroleptics being a hallmark of the latter (Jeste et al,1979) which may constitute some third of cases manifesting the disorder (Jeste and Wyatt,1979). Surveys done soon after cessation of drug therapy could therefore yield a high proportion of withdrawal dyskinesias, whereas restricting the diagnosis of TD to irreversible cases consequently results in lower estimates of the prevalence of the condition. Outpatient group studies are few, however as one American publication indicates some 25% to 50% of individuals may fail to take their medication (Blackwell,1973), the distinction between withdrawal and persistent dyskinesia is an important one when computing outpatient prevalence figures.

Populations Sampled - Prevalence figures are likely influenced by several variables dependent upon the patient type included in any particular survey, although the degree to which each of these contribute to reported

differences is uncertain. Some studies have been carried out exclusively on elderly populations whilst others have included patients of one gender only. Psychiatric inpatient groups have received most attention and outpatients regarded to be at nominal risk for development of TD, although a few surprisingly high outpatient prevalence figures (up to 40%) have been documented. Primary psychiatric diagnosis cannot be correlated with TD which has been reported to occur in patients with schizophrenia, dementia and manic-depressive disorders - however, in the case of the latter condition, symptoms may fluctuate cyclically possibly resulting in variable assessment of severity or prevalence (Holden et al,1984). Surveys using older patient groups are likely to include a greater proportion of persons with 'brain damage'; early reports indicated positive correlation of TD with such damage, which was seldom pathologically defined, and at present the contribution of 'brain damage' to the development of TD is far from clear, although it may be unwise to totally reject organicity as a predisposing element. The role of neuroleptics in the genesis of TD is also poorly understood but errors might have been reduced by separating neuroleptic treated cases from those who had received none or neuroleptics in small amounts for shorter periods, a precaution not adopted by most surveys. Studies on Japanese, Indian, Turkish, American and other European patients suggest that there is no racial predisposition to TD.

2.4.4 Age and sex prevalence

It would seem the view that TD is more common among elderly than among young patients is generally accepted; several reliable studies comparing

patients both with and without TD have shown a higher mean age among the former group. Utilising the figures from six selected studies Jeste and Wyatt (1981) have calculated the weighted mean prevalences in various age groups to be 6% at 40 years, 14% in 41-50 group, 19% in 51-60 group, 34% in 61-70 group and about 31% over 70 years. There appeared to be no progressive increase in TD after the age of 70 years although it should be noted that these studies were not prospective longitudinal studies of the actual incidence of TD with age. Irreversible TD is rare before the age of 40 years and it is possible that irreversibility could be accentuated by age related cerebral changes - which *per se* can produce a movement disorder resembling TD, namely senile dyskinesia - and hence reflected as a rise in TD with age.

The work comparing relative prevalence between men and women appears less conclusive and findings range from a markedly higher prevalence in females to a slightly higher prevalence in males, while others report virtually no intersex prevalence differences. Based on a sampling of 19 studies Jeste and Wyatt (1981) calculated the overall weighted mean prevalence in women to be about 41% higher than that in men. At present it is unclear whether gender prevalence differences reflect actual biological characteristics or simply differences in treatment. One interesting unexplained observation (Smith et al,1978) was that women showed linear increase in TD prevalence with age, while in men prevalence decreased after the age of 70.

2.4.5 Treatment practices

It would be rash to lightly cast aside indications that neuroleptic therapy is a major factor influencing prevalence of the TD syndrome. However drug type, mode and frequency of administration, cumulative drug exposure and concomitant use of anticholinergic medication have all been examined, but have failed to yield any clear pattern relating these variables to the onset of dyskinesia.

There is no hard evidence that certain types of neuroleptics are more likely to produce dyskinesia than others. Kane and Smith (1982) reviewed 15 studies on drug type and TD prevalence and found 5 which reported significant findings. Many of these latter studies tended to relate high potency depot fluphenazine to TD but for methodological reasons this finding cannot be considered conclusive.

It has not been possible to relate TD prevalence to maximum daily dose of drug administered or cumulative drug dosage despite a widely assumed notion that development increases with drug exposure. There are likewise no controlled data suggesting any association between neuroleptic polypharmacy and an increased risk for the development of TD.

The observation that anticholinergic agents frequently (though not by any means consistently) exacerbate already manifest TD has fostered the speculation that the use of such drugs might increase the risk of TD development. At present there is, however, insufficient adequate clinical data to implicate exposure to anticholinergic agents as a significant risk factor in the development of TD. It would nonetheless with the present state of knowledge in this area, be unwise to reduce the importance of judicious use of anticholinergic medication as an adjunct

to long term neuroleptic therapy.

Given concerns about the risk of TD, some have recommended 'drug holidays' or more lengthy drug free intervals as a way of reducing the liklihood of the problem. The data supporting this idea are minimal at best, and there is insufficient information to encourage or discourage drug free intervals in this context. Drug 'holidays' may be useful in identifying patients with masked or latent dyskinesias, but their role in increasing or decreasing the risk of TD development is speculative. Experimentally it has been shown that intermittent haloperidol treatment increased tritiated spiperone binding to the same degree as continuous haloperidol therapy (Bannet et al,1980), and at least two studies have been reported suggesting that drug free intervals may be related to an increased incidence of dyskinesias (Degkwitz et al,1967, Jeste et al,1979). Therefore there is a disquieting possibility that 'drug holidays' could actually lead to persistent dyskinesia.

2.4.6 Clinical assessment

The reliable and reproducible assessment of dyskinetic movements has been, and continues to be, a substantial clinical problem. The majority of studies on TD have employed essentially subjective measurement techniques, and have been based either upon analysis of cumulated clinical reports (used frequently in earlier surveys upon large patient samples) or upon individual direct global appraisal of dyskinesia. This latter approach was later elaborated into rating scale assessments giving discrimination of severity in different body areas. With more complicated

scoring techniques, so designed in order to identify fine quantitative fluctuations in dyskinetic movement, rater skill in terms of reproducibility (test:retest and inter-rater reliability) represents an area of technical weakness. It is possible that some reported variation in intensity of abnormal movements in fact represents subjective variation in rater rather than in objective clinical symptoms (Bergen et al,1984). Attempts to evolve too fine a system may thus be self-limiting and in fact achieve inconsistencies rather than degrees of precision perhaps not essential for the job in hand. No ideal system of measuring abnormal movements that is suited to all test requirements has been evolved, and methods convenient for use in prevalence surveys may not be sensitive enough to detect alterations in response, either amelioration or intensification of dyskinesia, to different drugs. Variety of methodological approaches over the years has contributed in no small way to the variation of reported TD prevalence figures found in different studies.

2.4.6.1 Global evaluation

Most of the better designed studies since 1975 have tended to employ detailed and standardised examination of each patient. Detailed individual clincial evaluation is difficult and time consuming when involving large patient groups, and big sample surveys have generally utilised simpler global evaluations of dyskinesia. In review of 56 case studies Kane and Smith (1982) found the prevalence of TD to average 13.9% in those studies employing nominal (yes/no) categorisation, while 24.4% was averaged in studies using severity scales; there was a clear tendency

for larger samples to yield lower prevalence rates. To date the lowest recorded prevalence rate is 0.5% derived from a massive sampling totalling some 10,019 patients (Hoff and Hoffman,1967); this large survey was based on heterogenous populations from 14 different institutions with many physicians contributing inconsistent data. The overall incidence of TD in the study ranges from 0% to 8% and is attributable to the fact that data was provided by staff members in charge of various wards. The weakness of this particular study is the system used to assemble clinical data which was similar to, and therefore having all the disadvantages of, the questionnaire technique of collecting epidemiological data, especially in the absence of objective criteria for the assessment of TD.

2.4.6.2 Movement frequency

This technique involves counting the number of oral movements, such as tongue protrusions, opening of the mouth or lip pouting, observed per minute. The timed count has been converted into a rating score by some investigators. Approaches based on movement counts are usually used as one of a number of different rating criteria, principally in trials of the therapeutic effects of drugs on TD (Quinn and Marsden,1984). Clearly measurements of this type reflect only focal dyskinetic activity, but as such are amenable to the application of more objective electrophysiological techniques. Oral dyskinesias have been recorded via electrodes placed on the right and left sides of the upper and lower lip, or signals from a pneumatic transducer placed in a balloon in the patient's mouth. Although sensitive, electrical methods present problems as to the validity of their results since the circumstances of the

investigation are stressful for the patient and there may be practical difficulties in getting patients to cooperate, also the recorded curve does not distinguish between physiological and pathological movements of various kinds.

2.4.6.3 Severity rating scales

Clinical rating protocols are currently accepted as the most practical, reasonably valid and consistent means for quantitative assessment of abnormal movements, and they are utilised regularly in literature dealing with the subject of TD. The intensity of dyskinesia in different regions of the body is evaluated by means of a global-item or multi-item rating scale, generally scored from 0 rising to 3 or 4 thus representing 4 to 5 points of severity, depending on individual test format. The variety of rating systems evolved differ mainly in the manner of breakdown of the hyperkinetic movement categories, the inclusion or otherwise of scores for amplitude or duration, and assessment of concomitant parkinsonian features such as tremor, facial expression, etc. None of the published scales are considered completely error-free and standardised videotaping with blind rating of cases is often added to sharpen rater reliability. Two of the more widely used of these rating systems are the Rockland Scale (Simpson et al,1979) and the Associated Involuntary Movement Scale (Guy,1976) - this latter is perhaps better favoured on account of design simplicity (Owens et al,1982), offering a brief yet adequate instrument for the assessment of TD (Smith et al,1979).

The AIMS measures the presence and severity of abnormal movements in 7 areas of the body, viz. muscles of facial expression; lips - perioral

zone; jaw; tongue; upper extremities; lower extremities and trunk (neck:shoulders:hips). Ratings of tremor are specifically excluded, and follow a 5 point severity scale in all areas (0 = none; 1 = minimal or extreme normal; 2 = mild; 3 = moderate; 4 = severe). Additional global items judge features such as overall severity of abnormal movements, patient's subjective awareness of, and distress by, the abnormal movements, and record comment on the past or present wearing of dentures.

Simpson's Rockland Scale records specified abnormal movements on a severity continuum of from 0 (absent) to 5 (severe), and allows construction of a detailed profile of abnormality. A total of 34 items schedule particular movements to be rated, and 9 are for other unspecified abnormal movements; the items are arranged regionally and numerically, viz. face, neck and trunk, upper and lower limbs, and whole body.

The more detailed and sensitive a scale, the greater the demands on the raters, and Gerlach (1979) has ennumerated the advantages provided by the application of video techniques as an aid to improved observations, increased sensitivity, reliability and validity.

With reference to the rise in popularity of severity ratings, Kane and Smith (1982) noted that increased use of such ratings could be positively correlated with increase in reported prevalence rates. One-way analysis of variance indicated that prevalences based on rating scales showed elevation from the 1960's to the 1970's, while those based on nominal categorisation failed to demonstrate any significant change from one decade to the next; it was concluded however that this increase in

reported prevalence could not be attributed entirely to the increased use of rating scales. Rating scale studies have contributed 2 of the highest TD prevalence figures published to date, namely 51.6% (Crane and Smeets,1974) and 56.4% (Jus et al,1976).

2.4.6.4 Instrumental methods

Test-retest reliability of rating scales has tended to be disappointing, and in the case of TD this has been suggested to be due to temporal fluctuations of the syndrome. In order to obviate subjective observer error a number of elegant and complex techniques have been evolved which, by virtue of their need for technically elaborate equipment, are often unsuitable for general routine application to large patient numbers (Buruma et al,1983).

Errors resulting from a high frequency of movements or shifting of the movements to different parts of the body can be remedied by the filming or videotaping of patients, a technique already alluded to above. In the case of orofacial dyskinesia film records should be supplemented with sound track to distinguish between voluntary speech and dyskinesia. Time-lapse photography has been employed in the 'flashlight hold test', which is a functional disorder assessment consisting of a flashlight attached to each hand of a patient seated in a darkened room.

Voice recording has further application in a variety of speech assessment tests. Since patients with TD display bucco - facio - lingual hyperkinesis and dyscoordination, it is postulated that these

disturbances are reflected in altered articulative abilities. Imprecise articulation, breathy voice quality, nasality and intensity range during conversation or on sustained vowel sounds have been analysed by sound separation electronic equipment. Such speech studies are usually used as adjuncts to rating scale assessments (Fann et al,1977).

Electrophysiological contact methods include triaxial accelerometry, oral pneumatic transducers and surface polygraph E.M.G. techniques. Although the precision of these instruments is far superior to observer judgement, the apparatus tends to hamper the patient and so may influence abnormal movements to some degree. Non-contacting unobtrusive techniques based upon ultrasound (Hains and Sainsbury,1972), and more recently doppler-radar (Buruma et al,1982), appear to have value in the investigation of drug effects but are clearly limited in application since they require a signal transmitter and receiver, as well as a transducing element with processor which converts motion into an electrical signal.

CHAPTER 3

PATIENTS AND METHODS

3.1 HOSPITAL PATIENT INFORMATION

This work surveyed the prevalence of abnormal body movements in a marginally selected large heterogenous group of ambulatory White patients from 14 extended stay wards. All cases were regarded as suffering from established serious mental illness in that they were either unable to subsist independently of institution staff care, or that their mental state fluctuated too widely to permit stable social interaction. Hospitalisation for not less than 4 years in Town Hill hospital was taken as the minimum to qualify for inclusion in the study but many of the patients had been hospitalised for considerably longer periods.

Most patients were receiving, or had received, antipsychotic medication with or without additional anticholinergic drugs, however difficulties with patient records made it impossible to obtain accurate prescription data in all cases and any attempt to establish overall neuroleptic intake patterns was abandoned as unreliable.

The psychiatric diagnosis attached to individual patients was taken as that recorded on the case file except that grouping of certain disorders

under collective headings was done to facilitate analysis as indicated below. No fully bedridden or cognitively incapacitated individuals from geriatric wards were included to avoid weighting with senile patients. A history of previous electroplexy was not considered to be of notable relevance since there is little controlled evidence to support an association between such therapy and TD (Kane and Smith,1982).

3.2 DYSKINESIA ASSESSMENT

In order to obtain unbiased blind ratings, whenever possible the physical assessment of abnormal movements was completed without reference to the psychiatric diagnosis of patients being scrutinised, although in some instances particular cases were already familiar to the examiner. Individual clinical ratings were determined by means of a standard three stage sequential examination.

3.2.1 Screening

Each patient was briefly checked for the presence of dyskinesia according to a modification of the Abnormal Involuntary Movement Scale (AIMS) in the following manner:

a) Kinetic examination, in which the subject was observed walking unassisted both in and out of the examination room, as well as walking to and fro some 5 paces with arms extended straight in front. Opposition of each finger to thumb several times separately with either hand was also

checked while standing.

b) Static examination, with the subject seated in a straight backed chair without arms, both feet firmly on the floor and hands resting unsupported on knees or lap. During this time the patient was engaged in quiet general conversation. Further examination was made with the patient standing erect to attention and with arms outstretched.

c) Examination of the tongue at rest in the mouth as well as extended from the oral cavity; if applicable a check on denture fit was done.

3.2.2 Scoring

Patients noted to manifest any abnormal involuntary movement were re-examined without any attempt to evaluate the nature of the dyskinesia, which was then measured on a 4 point duration rating, item grouped to define involvement of specific body areas (Kidger et al,1980) in the following format:-

Duration:

0 = movement absent.

1 = movement present < 50% of observed period.

2 = movement present > 50% of observed period.

3 = movement continuous.

Item Group:

Component 1 - Lips; Tongue; Jaw; Neck.

Component 2 - Trunk; Arms; Hands; Legs.

Component 3 - Lip/Hand tremor (0:absent, or 1:present).

3.2.3. Neurological check

A brief routine clinical examination was performed to identify individuals with isolated focal neurological signs of nonspecific diagnostic significance. Such patients were further excluded from the survey.

3.2.4. Diagnostic categories

Based upon individual ward file diagnosis, all cases manifesting abnormal movements were incorporated into 5 general 'type' diagnostic categories for further analysis:-

a) Schizophrenic disorder - all forms.

b) Affective disorder - all forms.

c) Organic brain syndrome and disorder which includes,

epilepsy;

Korsakoff psychosis;

senile psychosis/dementia.

d) Defective mental development.

e) Discrete neurological disorder.

CHAPTER 4

RESULTS

4.1 FINDINGS AND FIGURES

i/ The entire survey sample (SS group) was composed of 190 males (M) and 98 females (F), the mean age of the former being 50.8 years (ranging from 22 to 85) and the latter 57.2 years (ranging from 27 to 84).

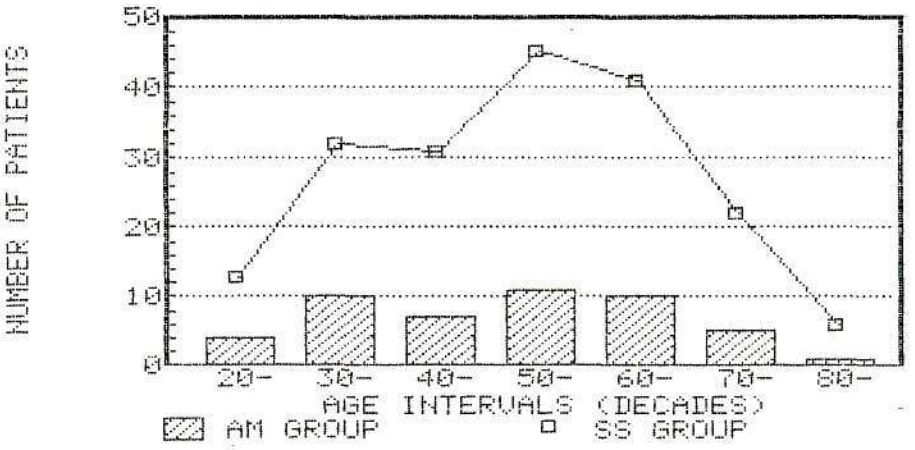
ii/ Of the SS group cases (N = 288), a total of 83 cases (48 M + 35 F) were identified as manifesting abnormal involuntary movements (AM group).

iii/ The ages of the SS group, both M and F patients, conformed closely to a normal distribution pattern, with the F curve showing a mild skewing to the right. Age distribution patterns of the AM group, both sexes, were almost identical with corresponding elements of the SS group (Figures 1 and 2).

iv/ Ward file diagnoses of the AM group are itemised in Table II (Appendix) and depicted in Figure 3. Combination of the various diagnoses into broad 'type' categories indicates that the largest number of cases with involuntary movements is represented by the 'schizophrenic disorder' group (26 M + 16 F), followed by 'organic disorder' (11 M + 10 F) and

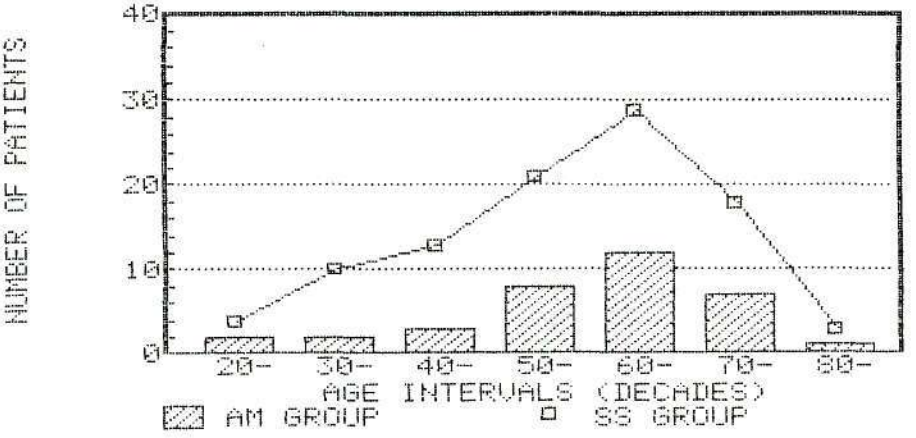
F I G U R E 1

AGE DISTRIBUTION (MALES)



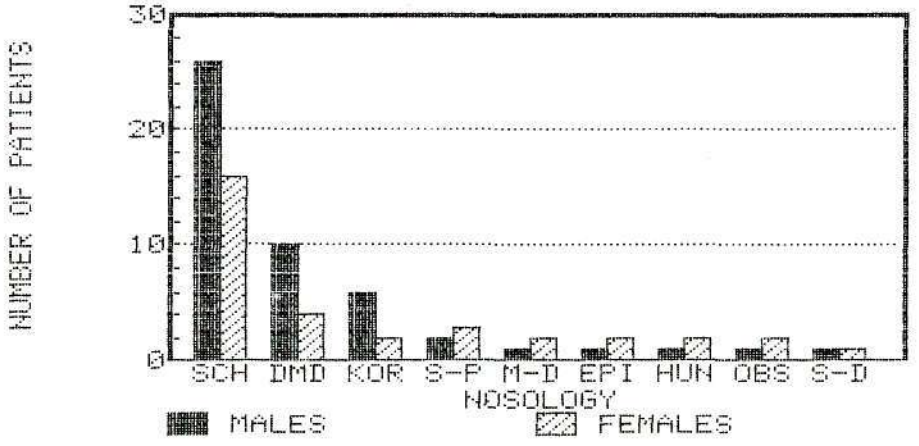
F I G U R E 2

AGE DISTRIBUTION (FEMALES)



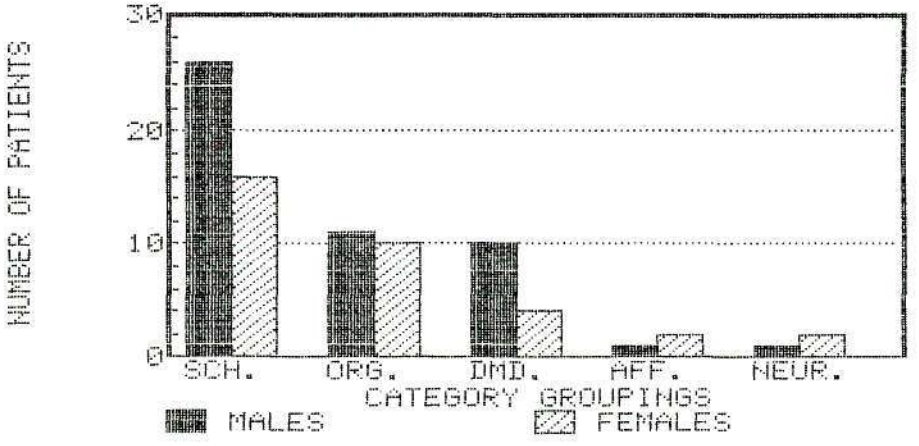
F I G U R E 3

WARD FILE DIAGNOSES (AM GROUP)



F I G U R E 4

CATEGORY DIAGNOSES (AM GROUP)



'defective mental development' (9 M + 5 F); very few cases of 'affective disorder' (1 M + 2 F) and 'neurological disorder' (1 M + 2 F) appear in this study (Figure 4).

v/ The 'affective disorder' group consists entirely of manic-depressive illness (N = 3) and the 'neurological disorder' group of Huntington's chorea (N = 3).

vi/ Abnormal movement subtype analysis of the AM group shows the following component distribution:-

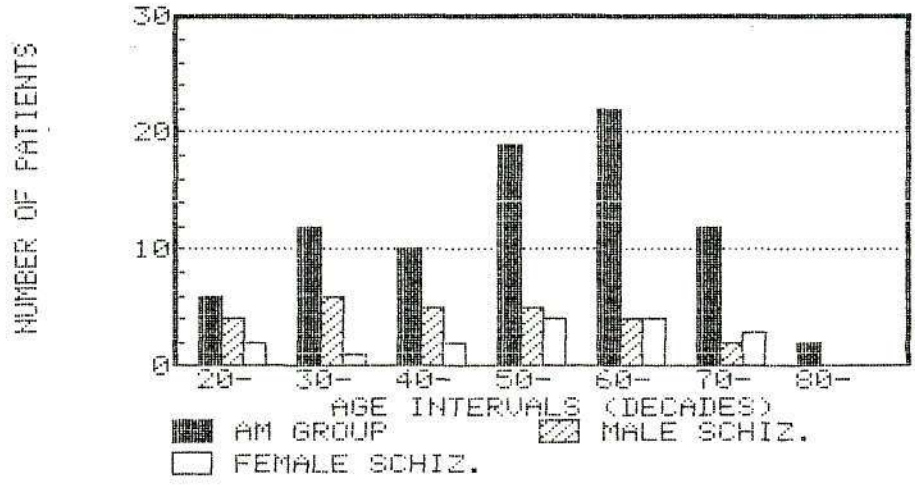
Component 1 (C/1)	-	21 cases (13 M + 8 F);
Component 2 (C/2)	-	44 cases (26 M + 18 F);
Component 3 (C/3)	-	2 cases (0 M + 2 F);
Component 1 & 2 (C/1&2)	-	16 cases (9 M + 7 F).

vii/ The subtype C/3 (hand-lip tremor) is considered to correlate with parkinsonian clinical features (Kidger et al,1980). In order to isolate a patient group whose abnormal movements equate most closely with the entity designated 'tardive dyskinesia', the C/3 cases and the 'neurological disorder' cases (all being C/2 subtypes) were excluded from the AM group, leaving a final TD sample of 78 patients (47 M + 31 F) and yielding an overall prevalence figure of 27% (16.31% M + 10.76% F).

viii/ Schizophrenia forms the major diagnostic category in the TD group, being distributed throughout the entire sample in patients below the age of 80 years (Figure 5). However the cumulative proportion of schizophrenic patients with dyskinesia tends to decline with increasing

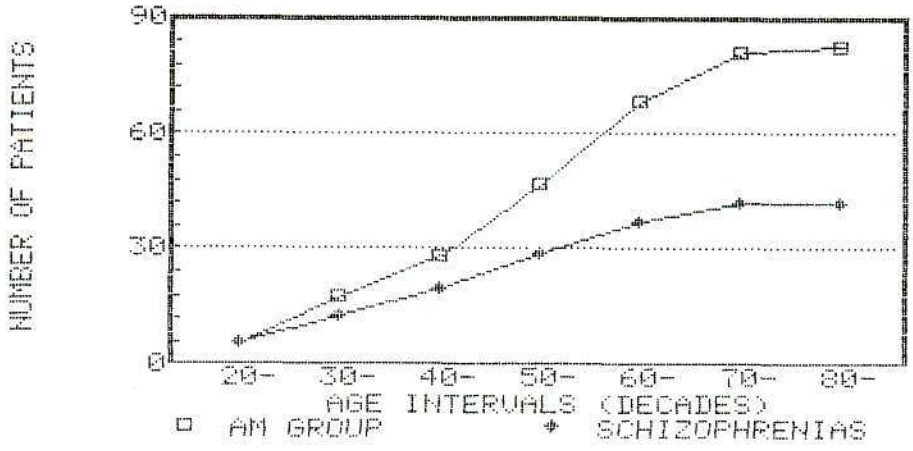
F I G U R E 5

AGE DISTRIBUTION (SCHIZOPHRENICS)



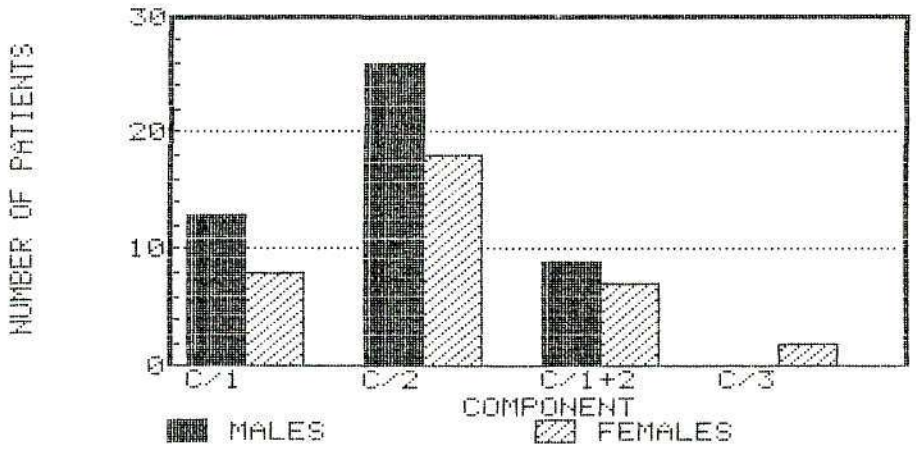
F I G U R E 6

CUMULATIVE AGE DISTRIBUTION (SCHIZOPHRENICS)



F I G U R E 7

DYSKINESIA SUBTYPES (TD GROUP)



age (Figure 6), and in the period from the fourth decade onwards organic disorders show increasing prominence. None of the schizophrenic patients examined were overtly psychotic and the abnormal movements observed were not considered to be mannerisms or stereotypies.

ix/ Patients with orofacial movements (subtype C/1) constitute some 27% of the TD sample (13 M + 8 F; average age: 64 years) and is the group that appears to most closely resemble the original 'bucco - linguo - masticatory' syndrome. Trunk-limb movements (subtype C/2) occur in 52.5% of cases (25 M + 16 F; average age: 48 years) and face-body combinations (subtype C/1&2) in 20.5% (9 M + 7 F; average age: 62 years). These findings suggest that midline dyskinesia of the lower face is a more common feature in older patients. The subtype distribution of the TD sample is shown in Figure 7.

x/ The most severe dyskinesias (rating 2 or 3) were encountered in the patients with Huntington's chorea. Within the TD sample 77% of cases (42 M + 18 F) achieved rating 1, with 19.2% (3 M + 12 F) and 3.8% (2 M + 1 F) achieving rating 2 and 3 respectively; no relationship trends could be discerned between the age, sex, diagnosis or dyskinesia subtype of cases and the rating scores obtained (Table II - Appendix). None of the rare dyskinesia syndromes were encountered, and none of the patients with orolingual dyskinesias (subtype C/1) were considered to have dental problems, although this was the group with highest mean age.

CHAPTER 5

DISCUSSION OF RESULTS

5.1 CRITICAL OVERVIEW

This survey of 228 White patients (190 M + 98 F) has shown that abnormal involuntary movements were present in almost 29% of cases examined. The prevalence of the various specific forms of dyskinesia in the entire sample were as follows:-

Huntingtons' chorea	-	1.04% (3 cases).
Parkinsonism	-	0.71% (2 cases).
'Tardive' dyskinesia	-	27.00% (78 cases).

Not surprisingly the vast majority of abnormal involuntary movements were representative of the clinical entity commonly designated as TD, presumed to be a morbidity consequent upon long term neuroleptic therapy. From the figures obtained then it appears that 24.7% of the men (47/190) and 31.6% of the women (31/98) examined showed features of the TD syndrome (male:female ratio approximately 1:1.3).

Unavoidable lack of methodological uniformity common in studies of this type - alluded to in a previous chapter - is a substantial problem, and

thus it may be inadvisable to draw too close comparison with prevalence figures appearing in other reports. However bearing this limited validity in mind, some comment is warranted in order to discern trends among the many variables associated with iatrogenic movement pathology.

The TD prevalence figure of 27% is somewhat higher than the 17% observed in White patients at Valkenberg hospital (Holden et al,1984) and below that of the Black Natal patients from Ekuhlengeni institution at nearby Amanzimtoti (Holden,1985); moreover it conforms substantially well with many other prevalence rate reports from overseas (Kane et al,1980). While the methodology is in general similar to that used by Holden et al (1984), there are points of difference which could contribute to differing results. Although an almost identical patient type and number was surveyed by Holden, the cases with abnormal movements were not isolated by individual examination but identified "on the basis of personal rounds and interviews with physicians - in - charge and nurses". It is possible that certain patients with minor and/or transient abnormal movement could have been overlooked in selection for further examination. Another significant point of difference is that each of Holden's cases were rated independently by 3 raters (although high agreement between raters was reported). In the present study examination and rating was carried out entirely by one person, a feature which is conducive to uniformity of assessment, but although eliminating the problem of interrater unreliability, is vulnerable to the objection that no independent validation of subjective clinical assessment was operative (fluctuating rater error). A further criticism in similar theme, also applicable to Holden's Valkenberg study, is that cases with abnormal movements were subjected to only single clinical examination so that no

test-retest validation was possible. Hence patients manifesting transient or fluctuating dyskinesias could either be missed (lowering prevalence) or included (spuriously boosting prevalence); single examination precludes identification of reversible or transient dyskinesias which in fact are regarded by some as not representing genuine TD. Although all effort was made to achieve 'blind' rating, the diagnoses of several patients screened was known to this examiner. It is possible therefore that certain minor trunk-limb (subtype C/2) movements, particularly in the many schizophrenic patients in the sample, could have been too sensitively perceived and interpreted as dyskinesia; this may be a point of some relevance particularly in view of the fact that 77% of the abnormal movements are of the rating 1 group, and 52.5% of cases of C/2 subtype. On the other hand chronic schizophrenic patients, both drug treated and untreated, have been found to manifest a remarkably high prevalence of involuntary movements (Owens et al,1982); Holden's Valkenberg sample reportedly comprised only 47% of schizophrenias whereas this study involves 54%, a feature which could to some extent contribute to a higher prevalence figure. Holden et al (1984) have not attempted to relate diagnostic categories to dyskinesia subtype.

As anticipated the overall TD prevalence rate is a function of the criterion level for inclusion. Disregarding minimal score ratings and using a criterion level of 2 and above, a reduction of computed prevalence to around 7% is obtained and indicates a remarkable paucity of obtrusive abnormal movements in the Town Hill patient sample.

This study shows an insignificant sexual difference in TD prevalence, a finding congruent with that of Holden et al (1984) and numerous other

publications, indicating that preponderance of women among TD patients is an inconstant feature. The classical buccolingual movements considered to typify TD were found to occur in only about one in four of cases, although an almost similar number manifested both face and body movements. The rest of the patients presented variations of trunk-limb dyskinesia and were classified as subtype C/2 in this study. This latter category thus comprises movements which many clinicians would recognise as congeners of the TD syndrome, although their inclusion is not widely accepted. Several of these movements of trunk and limbs could be interpreted as restless or fidgety movements such as appear in akathisia, however none of the patients included reported subjective feelings of restlessness and the symptom may be considered to represent 'late onset akathisia' or 'pseudoakathisia' in which the subjective aspects are less obtrusive. Since this movement disturbance is both difficult to treat and seems frequently associated with TD (Simpson,1977) it has been suggested that C/2 represents a peripheral subsyndrome of TD (Kidger et al,1980). The average age of patients in this study showing the peripheral TD syndrome was 48 years as opposed to an average in excess of 60 years in patients with the orofacial syndrome.

Since no untreated matched patient sample has been examined it is difficult to say exactly to what extent spontaneous dyskinesia contributes to the number of patients manifesting abnormal movements. However at least 12 of the patients were not currently under neuroleptic treatment and had, as far as could be ascertained, not been taking such medication for at least 4 months prior to the time of examination. If these cases were omitted from the TD group, the overall prevalence of TD in the study would be reduced to 23%.

CHAPTER 6

CONCLUSIONS

6.1 THE PROBLEM OF TARDIVE DYSKINESIA

Within the context of the findings reported in Chapter 5, and as a critical final summary of certain unresolved issues, it is possible to formulate three questions which form a framework for speculative thought on the problem.

6.1.1 Is TD a specific entity?

The abnormal movements that are described as typifying TD may occur spontaneously without prior drug intake, and similar movements - including the characteristic orofacial syndrome - have been known to occur in a variety of physical conditions. Such facts emphasise what has been pointed out by several writers (Altrocchi,1972, Turek,1975, Marsden,1985), namely, that spontaneous involuntary movements affecting predominantly lower-third, midline facial structures, with lesser limb and trunk involvement, is a syndrome of several or many causes. The terms 'orofacial', which is descriptive, and 'tardive', which makes an implication of cause, are not synonymous with regard to dyskinesias.

Senile dyskinesia presents hyperkinetic movements clinically indistinguishable from TD. This disturbance arises spontaneously in elderly subjects never exposed to neuroleptics and is localised mainly to the oral regions, especially in individuals having dental problems (Sutcher et al,1971). It is also clear that the 'peripheral' components of TD (limb and trunk dyskinesia) are in no way clinically unique phenomena and can occur as manifestations of senile dyskinesia as well as neurologically discrete movement disorders such as Huntington's chorea.

Seemingly the TD syndrome can be postulated to represent simply an expression of basal ganglia dysfunction, sometimes precipitated by a drug induced DA and ACH receptor activity imbalance. Since the features of TD mimic abnormal movements which would otherwise be viewed as 'normal' sequelae of senile degenerative changes in the basal ganglia (Barbeau,1973), at the pathophysiological level neuroleptics might conceivably duplicate changes usually accompanying aging processes.

6.1.2 Is TD a single entity?

There is accumulating evidence suggesting that TD likely cannot be viewed as a discrete disease. Some relevant points will underscore heterogenous features of this abnormal movement syndrome.

i/ Outcome Aspect : TD should not be regarded as synonymous with irreversible dyskinesia, and at least 2 prognostically different clinical forms of TD exist *viz.* persistent and reversible. When TD develops in

young patients following long term neuroleptic treatment or following withdrawal of such treatment, it often resolves rapidly and hence constitutes a relatively harmless phenomenon. Non-resolving TD on the other hand is a more frequent characteristic in older patients and can be seriously disabling (Jeste and Wyatt,1979).

ii/ Therapeutic Response Aspect : Chronic neuroleptic administration is thought to induce DA receptor denervation hypersensitivity with cholinergic - dopaminergic imbalance. However results of clinical trials with cholinergic agents have been mixed, some patients improved remarkably while others responded little or not at all and still others became significantly worse (Moore et al,1980). Such finding reveals that only a subgroup of TD patients fits the above transmitter imbalance theory and suggests heterogeneity at the neurochemical level.

iii/Phenomenological Aspect : Analysis of the principal movement components observed in patients exposed to neuroleptics indicates the presence of 3 separate movement dimensions (Kidger et al,1980). One group of movements resembles a parkinsonian syndrome, while the other movement groups conform to generally accepted criteria for TD, comprising (1) head and neck movements, and (2) a range of trunk and limb movements.

6.1.3 What is the nature of TD?

Some authors have questioned whether any part of the syndrome described as TD can really be attributed to long term neuroleptic administration

(Crow et al,1981), and have concluded that spontaneous involuntary disorders of movement can be a feature of severe chronic schizophrenia unmodified by neuroleptic drugs (Owens,1985). Whatever the merits of such arguments may be, it cannot be refuted that the evidence incriminating chronic neuroleptic intake as a common cause of abnormal movements is epidemiological and inferential. Should it be accepted that usage of neuroleptics is causally related to the appearance of TD, it still remains to be explained why only some 15%-25% of cases at risk ever develop the syndrome. At present there is absolutely no clinical or experimental evidence in support of a heredofamilial factor that would predispose certain individuals to development of TD.

If neuroleptics cause potentially irreversible TD then it might be expected that these drugs would produce identifiable degeneration of the basal ganglia, also that patients with TD would manifest macroscopic or microscopic structural pathological changes in the brain. Studies of tissue from patients treated with neuroleptics for long periods have indeed shown a variety of pathological changes, notably neuronal changes and gliosis of the globus pallidus and putamen, inferior olive and medulla oblongata, but these changes cannot be regarded as specific. In general all investigations, including animal experiments, have failed to provide firm evidence of a relationship between neuroleptic treatment or TD and neuropathological changes (Gerlach,1979).

It would seem there is substantial evidence in support of the contention that TD is not at core a loss of structural organisation but is the expression of loss of functional resiliency in underlying neurotransmitter substrate. This could be viewed as a composite of two

processes which may contribute variably and concurrently to the production of movement disturbance, the first being a transient drug induced effect (reversible TD), and the second being a decreased plasticity due to aging processes of a 'buffer' which allows neurotransmitter mechanisms to absorb neuroleptic drug effects culminating in permanent disorder (irreversible TD). In certain constitutionally predisposed individuals this latter 'buffer rigidity' can manifest spontaneously as senile dyskinesia.

The finding of an unusual E.E.G. pattern termed 'B-mitten E.E.G. dysrhythmia' (Wegner et al,1979) in both TD patients and matched controls may be indicative of a pre-existing structural or functional vulnerability of the nigrostriatal system to neuroleptic induced dysregulation. It is tempting to hazard that this dysrhythmia is an electrophysiological reflection of depleted neuronal 'buffer' plasticity. In conclusion the crisp comment of Waddington is particularly apt - "Vulnerability to involuntary movements seems to reside more within the brain of the individual patient rather than in how he or she is treated" (Waddington,1985).

6.2 LINES FOR FURTHER RESEARCH

Clearly the quantity of information emanating from cross sectional studies of TD prevalence is substantial, however the numerous problems encountered in the control of the many variables involved tend to restrict severely the quality and value of data derived therefrom. The present cross sectional study, and others of similar design, indicate

unambiguously that only carefully planned long term prospective surveys on selected large population samples are likely to yield findings that will provide clear definition of the risk factors that predispose to, and perpetuate the clinical movement disorders associated with neuroleptic drug therapy. Of prime importance would be a protocol so designed that in the first instance spontaneous senile and 'organic' choreiform movements can be differentiated from the iatrogenic variety, and secondly that reversible be distinguished unequivocally from irreversible dyskinesias.

At the same time more laboratory orientated research should be directed towards elucidating precisely the neurophysiological brain mechanisms fundamentally involved in the genesis of dyskinetic movements. Although coarse morbid anatomical and histological examination of the basal ganglia has revealed only nonspecific degenerative pathology, more sophisticated techniques such as enzyme histochemistry and radioimmunofluoresence would resolve intraneuronal enzyme deficiencies or abnormality of cell surface receptor sites. These latter techniques, as well as the ligand binding strategies mentioned in an earlier chapter, cannot yield reliable information unless applied to fresh brain tissue, a stricture that limits applicability of such *in vitro* approaches essentially to work on animal material.

More practical from the point of viéw of *in vivo* human application are non-invasive techniques which could detect levels of metabolic activity in selected areas of the central nervous system, such as positron emission scanning and nuclear magnetic resonance. It also seems feasable that well controlled E.E.G. studies enhanced by the use of brain electrical activity mapping (Duffy et al,1979, Morihisa et al,1983) could

be helpful in the identification of brain changes that predispose to movement disorders.

Lastly it appears obvious that understanding of drug induced dyskinesias awaits an in depth resolution of the neurophysiological processes involved in terms of neurotransmitter interaction and disequilibrium. Next to the brain tissue itself, the cerebrospinal fluid is the medium which may best reflect neurochemical dysfunctions in the brain. Analysis of neurotransmitter metabolites in the cerebrospinal fluid is probably the most valuable relatively straightforward technique likely to throw light on the pharmacological profile of neuroleptics, both under short and long term treatment, thereby evaluating indirectly the mechanisms behind the neurological side effects.

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A P P E N D I X

T A B L E II : PATIENT DATA - AM GROUP

DIAGNOSIS	SEX	AGE(yrs)	C/1	C/2	C/3
SCHIZOPHRENIA	M	27	0	1	0
SCHIZOPHRENIA	M	27	0	1	0
SCHIZOPHRENIA	M	28	0	1	0
SCHIZOPHRENIA	M	29	0	1	0
SCHIZOPHRENIA	M	30	0	1	0
SCHIZOPHRENIA	M	33	0	1	0
SCHIZOPHRENIA	M	33	0	1	0
SCHIZOPHRENIA	M	35	0	1	0
SCHIZOPHRENIA	M	36	1	0	0
SCHIZOPHRENIA	M	39	0	1	0
SCHIZOPHRENIA	M	40	0	1	0
SCHIZOPHRENIA	M	45	0	1	0
SCHIZOPHRENIA	M	45	0	1	0
SCHIZOPHRENIA	M	48	0	1	0
SCHIZOPHRENIA	M	49	3	3	0
SCHIZOPHRENIA	M	52	0	1	0
SCHIZOPHRENIA	M	52	0	1	0
SCHIZOPHRENIA	M	56	1	1	0
SCHIZOPHRENIA	M	57	2	2	0
SCHIZOPHRENIA	M	58	0	1	0
SCHIZOPHRENIA	M	60	1	1	0
SCHIZOPHRENIA	M	62	1	0	0
SCHIZOPHRENIA	M	68	2	2	0
SCHIZOPHRENIA	M	69	1	0	0
SCHIZOPHRENIA	M	70	1	1	0
SCHIZOPHRENIA	M	77	1	1	0
				(N=26)	
SCHIZOPHRENIA	F	27	0	2	0
SCHIZOPHRENIA	F	27	0	2	0
SCHIZOPHRENIA	F	38	0	1	0
SCHIZOPHRENIA	F	45	0	1	0
SCHIZOPHRENIA	F	48	0	1	0
SCHIZOPHRENIA	F	52	0	1	0
SCHIZOPHRENIA	F	57	1	0	0
SCHIZOPHRENIA	F	58	2	0	0
SCHIZOPHRENIA	F	58	1	0	0
SCHIZOPHRENIA	F	61	0	1	0
SCHIZOPHRENIA	F	65	2	2	0
SCHIZOPHRENIA	F	67	1	0	0
SCHIZOPHRENIA	F	69	3	3	0
SCHIZOPHRENIA	F	72	0	1	0
SCHIZOPHRENIA	F	74	1	0	0
SCHIZOPHRENIA	F	76	1	0	0
				(N=16)	

T A B L E II : PATIENT DATA - AM GROUP (continued)

DIAGNOSIS	SEX	AGE(yrs)	C/1	C/2	C/3
KORSAKOFF	M	59	1	0	0
KORSAKOFF	M	59	0	1	0
KORSAKOFF	M	66	1	0	0
KORSAKOFF	M	67	0	2	0
KORSAKOFF	M	69	0	1	0
KORSAKOFF	M	74	1	0	0
				(N=6)	
KORSAKOFF	F	57	0	1	0
KORSAKOFF	F	70	0	1	0
				(N=2)	
DMD	M	35	1	1	0
DMD	M	36	0	1	0
DMD	M	47	1	0	0
DMD	M	55	0	1	0
DMD	M	55	1	0	0
DMD	M	59	0	1	0
DMD	M	68	1	0	0
DMD	M	69	1	0	0
DMD	M	70	0	1	0
				(N=9)	
DMD	F	37	0	2	0
DMD	F	58	0	2	0
DMD	F	62	2	2	0
DMD	F	75	1	0	1
DMD	F	77	2	0	2
				(N=5)	
MANIC-DEPRESSIVE	M	35	0	1	0
				(N=1)	
MANIC-DEPRESSIVE	F	61	0	1	0
MANIC-DEPRESSIVE	F	66	0	2	0
				(N=2)	
EPILEPSY	M	53	0	1	0
				(N=1)	
EPILEPSY	F	65	0	1	0
EPILEPSY	F	68	2	2	0
				(N=2)	
HUNTINGTON	M	37	3	3	0
				(N=1)	
HUNTINGTON	F	40	2	2	0
HUNTINGTON	F	51	3	3	0
				(N=2)	

T A B L E II : PATIENT DATA - AM GROUP (continued)

DIAGNOSIS	SEX	AGE(yrs)	C/1	C/2	C/3
SENILE PSYCHOSIS	M	68	1	0	0
SENILE PSYCHOSIS	M	83	1	0	0
				(N=2)	
SENILE PSYCHOSIS	F	63	0	1	0
SENILE PSYCHOSIS	F	69	1	1	0
SENILE PSYCHOSIS	F	81	2	0	0
				(N=3)	
SENILE DEMENTIA	M	70	1	0	0
				(N=1)	
SENILE DEMENTIA	F	73	2	2	0
				(N=1)	
ORGANIC B/S	M	47	3	3	0
				(N=1)	
ORGANIC B/S	F	55	1	0	0
ORGANIC B/S	F	65	2	2	0
				(N=2)	

TOTAL CASES = 83

(NOTE : DMD = DEFECTIVE MENTAL DEVELOPMENT)