THE DISABILITIES OF CHRONIC SCHIZOPHRENIA

- A Search for Neurological Correlates

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IO NON MORI, E NON RIMASI VIVO

(I did not die, yet nothing of life remained)

DANTE

CONTENTS

PART III
RADIOLOGICAL IMAGING

FIGURES AND TABLES

FIGURES

PART 1

PART 2

PART 3

TABLES

PART 1

PART 3

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In a work of this size it is hardly possible to thank individually all those who have contributed to its execution. I would however wish to express my thanks to a number of individuals whose cooperation and advice were invaluable.

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professed wisdom failed to percolate through, the fault lies not with the giver but with the receiver. I gladly acknowledge his fundamental contribution to this work. Most of all, I wish to offer my profoundest gratitude to my supervisor and collaborater, Dr. Eve C. Johnstone, without whose advice, energy and constant encouragement this project would have proved an impossibly daunting endeavour. Mrs. M. Hoyle and Miss A. Kapoor cheerfully undertook the mammoth task of typing the manuscript and I thank them for their diligence.

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Finally, in the context of a work whose roots go back to an interest fostered in my early medical career, I remember with affection and gratitude my early teachers, especially Dr. Stewart Renfrew, formerly of Glasgow Royal Infirmary who set my course and Dr. I.M. Ingram of the Southern General Hospital Glasgow, who kept me to it.

STATEMENT OF AUTHORSHIP

The idea of investigating the neurological status of schizophrenic patients was my own though without the collaboration of a number of colleagues the project as described here could not have been undertaken.

The design and execution of Part I was a collaborative undertaking with Dr. E.C. Johnstone. I was responsible for the organisation of the schedule for recording neurological data (Appendix III), and I participated with others in the CRC Division of Psychiatry, Northwick Park Hospital in the design of the other schedules devised by ourselves (Appendices IV and V). Case-note review to identify the sample and record personal and historical data was divided between Dr. Johnstone and myself. Examination of patients was likewise shared. As I was responsible for conducting all the neurological examinations, this meant that in practice Dr. Johnstone performed almost all the cognitive assessments, the mental state evaluations being shared. Interviews with the nurses were divided equally. Dr. Johnstone and myself achieved good inter-rater reliability on those examination procedures that were shared. Analyses of data were jointly undertaken by myself, Dr. Johnstone and Dr. C.D. Frith, who in addition provided statistical advice throughout.

The idea of specifically evaluating spontaneous involuntary movements in standardised fashion (Part II) was my own, as was the choice of schedules used. Standardised examinations of the population were performed by myself with a joint decision in cases of doubt being agreed with Dr. Johnstone. The analyses were undertaken by myself with Dr. Frith's guidance.

The C.T. scan project (Part III) was an extension both of previous work done at Northwick Park and of Part I of the present

study. I was responsible for the identification of a number of the groups studied, and for the selection of all subjects by detailed matching within groups. I was also responsible for the practical arrangements to ensure the smooth execution of this part of the work. At my suggestion Dr. G.M. Bydder provided bromide pictures of the maximal ventricular cut at two different window widths to enhance the accuracy of VBR evaluations. I performed the necessary measurements on each scan twice and the data presented in Part III are based on the average of these two assessments. Dr. Johnstone and Dr. Crow kindly provided reliability data by measuring alternative scans in the first half and the second half of the series respectively. Analyses of scan data were undertaken by myself with advice from Dr. Frith.

SUMMARY

This study was designed to define in standardised fashion, the deficits of chronic schizophrenia and the correlates of these, and to evaluate two neurological parameters - spontaneous involuntary movements and lateral ventricular enlargement - in relation to the illness and its treatment.

The study population comprised all those schizophrenics receiving long-term care in the one mental hospital who conformed to the St. Louis criteria for schizophrenia and who had been in-patients for at least 1 year continuously. This basic group consisted of 510 subjects.

Analysis of standardised assessments covering mental state, cognition, neurological status and behaviour showed these patients to be extremely impaired. While historical correlates of functioning in particular spheres could be identified, the present clinical picture was in general related to the form of the initial illness and to factors reflecting the passage of time. Past physical treatment was not related to present deficits. Two broad patterns of disability were established. While the presence of prominent productive features in the mental state was not associated with the presence of deficits in other areas examined, prominent 'negative' features were related to the presence of cognitive impairment, extrapyramidal neurological signs and behavioural deterioration.

Involuntary movements were assessed in 411 subjects using two standardised recording schedules. Abnormality was extremely common. The base-line prevalence of disorder in those with no history of neuroleptic exposure was comparable with that of those treated with neuroleptics, although with factors reflecting the passage of time

accounted for, movement disorder was associated with past neuroleptic treatment. In addition however, the presence of abnormal movements related to features of the illness itself - namely 'negative' mental state features, cognitive impairment and behavioural deterioration.

C.T. scans from 110 of the total population described above and controls representing non-institutionalised out-patient (18) and first episode (8) schizophrenics, institutionalised and out-patient manic-depressives (10 and 22 respectively) and neurotic out-patients (19), demonstrated that schizophrenia is associated with enlargement of the lateral ventricles, although only the institutionalised schizophrenics differed significantly from the neurotic controls. The group mean differences were not great and there was considerable overlap between groups. There was no evidence of a characteristic radiological change associated with schizophrenia. Lateral ventricular enlargement in schizophrenia was not consequent upon physical treatments administered in the past. The historical and examination variables which related to increased ventricular size in the long-stay schizophrenic population were few and the nature of certain relationships surprising. While behavioural deterioration and involuntary movements were significantly and linearly associated with ventricular enlargement, 'negative' mental state features, cognitive impairment and an absence of hallucinations were more commonly found in those at both extremes of ventricle size. The results suggest that although brain structure is genuinely altered in certain schizophrenics, the relationship between cerebral structure and clinical aspects of the condition is not straightforward.

This study indicates that both neurological abnormality and

structural brain change can be related to certain clinical features of established schizophrenia when other potentially relevant historical and treatment variables are accounted for. Such a general conclusion refers to statistical associations within large groups of patients and the relationship between neurology and psychopathology is complex. Nonetheless, the findings lend support to the view that in some patients at least, schizophrenia is a brain disorder whose cerebral basis can be inferred from the nature of some of the associated multiple deficits.

INTRODUCTION

"Suffering is one very long moment. We cannot divide it by seasons. We can only record its moods, and chronicle their return"

OSCAR WILDE
DE PROFUNDIS

INTRODUCTION

1. GENERAL

Schizophrenia is a common condition, presenting a life-time expectancy of illness of approximately 8 per 1000. (Shields & Slater 1975). The mean annual incidence in the United Kingdom has been calculated as 3.3 per 1000 (Cooper 1978), and estimates suggest that about 150,000 individuals are affected at any one time (The Office of Health Economics 1979). More people of working age suffer from this illness than any other, and with the control of the infectious diseases, schizophrenia has now been identified as the major public health problem of developed societies (Freeman 1980).

Unlike the infectious diseases, this problem is not one of acute mortality, but rather one of chronic morbidity. Schizophrenia tends to become manifest in early adult life (Slater & Roth 1969; Wing 1978), and to be associated subsequently with deficits which are both incapacitating and enduring. The burden of the illness remains to be measured in decades.

It has been estimated that the cost of schizophrenia in the United States amounts to approximately 2 % of the Gross National Product, only about one-fifth of which is incurred in delivery of services (Gunderson & Mosher 1975). These figures are likely to be comparable for all developed nations. In purely financial terms therefore the problem is substantial.

In contrast to the size of the problem, the research commitment to long-standing schizophrenia has been small, as Arieti has pointed out (Arieti 1974). It has been suggested that

the now predominant interest in the florid, productive manifestations of the condition can be dated to the Second World War and the associated concern about the acute manifestations of psychotic disturbance at such a time (Shakow 1972). However it is likely that the war was a catalyst precipitating a change that began over the previous decade with the introduction of physical therapies. The advent of the neuroleptic drugs in 1952 (Delay et al 1952) maintained this shifting emphasis. Not only were these preparations therapeutically efficacious in productive psychotic states (National Institute of Mental Health, Collaborative Study Group 1964), but their mode of action offered the prospect of investigating the pathophysiology underlying the florid symptomatology (Matthysse 1973 ; Snyder et al 1974; Carlsson 1978).

In recent years there has been a growing interest in the study of chronically incapacitated schizophrenic patients. This has largely evolved out of an awareness of the limitations of traditional clinical classifications and an increasing desire to identify biological parameters on which new classifications may be based (Meltzer 1979, Wyatt et al 1981).

2. THE CONCEPT OF SCHIZOPHRENIA

By the 1870s, the work of Griesinger, Emminghaus and others had resulted in general psychopathology reaching a new level of comprehensiveness and refinement, yet the practical implementation of this clinical dimension alone did not result in the anticipated advances (Jaspers 1963). While in other branches of medicine disease concepts were being validated and defined on the basis of pathological and laboratory techniques, within psychiatry these same techniques yielded little of diagnostic significance.

The idea that evolution of the illness over time might be a legitimate additional dimension in clarifying diagnostic groupings was not new at the end of the last century. It can be traced back to Pinel and his studies on 'mania' (Ackerknecht 1968) but it was Kahlbaum who brought it to the fore as a valid extension of clinical observation in diagnosis. He wrote :

> The task is "to use clinical methods for the development of pictures of disease, in which as far as possible all the phenomena of the individual patient's life are evaluated for purposes of diagnosis and the whole course of the illness is taken into account" (Kahlbaum 1874).

Emil Kraepelin made this approach pivotal in diagnosis and classification. Kraepelin was in the descriptive tradition and believed that psychopathological symptom clusters which could be shown to have similar aetiologies, forms, outcomes and pathologies were, what Jaspers later called "natural disease entities" (Jaspers 1963). Failures and limitations in the other areas, made outcome not only a legitimate, but according to Kraepelin, <u>the</u> valid index on which to base diagnosis and classification . (Kraepelin 1919). His dementia praecox concept was far from static and underwent many refinements following its introduction in 1896, but it remained firmly rooted in adversity of outcome (Havens 1965).

Bleuler, while acknowledging Kraepelin's initial proposals, did not concur with the subsequent development of the dementia praecox concept. He was much more an analyser than the essentially descriptive Kraepelin (Jaspers 1963), and shifted the emphasis in diagnosis away from the outward psychopathology of the descriptive writers. Bleuler believed the characteristic disturbance of 'schizophrenia' lay in the underlying psychic "processes", and hence that the diagnosis should be based on recognition of these underlying abnormalities(Bleuler 1911). He radically de-emphasised outcome,

devoting only a brief review to this in his substantial monograph. Bleuler was in effect advocating the psychoanalytic principle of inferred dynamics, and sought to establish diagnosis and classification on the identification of an 'essential property' characteristic of that diagnosis and the basis of its clinical manifestations.

These two conceptualisations remain the theoretical references of most psychiatrists with regard to schizophrenia. The Kraepelinian view is identified with a narrow concept of schizophrenia and is in general the one that has been adhered to in Europe (Neale & Oltmanns 1980). In classificatory work, the tendency here has been to maintain the integrity of the poor - outcome concept by allocating atypical cases to discrete categories, varyingly independent of schizophrenia itself - e.g. Langfeldt's schizophreniform psychosis ; Leonhard's cycloid psychoses etc. Adopting this generally conservative approach to what constitutes schizophrenia has ensured a relative consistency in the proportion of patients thus diagnosed over almost half a century (Kuriansky et al 1974).

For many, however, the Kraepelinian approach was too restrictive and dogmatic. Many conditions with a consistent aetiology and symptomatology have varying outcomes and to ascribe the authentic illness to only those patients with one particular pattern of outcome was seen as fallacious. Furthermore, a diagnosis whose implication was, by definition, one of poor outcome and decline suggested a degree of therapeutic impotence which many found unacceptable. The Bleulerian concept avoided these objections. Under the tutelage of Adolf Meyer among others, Bleuler's writings found widespread

acceptance in the United States where they dominated psychiatric thinking for many decades.

This metaphorical legacy of diagnosis based on "interrupted" or "torn threads","sometimes single threads, sometimes a whole group", was however a confusing one. Bleuler repeatedly emphasised that

> "as far as the true schizophrenic symptoms are concerned .....they are distortions and exaggerations of normal processes ..... Thus, the individual symptom itself is less important than its intensity and extensiveness, and above all, its relation to the psychological setting" (Bleuler 1911, pp 294 - 295).

Bleuler thereby opened the flood-gates to multivarious interpretations and applications of his principles. With diagnosis based on nebulous characteristics, atypical cases were readily incorporated into the concept (e.g. Kasanin's schizoaffective psychosis, Hoch & Polatin's, pseudoneurotic and Hoch and Dunaif's pseudopsychopathic schizophrenias etc) resulting in its degeneration to the point where it became virtually devoid of meaning (Stierlin 1967). In the New York State Psychiatric Institute, the prevalence of schizophrenic diagnoses rose from approximately 20 % in the 1930's to a quite astonishing 80 % in the 1950's (Kuriansky et al 1974).

In recent years, American psychiatry has moved closer to European thought in taking an interest in outcome as a validating parameter of the schizophrenic condition. Applying a liberal interpretation of 'recovery', a number of studies have shown that it is valid to state that a diagnosis of schizophrenia still carries an implication of negative outcome (Hoenig 1974; Stephens 1978; Harrow et al 1978; Pfohl & Winokur 1982). Such an evaluation is true today as it was at the beginning of the century, and stands in

contradistinction to general assessments regarding the outcome of other non-organic psychiatric diagnoses (Norris 1959; Hawk et al 1975; Harrow et al 1978; Strauss & Carpenter 1979). Adversity of outcome is now a stated criterion in a number of operational definitions of schizophrenia - for example, the St. Louis criteria (Feighner et al 1972). The latest edition of the Diagnostic and Statistical Manual of the American Psychiatric Association (D.S.M. - 111) (American Psychiatric Association 1980) states that "schizophrenia always involves deterioration from a previous level of functioning" (p 181), and by requiring 6 months duration of symptoms to qualify, the authors "suggest that schizophrenia is a disorder with a tendency to chronicity" (Fox 1981).

The Kraepelinian concept, despite its limitations, has therefore continued to find widespread acceptance in clinical and research practice, and at the level of our current knowledge, adversity of outcome has, with some qualification, stood as a reliable parameter on which to base diagnosis and classification.

Using outcome as a validating criterion is not, however, as straightforward as may at first seem. Outcome data depend on such factors as the era during which the study was performed, the duration of follow-up and, perhaps most importantly of all, the definitions of outcome categories (W.H.O. 1979). Many studies show recovery to occur frequently (Stephens 1978; M. Bleuler 1978), but within these groups are patients whose post-psychotic potential is reduced from pre-illness expectations. Some workers view with optimism independence at any level after an acute episode (M. Bleuler 1978), but when the total morbidity of an illness is to be recorded and its costs evaluated, loss of potential and productivity are essential

considerations (Gunderson & Mosher 1975).

Schizophrenic patients who experience loss of potential and, consequently, a poor outcome, tend to be designated 'chronic'. As applied to schizophrenia, the term 'chronic' is misleading. In addition to an implication about the mode of onset and of irreversibility, there is the understanding of a qualitative difference in symptom pattern from that of the illness in an acute phase. It has even been suggested that these two states represent different disease entities (Robins & Guze 1970; Ollernshaw 1973; Strauss et al 1974) or different syndromes mediated by different pathophysiological mechanisms (Crow 1980).

What constitutes 'chronicity' when applied in this fashion is not clear. Studies which have sought to investigate such patients show little agreement on the features comprising the clinical picture (cf, for example, Wing 1961; Strauss et al 1974; Johnstone et al 1978 (a) and (b); Crow 1980; Angrist et al 1980; Andreasen 1982). The position is further complicated by the widespread use of the term 'defect state'. In English-language psychiatry the tendency has been to apply 'chronic' and 'defect state' interchangeably, using both to indicate a loss of certain attributes that go to make up a healthy, integrated personality (Jilek 1968). Persistent, post - acute schizophrenic features, however, may not be restricted to deficits of this type, as continental - and especially German - workers have pointed out (Huber 1966).

At a clinical level, both these terms allow patients to be categorised as disabled without having to specify in what areas of mental functioning the disabilities lie. Whether they have a more specific potential in implying differing patterns of deficit is not

clear. Furthermore, if schizophrenia itself is viewed as implying 'adversity of outcome', the relationship between the concepts of 'chronicity' and 'defect state' and that of the illness - if not tautological - is confused.

Recently, the terminology 'positive' and 'negative' has been applied to schizophrenia, based on Hughlings Jackson's ideas on the functional organisation of the central nervous system (Jackson 1887, 1894; Levin, 1936), and has gained widespread, though not uncritical (Freeman 1982), acceptance. However, changing the terminology does nothing to unravel the psychopathological deficits behind that personal decline viewed by many as the major validating criterion of schizophrenia. If the new terminology results in no meaningful distinction based on clinical data, it will serve only to complicate an already confused situation.

The European/American distinction in conceptualisation of the condition was, understandably, reflected in differences regarding aetiology. In the United States, the approach to schizophrenia has always been what Neale & Oltmanns describe as "theoretical" - with numerous theories attempting"to derive the main symptoms of schizophrenia from a core problem" (Neale & Oltmanns 1980). These authors add :

> "This focus on theory building seems to have deflected attention from the definition and description of the disorder itself. Indeed, many of the early theorists went on to define the disorder in terms of the defective hypothetical constructs they inferred rather than in terms of observable behaviour".
> (Neale & Oltmanns 1980 p 12).

In Europe, 'theory building' has always been less prominent. It has in general been accepted by many psychiatrists that the underlying disturbance lies in some as yet undefined physical disruption

of brain function. This view was characterised in its purest form by Wernicke and the school of Brain Psychiatry which flourished in Germany at the end of the last century - though even the analytical Bleuler could write

> "Complete justice to all these factors can only be done by a concept of the disease which assumes the presence of(anatomic or chemical) * disturbances of the brain". (Bleuler 1911. p 463).

This view has been maintained despite the relative absence of clinically useful, objective parameters of specific brain dysfunction. Indeed, the prevailing practice has been to avoid a diagnosis of schizophrenia if signs of brain dysfunction present themselves. Hence while the theoretical stance is in favour of an aetiology based on brain abnormality, routine diagnosis continues to be predicated on the specific absence of evidence of such abnormality.

Many psychiatrists would accept the views of Gerstmann and the Viennese school (Gerstmann 1958) - that the conventional functional/organic dichotomy of mental illness is more apparent than real, and depends on a quantitative evaluation, the basis of which lies in our inability to detect brain change rather than its absence. Schneider put it thus :

> "Our concept of psychiatric illness is based entirely on morbid bodily change. General pathology may be unable at present to give any uniform answer to the exact point at which a bodily change becomes morbid, but this need not prevent us holding to the above definition for theoretical purposes". (Schneider 1959. p 7).

In recent years advances in neuroscience techniques have led to a number of findings which indicate that the views of Gerstmann, Schneider and others do have foundation. Increasingly psychiatrists

* Bleuler's parenthesis.

on both sides of the Atlantic are searching for biological variability in schizophrenic patients, especially variability indicative of brain dysfunction. Indeed, some workers now feel able to state categorically that

> "multiple lines of evidence ..... clearly point to biological alterations in the schizophrenic brain" (Henn & Kety 1982 p 13).

This evidence is nascent and requires consolidation though one direction for future progress may lie in a combination of meticulous clinical observation and application of the new and sophisticated investigative techniques.

3. THE PRESENT STUDY

I) BACKGROUND

From what has been said, Kraepelin's concept of functional illness predicated on adversity of outcome is still accepted by a large, and possibly increasing, body of psychiatric opinion. The characteristics which constitute the decline and the substrate out of which it emanates are, however, poorly understood. While many would favour an aetiology based on brain dysfunction, the evidence for this remains elusive and the widespread use of neuroleptic drugs now makes it difficult to evaluate whether potential neurological abnormality is a consequence of the illness or its treatment.

No large scale study of the deficits of long-standing schizophrenia has been undertaken for many years, and to the author's knowledge, no systematic investigation of an entire, diagnostically homogenous mental hospital population of such patients has ever been undertaken. Furthermore, although in widespread use for almost half a century, the role of physical forms of treatment in contributing to the clinical deficits has not been comprehensively evaluated.

In particular, modern standardised assessment and recording techniques have not been applied in this area since the use of neuroleptic drugs became generalised.

II) THE GENERAL QUESTIONS

The present study was designed to assess the deficits associated with long-standing, disabling schizophrenia and to identify factors associated with their development. This was intended to provide basic descriptive data of relevance in itself. In addition, this generated a range of parameters of importance in evaluating two neurological questions :

a) In established schizophrenia, can damage to the central nervous system be implied from the findings of clinical neurological examination ?

b) In established schizophrenia, can damage to the central nervous system be implied from examination of brain structure in vivo ?

In response to the first general question, the clinical neurological feature selected for evaluation was spontaneous involuntary disorders of movement.

It was clear, for reasons set out in the Introduction to Part 1 (pp 52/3), that gross localising signs would not be a rewarding area of study and that 'soft' signs would be difficult to administer and evaluate. Involuntary movements were chosen as they represent a relatively objective sign of brain dysfunction. With regard to the study population, they offered a particular attraction. Considerable evidence from the early descriptive literature suggested that involuntary movements were to be found in long-standing schizophrenic patients. This whole question has however been overtaken by the putative effects of neuroleptic drugs, which are themselves implicated in the production of involuntary movements. Because of their varied treatment histories,

the present population offered an ideal opportunity to address two neurological issues, embodied in a refinement of the general question, a), above :

i) Is established schizophrenia, unmodified by neuroleptic drugs, associated with the development of spontaneous involuntary movements ?

ii) In established schizophrenia, can the concept of tardive (neuroleptic - caused) dyskinesia be shown to have validity, and if so, what are its correlates ?

III) THE SPECIFIC HYPOTHESES

The first stage of the work was descriptive and no specific hypotheses were formulated. For subsequent parts, the basic postulate was that :

> Long-standing schizophrenia, inherent to which is personal decline, is a subtle disorder of brain function, evidence of which can be established both clinically and by the application of radiological imaging.

The specific hypotheses were :

i) a) That schizophrenia in patients of this type would, of itself, be associated with spontaneous involuntary disorders of movement.

b) Even if the concept of tardive dyskinesia can be shown to have validity, involuntary movements in the context of neuroleptic ingestion in such patients would relate to features of the illness, independent of drug history.

ii) That such schizophrenics would show evidence of structural brain change (atrophy) and that this would relate to aspects of the illness and its severity, but not to physical treatments.

IV) THE STUDY SAMPLE

The study sample conforms to the Kraepelinian concept of schizophrenia, in that deterioration was an explicit inclusion criterion. It was drawn from the hospitalised, long-stay, schizophrenic population of Shenley Hospital, Radlett, Herts, the institution providing continuing care facilities for the London Boroughs of Brent and Harrow.

In the United Kingdom, most schizophrenics with illnesses of

long-standing do not now come to long-term care, and so the present population may be said to be unrepresentative. This mental hospital group was chosen for several reasons :

i) It provided ready access to a sufficiently large sample.

ii) Detailed records were available of past historical information, progress and treatments administered, going back over many years, which provided an incomparable and, in general, reliable source of data.

iii) It was likely that the deficits of such patients would reflect the spectrum of abnormality characteristic of the illness in its severe form(s). While there are many reasons why patients remain in hospital severity of illness is likely to be one (Pryce 1972).

iv) The treatment policies for schizophrenia that operated in this hospital over many years varied widely, from dynamically - orientated psychotherapy through the gamut of physical therapies. Consequently different groups of patients had been exposed to different ranges of treatment. This population thus allowed a unique opportunity to distinguish between the long-term effects of the illness and those of its treatment.

v) The hospital was close at hand and readily accessible and the staff were happy for the project to be conducted. This accessibility and co-operation greatly aided its execution.

V) EXECUTION OF THE STUDY

The study was executed in three parts.

Part I : This was designed to identify the deficits exhibited by the patients at examination and to relate these to historical information of a personal nature and regarding the illness itself, including past physical treatments.

Part II : This concentrated specifically on spontaneous involuntary movement disorder, and used standardised examination procedures and recording techniques.

Part III : This concerned the application of computerised axial tomography to the study of brain structure in selected subjects from the total sample.

Each of these three stages of the investigation will be presented separately and comprehensively (Parts I - III), with introduction, methodology, results and discussion relevant to each. The final part (Part IV) comprises a general comment and conclusions.

PART I

THE CLINICAL DEFICITS

"The tower of Babel never yielded such confusion of tongues as the chaos of melancholy doth variety of symptoms .... As in a river we swim in the same place, though not in the same numerical water ... so the same disease yields diversity of symptoms"

ROBERT BURTON
THE ANATOMY OF MELANCHOLY

PART I

THE CLINICAL DEFICITS

Chapter 1 - Literature Review

1.1 INTRODUCTION

Early descriptive psychiatrists would have found a rigid acute/chronic dichotomy in schizophrenia somewhat surprising. In the era before the introduction of physical treatments, long (often life-long) periods of institutional care were the norm. Living in close proximity to their patients, their work was largely with long-stay, 'chronic' cases and much of their typology was founded on the observations of such patients over many years. Their writings reveal little attempt to separate 'acute' and 'chronic' manifestations of the condition in the way that it was suggested earlier these terms are now used. This contrasts sharply with a modern text where great emphasis is laid on acute symptoms and signs, the more chronic sequelae usually being included under outcome headings (cf for example Slater & Roth 1969).

Attempts have been made however to study the clinical features of the chronic state per se, though investigators have tended to focus on particular areas of functioning. This work is largely descriptive, and, as Hall has pointed out, much uses unstandardised or unpublished methodology, rendering the findings non-reproducible (Hall 1980). Any review of the literature in the field of long-standing schizophrenia has, of necessity, to be selective. This review will therefore focus on studies of relevance to the present work, considered under three main headings:

i) Psychopathology and behaviour
ii) Cognition
iii) Neurology

1.2 The psychopathology of chronic schizophrenia.

It is to the German literature that one must turn for the most detailed descriptions of the psychopathological features associated with established schizophrenia, a fact that has made most of this work inaccessible to English-speaking psychiatry. Kraepelin in particular has provided meticulous accounts of the clinical features of long-standing schizophrenic illnesses which remain some of the finest sources of descriptive psychopathology (Kraepelin 1919).

In the post-Kraepelinian era the most outstanding examples of descriptive symptomatology come from the works of Kleist (Fish 1957) and Leonhard (Fish 1958; Van Epen 1969; Astrup 1978; Leonhard 1979). Both these workers detailed the clinical pictures of large numbers of established schizophrenic patients over many years, though they used rather different methods. Kleist studied all referrals to a psychiatric clinic while Leonhard started with a sample of patients ill for at least 10 years.

Their conclusions are not specifically comparable and, in particular, their terminology is not synonymous. However, both observed two broad groups of patients - a specific schizophrenic form (termed 'typical' and'systematic' respectively) and a separate group(termed 'atypical'and 'non-systematic') having a distinctive episodic course and more favourable outcome. Kleist believed the separate schizophrenic subtypes he defined were the clinical representatives of "psychic system diseases" analogous to the neurological system disorders such as motor neurone disease (Fish 1957; Kleist 1960). This view was generally accepted by Leonhard who stated that these established 'chronic' schizophrenic states could be defined by the presence of a characteristic feature that, once elicited, was stable over time and which, having

genetic and biological foundations, could be reliably used to identify true and separate disease processes (Leonhard 1979).

The descriptive German psychiatrists were attempting more than a presentation of the range of mental state and behavioural features to be found in established schizophrenia. They were aiming at organising clinical typologies based on symptomatology. To this extent they were largely unsuccessful and their views have not received widespread attention. Kleist's system is particularly unwieldy (Fish 1958), and while incidental attempts to match the Leonhard subtypes to long-stay samples in the U.K. have shown some coincidence (Wing 1961), the system remains largely untried in English-speaking circles. Several publications in English by German-speaking practitioners have attempted to validate the Leonhard system outside Germany (Fish & Astrup 1964 ; Van Epen 1969) of which Astrup's survey in Norway is the largest (Astrup 1978). With slight modification he found the system useable and, when retrospectively applied, it did identify groups of varying outcome severity.

It is unlikely that these systems will gain widespread acceptance by English-speaking psychiatrists. Partly, this is due to the relative inaccessability of most of these writings. Although English translations of both Kraepelin and Leonhard's works are available their heavy, unfashionable style is against them being widely studied. Partly also these systems were devised before the introduction of neuroleptic drugs and whether they could now be meaningfully employed is uncertain. Mainly however their neglect is likely to stem from a widespread scepticism in the English-speaking world that valid typologies can be established on the basis of symptomatology alone. Despite this, the writings of the

German school of descriptive psychiatry remain a rich and neglected source of information on the varied clinical states associated with established schizophrenia.

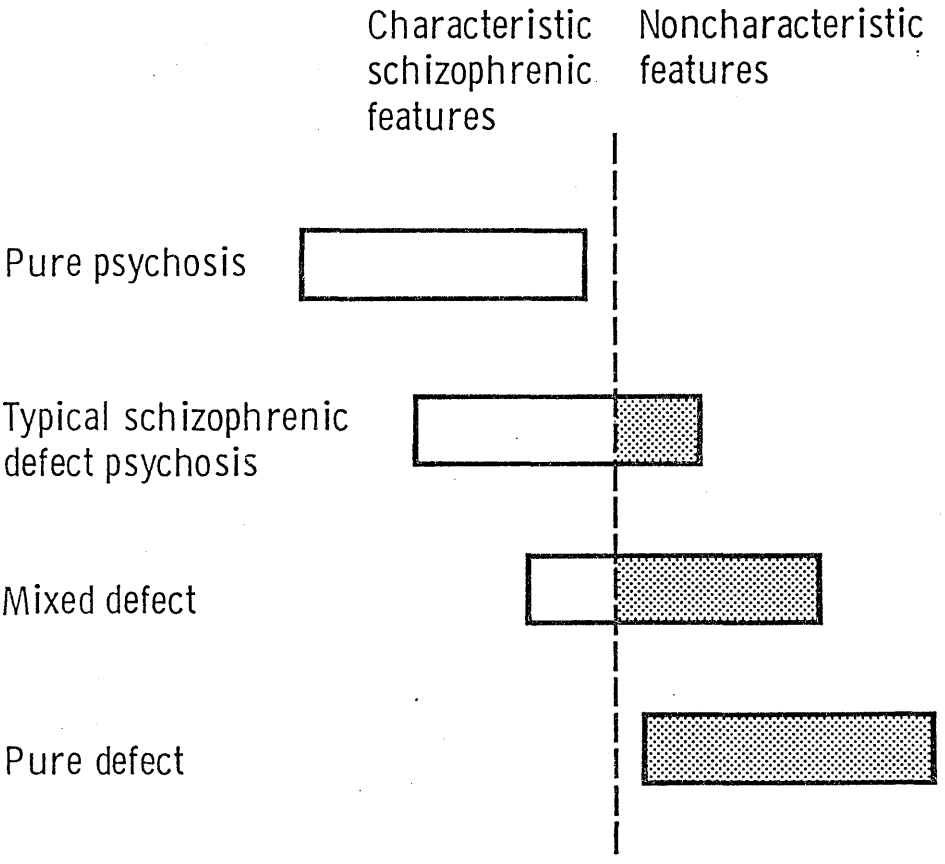
Whatever the pragmatic and theoretical objections to these systems, the writings highlight the restricted view of schizophrenic deficits employed in English-speaking practice. The descriptive German literature emphasises that the post-acute state may be characterised by more than just 'negative' type deficits, and can in fact be largely coloured by productive features.

In a theoretical paper, Huber has provided one of the few recent discussions of schizophrenic defects (Huber 1967). In contrast to English-language psychiatry's conventional emphasis on the affective disturbance in post-acute schizophrenic defects, Huber, in line with Germanic tradition (Conrad 1958), believed the problem to be one of motivation. The importance of this according to Huber, is that motivation is only amenable to quantitative change, unlike affect which may also be qualitatively altered. Consequently a 'defect state' based on the concept of "impoverished drive" or motivation is not seen as a specific schizophrenic phenomenon, but could result from any psychosis, functional or organic. Huber used the term "uncharacteristic" to highlight the non-specificity of drive reduction, and emphasised that only the presence of additional characteristic features allowed any defect to be attributed to schizophrenia as opposed to any other psychosis.

Huber divided post-acute, residual schizophrenic states into four types, represented schematically in Fig 1:1:1. Patients with pure psychosis, mainly on-going paranoids, are able to function intact despite their symptomatology. The typical schizophrenic defect psychosis

FIG 1:1:1

Schematic representation of Huber's classification of defect states



is also dominated by productive features, and decline associated with the loss of motivation can only be detected by observation of performance over time. In mixed defect, "uncharacteristic" lack of drive impairs the patient markedly and only the presence of additional characteristic features - which increasingly lose their impact on the patient - allows this state to be attributed to schizophrenia. Pure defect is not at all specific to schizophrenia. No residual characteristic schizophrenic features persist, the dominant abnormality being marked lack of drive, of which the patient may be aware. They may, in addition, have minor neurotic-type symptoms such as depression and especially hypochondriacal preoccupations. Pure states are, according to Huber, irreversible, unamenable to pharmacotherapy and organic (diencephalic) in origin, being highly correlated with pneumoencephalographic evidence of cerebral atrophy. They are not caused by neuroleptics, as they were described before the drug era, though it is possible that drugs may facilitate their development.

Huber's approach is novel to English-language psychiatry. Its strength is to highlight that the terms 'chronic schizophrenia' and 'defect state' may not be synonymous and that distortions of affective display may not be essentials of either. However, his views have not been subjected to experimental evaluation and the idea that the established deficits of divergent psychiatric states do not qualitatively differ in their fundamental aspects would be challenged by many. Huber's pneumoencephalographic work will be reviewed subsequently (Part III).

The belief that socially impoverished environments of the sort that especially characterise institutions could be detrimental to the individual has been a popular sociological idea since the war, and

many workers have described these effects graphically (Goffman 1968). Barton, in an influential monograph, attempted to identify clinically specific features of this which manifest as 'symptoms' in long-stay psychotic patients (Barton 1959).

Since the late 50s, Wing, Brown and their colleagues have attempted to clarify some of these issues by objectively studying the influence of social factors upon the clinical features of established schizophrenic illnesses (Wing & Brown 1961, Wing & Freudenberg 1961). Their most pertinent study was an investigation of long-standing female schizophrenics hospitalised in three different mental hospitals which represented different social milieus (Wing & Brown 1961, Wing & Brown 1970). The examination indices and classifications, combined with the aims of the work, dictated an uneven emphasis in this study. However, in terms of the ratings performed, only 11 % of their randomly chosen sample had normal mental states - though such features as hallucinations, anxiety and depression were not evaluated.

A strong relationship was demonstrated between the presence of what they called the "clinical poverty syndrome" (the predominance of features such as poverty of speech and flattened affect as defined in the study) and a socially unstimulating and restrictive environment. Four years later, during which time improvement had occurred in all measures of environment, approximately one third of the non-discharged patients (i.e. one third of 250) had improved - this ranging from "fairly marked" (about 20%) to "less definite changes for the better" (about 10 %). Improvement was most pronounced in 'negative' type features and occurred most in the hospital where social changes were greatest. The greater part of this improvement seemed to have taken place in the first 2 years of the study, but after 8 years, most of it

had receded - a finding the authors describe as "disappointing".

This work represents one of the most comprehensive investigations of the clinical and behavioural characteristics of patients with established schizophrenia in institutional care, and was the first to apply reliable and standardised techniques in this area. Although designed to test particular sociological theories, it illustrates the degree of mental state and behavioural abnormality to be found in such patients and the relative intransigence of these in the majority. Despite the orientation of this work, Wing and Brown state that "a substantial biological component is involved" in the production of 'negative' type deficits (Wing & Brown 1970, p 18), and elswhere Wing has concluded that :

> "Social withdrawal is a characteristic of most forms of chronic schizophrenia, irrespective of social setting, and a biological component ..... must be accepted". (Wing 1963)

1.3 COGNITION

1.3.1 GENERAL

Since the first delineation of the condition, a persistently controversial area has been that of intellectual ability in schizophrenic patients. The first question has been :

Is schizophrenia associated with impaired intellectual performance ? The second, and more fundamental one is:

If so, is this impairment permanent and 'real', and a primary manifestation of organic disorganisation of neural substrate, or is it apparent, but reversible and a secondary consequence of other mental state abnormalities, such as apathy, autistic withdrawal, preoccupation with psychotic phenomena and the like ?

The term dementia (la Démence) can be traced back to

Phillipe Pinel who used it to describe a group of insane patients without emotional excess colouring the clinical picture (Neale & Oltmanns 1980). However in the 19th century differentiation between cognitive and affective components of mental life was poorly understood and 'dementia' continued to be applied to "mental enfeeblement" or "deterioration" in the most general sense. Bleuler says of the term, that it was "applicable to all cases at hand" (Bleuler 1911, p 7). It did not have the specific implication - organic, i.e. structural, aetiology and irreversibility of symptom pattern - that it has since acquired.

Nonetheless, in the introduction to his book, Kraepelin justified his use of the term 'dementia' thus :

> "It appears that this form of mental weakness, in spite of great differences in detail, exhibits many features in common with other forms of dementia, such as are known to us as the result of paralysis, senility or epilepsy". (Kraepelin 1919. p 1).

Thus the term was already becoming refined by the begining of the century and Kraepelin was drawing the clear conclusion that 'deterioration' associated with the illness he was describing was similar to that found in other organic brain conditions. While he hesitatingly accepted the view that 'deterioration' could be halted or sometimes reversed, he left open the possibility that in some cases it may indeed be organically mediated.

Although Bleuler believed in a basic anatomical or chemical abnormality as the ultimate 'cause' of schizophrenia he remained adamant that structural degeneration and immutability of clinical features were not associated with this condition. Intellectual deterioration was more apparant than real, being secondary to autistic withdrawal from reality (Bleuler 1911). He did not believe the

illness permitted " a full restitutio ad integrám " (p. 9) but did believe that within every chronic schizophrenic lay the dormant potential for recovery and behind every deteriorated facade was an active mental life awaiting release - the latter in particular being recently reiterated by M Bleuler (M. Bleuler 1978).

These two poles of opinion represented the prevailing views within psychiatry for most of this century. In the 50s and 60s tentative steps were taken to explore these questions using standardised test techniques, though by the early 70s cognitive testing in schizophrenia had become an unpopular area of investigation (Payne 1973, Rabin et al, 1979). In recent years however effort has once again been invested in this area, inspired partly by improved tools for cognitive evaluation and partly because the introduction of imaging techniques has opened up the prospect of producing an objective correlate for any abnormalities that may be found. The older and the newer studies will be reviewed separately.

1. 3. 2. OLDER STUDIES OF COGNITIVE PERFORMANCE IN SCHIZOPHRENIA

The earliest work in this field used the Stanford-Binet test which, as it is only standardised for children, left age as an uncontrolled variable (Payne 1960). Subsequently the Wechsler Adult Intelligence Scale (WAIS) was used, which overcame this problem.

Tested when acutely ill, schizophrenics as a group perform in the low average range of intelligence (Payne 1960, 1973). However they clearly represent a heterogeneous group, having a wider range of scores than the normal population. This has been attributed to differential abilities within the classical subtypes of the illness with some agreement that hebephrenic and catatonic patients perform particularly badly compared to paranoids. (Payne 1960, 1973).

While paranoids may appear to remain relatively preserved (Payne 1960; 1973), the conventional view of intelligence holding up intact in such patients has been challenged (Lubin et al 1962; Kingsley & Struening 1966). Whether differential subtype capabilities represent sampling bias or reflect the fact that those who perform badly tend to be specifically labelled is unclear (Payne 1960).

None-the-less it can be said that, for whatever reason, intellectual ability is compromised during the more active shifts of the illness - according to reasonable estimates by about two-thirds of one standard deviation (Payne 1973) or 10 IQ points on the Wechsler-Bellvue scale (Winder 1960).

With regard to the more established (or 'chronic') state, the question as to whether the deficits believed to accrue are ireversible or not, and if not, whether they are progressive, remained largely unresolved in the older literature. While quite marked improvements in IQ scores, including those of chronic schizophrenics who had been 'activated', were reported (Goldstein & Salzman 1967; Haywood & Moelis 1963; Hamilton 1963), most studies found either no progressive deterioration (Payne 1973; Smith 1963) or reported that intellectual deterioration could continue throughout prolonged periods of hospitalisation (Payne 1960; Schwartzman et al 1962; Haywood & Moelis 1963). It was in addition suggested that scores on cognitive testing had certain prognostic value (Payne 1960; Hamlin & Ward 1973; Heffner et al 1975).

A further unresolved question was whether schizophrenic patients had premorbid cognitive disadvantage and hence were potentially predisposed to the psychosis, or whether their

intellectual deficits arose with the illness itself - the so - called prodromal and concomitancy hypotheses (Martin et al 1977).

Evidence exists in favour of both these theories. The prodromal theory is supported by the finding that schizophrenic adults achieve lower IQ scores in childhood than their siblings (Lane & Albee 1965; Offord & Cross 1971) and matched peers (Offord 1974; Watt & Lubensky 1976), and by the fact that IQ scores in the premorbid phase can show a deficit (Schwartzman & Douglas 1962). Mason examined the IQ results of conscripts who subsequently developed a functional psychiatric disorder and compared them with controls (Mason 1956). While the psychiatric group as a whole showed no significant deviation from controls, those who subsequently became schizophrenic were significantly duller prior to the onset of the psychosis. Against this, is the finding of some workers that schizophrenics perform at a poorer level in the morbid than in the premorbid state (Kingsley & Struening 1966; Schwartzman et al 1962), thus supporting the concomitancy theory. The difficulty in deciding when premorbid becomes morbid, the selection of patients and especially the lack of strict, standardised criteria for schizophrenia, account for some of these discrepancies.

Thus the older literature was inconclusive in its findings. In addition, the question of whether demonstrable deficits were the result of psychological factors such as impairment of "attention and effort", "mental control", "volition" or the like (Hunt & Cofer 1944; Huston & Shakow 1949) or of "organic" ones (Lubin et al 1962) could not be readily answered. Based on qualitative comparisons of test performance it was possible to speculate on the

likelihood of schizophrenic cognitive deficits being organically mediated (Lilliston 1970, 1973; Depue 1976) but prediction regarding an organic pathology or aetiology was not possible at high levels of confidence. The Kraepelin/Bleuler polarity remained essentially unresolved.

Perhaps for this reason, interest wained. In recent years the area has once again received attention, largely following the introduction of CAT scanning, and the development of more refined psychometric tests.

1.3.3 NEWER STUDIES OF COGNITIVE PERFORMANCE IN SCHIZOPHRENIA

Newer work in this field has been less concerned with purely IQ assessment than with more widespread neuropsychological evaluations. The interest of recent studies lies in attempts to correlate cognitive performance with objective parameters of structural brain change. Findings to date however tend to be 'spin-offs' from larger C.T. investigations, and serious endeavour has yet to be applied to this area on its own. The literature is summarised in TABLE 1:1:1.

Four of these studies used intra-group comparisons and only that of Johnstone et al used a normal and a morbid control group. These workers found their schizophrenics were more impaired than both control groups on three different cognitive tests, but only impairment on Wither[5] and Hinton total scores correlated with one parameter of brain pathology, namely ventricular enlargement. No correlations were noted with cortical indices. Weinberger et al reported that WAIS total and subtotal scores were significantly lower in a group of 14 chronic schizophrenics compared to a small group

TABLE 1.1.1

SUMMARY OF RECENT STUDIES OF COGNITIVE ABILITY IN SCHIZOPHRENICS

STUDY	N	CONTROLS	TESTS	FINDINGS
JOHNSTONE et al 1976 1978b	18	Age matched hospital staff Institutionalised patients with non-cerebral neurological disorders	Withers and Hinton Inglis paird associate learning test Memory for faces	Schizophrenics signif. worse than controls Impairment on H & W totals correlated with vent. size
WEINBERGER et al 1979	14	5 - nature not clear	WAIS	Schizophrenics significantly worse on subtests and totals No C.T. correlations
RIEDER et al 1979	17	None (intra-group comparison)	Halstead-Reitan battery	4/4 with, and 1/4 without sulcal prominence beyond cut-offs for brain damage
DONNELLY et al 1980	15	None (intra-group comparison)	Halstead-Reitan battery	8 with "morphological abnormalities" had significant impairment compared to 7 with normal scans
GOLDEN et al 1980b	42	None (intra-group comparison)	Standarisded Luria-Nebraska battery	Impairment on 8 of 15 subscores correlated with vent. enlargement
ANDREASEN et al 1982b	32	None (intra-group comparison)	Mini-mental status exam	Significantly lower scores in 16 patients with large vents. compared with 16 matched patients without enlargement

of controls, though the nature of their controls is unclear. Rieder et al found that the 4 schizophrenics in their study who had cortical prominence also had cognitive test scores that "substantially exceeded accepted cut-offs for brain impairment" while only one of a matched quartet without C.T. abnormality exceeded the limits. The study of Donnelly et al used a similar methodology, comparing neuropsychological performance in members of a group with C.T. change, with that of those in whom scans were normal. The 8 of their group who had "morphological abnormalities" (ventricular enlargement and/or sulcal prominence) performed significantly worse than the 7 with no abnormality. The scan status of 12 of the 15 subjects could be predicted from their neuropsychological results. Golden et al likewise found test scores could predict 90 % of those with ventricular enlargement. Results on 8 of the 14 subscales of the Luria -Nebraska battery correlated with ventricular size. More than half their sample however was referred for testing because of a clinical suspicion of brain damage. Andreasen et al found deficits on tests of "the sensorium" in 16 patients with ventricular enlargement selected from a larger C.T. group, compared with 16 matched subjects without ventricular enlargement.

Evidence from investigations of dementia alerts one to the likelihood that any relationship between brain structure and function will be far from strong (Roberts & Caird 1976; Kaszniak et al 1979), and the need for large samples, carefully documented, is obvious. This requirement has not yet been met in this type of work. Furthermore, it is necessary to be clear about what is being measured with neuropsychological batteries and what is meant by the word 'cognition' in the context of their use. These newer studies are less concerned

with IQ in schizophrenia than the older ones reviewed previously (only Weinberger measured IQ alone) but assess a range of higher cerebral activities. It is important that general statements regarding 'cognitive' ability assessed by neuropsychological batteries do not detract from the fact that total performance may be compromised by subscores reflecting the presence of abnormality of a 'soft' neurological kind.

There is much scope for work of this type, offering as it does the prospect of correlating clinical parameters of brain dysfunction with objective features of cerebral structural change in schizophrenia. Studies thus far, however, are not of sufficient size or quality to allow any dogmatic conclusions of a link between the two.

1.4 NEUROLOGY

1.4.1 GENERAL

The belief in an unequivocal structural abnormality underlying schizophrenic illnesses and the wish to demonstrate it have a long tradition.

The classical Greek physicians never considered any view other than that madness had a physical basis, though with their virtually non-existant knowledge of the brain, they believed the abnormality to be a bodily one (Ackerknecht 1968). Descriptions of insanity were fully integrated into their medical treatises with no attempt at segregation (cf, for example, Aretaeus The Cappadocian 1972). The mind-body dualism of contemporaneous philosophy was an alient concept to them.

Despite repeated criticism and persuasive alternate theories

from the dynamic school, belief in an underlying brain disorder has remained the dominant orientation of many psychiatrists with regard to the aetiology of schizophrenia, especially in the United Kingdom. It is somewhat surprising that this should be the case, not because there is strong negative evidence to contradict it, but rather because there is a certain lack of positive evidence to support it. Some of the evidence that is available will be reviewed.

1.4.2. NEUROPATHOLOGY

Neuropathology was the obvious starting point and many psychiatrists made important contributions to the understanding of brain structure in health and disease,(for example Gudden, Wernicke, etc). Yet to date, neuropathological investigations have not revealed any abnormality in the brains of schizophrenics that can be consistently associated with the clinical condition far less one that can be said to be pathognomonic (Weinstein 1954; Dastur 1959).

Perhaps as a result of past disappointments, such investigations have attracted little interest among neuropathologists in recent years and virtually all the reports of negative or inconclusive findings arose from work done many years ago. As Stevens has pointed out, most of this work focused on the cortex (Stevens 1982a)which undoubtedly reflects - like Wernicke's cortical localisation theories - the preoccupation of the post-Darwinian age with that area.

Recent neurochemical work however has shifted interest to subcortical structures (Crow et al 1976). Stevens, reviewing the literature, provides evidence to suggest that a re-evaluation of the neuropathology of these subcortical regions may prove more rewarding

(Stevens 1982a). In her own controlled study, she reported the presence of discrete areas of gliosis with a predominantly periventricular distribution in 75 % of her schizophrenic sample. Furthermore, electronmicroscopy has not been widely used, though Miyakawa et al (1972)described the finding of intracellular irregularities and inclusions in schizophrenic brains by this method.

Thus, although neuropathological techniques have not so far produced consistent or characteristic abnormalities to support the idea of schizophrenia being an organic brain disorder, the application of improved clinical classifications, the study of subcortical areas and the use of new techniques, may yet provide important information on this question.

1.4.3. CLINICAL SIGNS

a) Gross signs

The first classification of major psychiatric disorders on the basis of gross neurological signs was probably also the last. When in 1822, Bayle separated out those insane patients who had progressive neurological signs from those who had not (Bayle, 1822)he cleared the way for the study of a discrete form of insanity with an organic neurological basis. This was one of the major discoveries in the history of psychiatry (Moore & Solomon 1934). His dichotomy allowed Esmarch & Jessen to make the connection between general paralysis and syphilis more than 30 years later (Esmarch & Jessen 1857) though conclusive demonstration of the cause being due to spirokaetal infection of the brain had to await Noguchi's work at the begining of the century (Noguchi 1909, 1910).

As to those for whom the diagnosis of general paralysis did

not apply, little comparable progress has been made in the past century and a half. Few would disagree with Arieti's statement that the chronic schizophrenic illness often appears to reach a stage "where psychology and neurology coalesce" (Arieti 1974 p 423), but the clinical evidence for gross neurological disturbance has remained elusive.

Kraepelin in particular among the early descriptive psychiatrists considered the neurological status of his patients in detail (Kraepelin 1919). It was clear even then that localising neurological signs indicative of gross cerebral disorder were not a feature of dementia praecox. Indeed Bleuler wrote that "organic paralysis will hardly be manifested as partial symptoms of schizophrenia" (Bleuler 1911 p 171). Kraepelin however, remained intrigued by certain findings which, although not pointing to specific brain pathology, were sufficiently prevalent and persistent to be worthy of note. These included irregularity of the pupil and its absent response to pain and other stimuli, asymmetry of the tendon jerks and muscle spasms.

Half a century later, Lemke found similar subtle but definite neurological abnormalities in 25.3 % of 1000 untreated schizophrenics. This was ten times that found in control samples of soldiers and students (Lemke 1955). However, Lemke examined all the schizophrenics (criteria unspecified) himself and in full knowledge of their diagnosis, while examination of most of the controls fell to a second physician.

The question of gross neurological abnormality in schizophrenia has, surprisingly, received only cursory attention to date. Stevens, in a recent review adopts an unequivocal stance in favour of the validity and relevance of such findings as have emerged,

and states :

> "... neurological signs associated with schizophrenic illnesses strongly resemble experimental and clinical disorders of the limbic forebrain". (Stevens 1982 b).

The establishment of such a relationship would represent a major clinical advance, but confirmation remains to be forthcoming.

b) Non-localising signs

In recent years, interest has grown in what have become known as 'soft' neurological signs and their possible relevance to schizophrenia. It is hypothesised that the presence of such signs would be evidence of central nervous dysfunction of a different order, although not of a lesser degree of severity, than 'hard' or localising signs (Rochford et al 1970).

'Soft' signs are varied and difficult to characterise, different workers using different tests to elicit 'abnormality'. In general they assess involuntary activity and subtle motor function within and across different sides of the body in response to verbal instructions, aspects of co-ordination, balance and gait, and aspects of complex sensation such as graphaesthesia and stereognosis. Additional complex tests of cerebral 'integration', such as the Auditory-Visual Integration Test (Birch & Belmont 1965) have also been widely used.

Such tests have received their most widespread application in paediatric psychiatry (for review see Erlenmeyer-Kimling et al 1982) with children who have in common severe behavioural disturbance - of whom childhood schizophrenics represent extreme examples. 'Soft' neurological abnormality appears to predict children at risk of developing schizophrenia with relatively high degrees of confidence.

In children, a certain objectivity is inherent in the tests

and their execution, adding to their validity as pointers to cerebral disorder. In adults, however, this type of investigation becomes much less an evaluation of uncorrupted neurological status than of motor responses which involve aspects of cognition such as concentration and comprehension. Performance is much more likely to be influenced by mental state factors and hence findings may reflect in large part the subjects' general level of competence rather than any putative cerebral lesion(s). It might therefore be predicted, for example, that a higher prevalence of 'soft' abnormality would be found in those of low IQ, as has been reported (Quitkin et al 1976).

In recent years a number of studies have found a greater prevalence of 'soft' neurological signs of varying type in schizophrenics compared with a number of control groups (Tucker et al 1974; Quitkin et al 1976; Cox & Ludwig 1979 (a) and (b); Torrey 1980). However, straight comparisons of prevalence in schizophrenics as against other groups, which leave major factors such as intelligence and general cognition as uncontrolled variables must remain of doubtful validity as specific pointers to brain damage. While this area of study offers the interesting prospect of establishing parameters of brain dysfunction in schizophrenia by purely clinical means, much more careful investigation requires to be undertaken in validating the techniques applied.

c) Involuntary movements

In 1857, Griesinger wrote :

> "..... of far greater significance are .... the persistent automatic grimacing, strabysmus originating during the disease..... painful convulsions of the muscles

> of the neck .... their continuance usually (indicating) a transition to a state of incurability. A constant trembling, grinding of the teeth, chorea-like movements in adult lunatics .... at least in the majority of cases, symptoms of the development of serious organic disease of the brain" (Griesinger 1857)

Griesinger was writing after the identification of general paralysis but before the dementia praecox concept was formulated, so although one cannot transpose his comments directly to schizophrenia as now defined, it is unlikely that the spectrum of movements he recorded in "the insane" was confined to patients now recognised as having progressive neurological disorders.

However, since the delineation of dementia praecox a number of authors have commented on the presence of involuntary movement activity in schizophrenics (Kraepelin 1919; Reiter 1926; Jones & Hunter 1969; Yarden & DiScipio 1971; Brandon et al 1971). Kraepelin described them thus :

> "The spasmodic phenomena of the musculature of the face and of speech, which often appear, are extremely peculiar disorders. Some of them resemble movements of expression .... which we bring together under the name of making faces or grimacing; they remind one of the corresponding disorders of choreic patients. Nystagmus may also belong to this group. Connected with these are further, smacking and clicking with the tongue ...(and) we observe especially in the lip muscles, fine lightening-like or rhythmical twitchings, which in no way bear the stamp of voluntary movements .... The outspread fingers show fine tremor. Several patients continually carried out peculiar sprawling, irregular, choreiform,outspreading movements, which I think I can best characterise by the expression "athetoid ataxia". (Kraepelin 1919 p 83).

Bleuler, too, wrote of patients

> "performing all kinds of manipulations with their teeth... (with) grimaces of all kinds, (and) extraordinary movements of the tongue and lips" (Bleuler 1911 p 185/191).

Bleuler tended to classify such movements as manneristic/stereotypic and chastised those who called them, "quite mistakenly" (p 191),

choreic. However, he himself used, at different points, words such as "involuntary" (p 191) and "unco-ordinated" (p 215) to describe some of these movements. In addition, in describing other motor activity, he wrote :

> " I cannot immediately differentiate many (such) acts from organic apraxia "

but concluded :

> " I am convinced that all these various elements represent concomitant influences " (p 196)

Thus although Bleuler recognised that many of the movements he observed were virtually indistinguishable from organically mediated disorders, he remained "convinced" that the underlying causes were the emotionally laden psychic complexes, despite the views of others to the contrary. One of the recurrent pieces of evidence he quoted in favour of his view was the changeability of these motor signs with mental state ("complexes"). It is however now widely accepted that mental state is one of the major modifying variables determining the clinical appearance of extrapyramidal (i.e. organic) involuntary movements (Marsden et al 1975, APA Task Force 1979).

More recently, involuntary movements have been described in drug-free schizophrenic patients. Jones & Hunter, noted tremors, choreoathetoid movements and tics, in addition to 'mannerisms' in 40 % of a drug-free group admitted to hospital prior to 1946, while Brandon et al found a comparable prevalence of orofacial movements (BML triad) in schizophrenics never treated with neuroleptics as in those treated. Yarden & DiScipio noted "choreoathetosis" in 18 young newly admitted schizophrenics, though some of these were believed to have had pharmacotherapy at some point. They, like Griesinger & Kraepelin, believed the appearance of these signs

augered a poor prognosis.

The whole question of the relationship between involuntary movement disorder and schizophrenia has now been overtaken by the introduction of neuroleptic drugs and the issues surrounding what has become known as tardive dyskinesia. Notwithstanding, the older literature clearly indicates that schizophrenia was associated with spontaneous motor activity. Many of these accounts were written before the era of encephalitis lethargica and an association with this cannot be readily made.

Involuntary movements therefore may offer an objective neurological marker in schizophrenics if the effects of treatment can be accounted for. The present population offered such a prospect and these questions will be addressed in detail in Part II of the present work.

1.4.4 BRAIN STRUCTURE IN LIFE

The literature relevant to this question will be reviewed in Part III.

1.5 THE PRESENT STUDY

The present study was designed to record in standardised fashion the clinical deficits elicited at examination of a homogeneous population of long-stay schizophrenic patients and to seek correlations among the deficits, and between them and relevant aspects of historical information. The purpose of this was to clarify the nature of the deficits themselves, the terminology used to describe patients who exhibit them and the factors related to their development. It was further proposed to use this information to elucidate specific questions posed subsequently.

Chapter 2 - Methods

2. 1. GENERAL

At the begining of 1977, the case records of the entire in-patient population of Shenley Hospital were surveyed. Of the 1227 persons then receiving in-patient care, 635 had a case note diagnosis of schizophrenia and had been continuously hospitalised for at least one year at that time. Application of the criteria for schizophrenia proposed by Feighner et al(1972) to the records of this group produced 524 Feighner positive schizophrenic subjects. Of these, 14 died or were discharged before further work could be undertaken. The study sample therefore consisted of 510 Feighner positive schizophrenic in-patients.

The current status of the index subjects was assessed in terms of their present mental state, their cognitive ability, the integrity of their gross neurological functioning, and their overall behavioural competence. These four examination variables will subsequently be referred to as 'Assessed Abnormalities'.

Points of demographic and historical information, such as past physical treatments which the patient may have had, and the details of their illness at its worst were extracted from the notes. These data extracted from the case records will be referred to as 'Recorded Information'.

2. 2. ASSESSED ABNORMALITIES

2:2:1. MENTAL STATE

The features of the current mental state were recorded on the scale devised by Krawiecka et al for use with chronic psychotic

patients (Krawiecka et al 1977). This allows for assessment of eight variables, each graded on a five point scale of severity, and is based on a semi-structured interview. For the purpose of the present study, the item on affect was subdivided to allow the separate recording of incongruity and flattening. Thus, nine mental state features were scored. These are shown in Appendix 1.

Throughout this study a division is maintained between mental state phenomena described as being (at least relatively) specific to schizophrenia - that is the 'positive' and 'negative' features - and those which are relatively non-specific, being found in a wide range of psychiatric disorders - namely depression, anxiety and psychomotor retardation. This distinction is illustrated in the Appendix.

2.2.2 COGNITIVE PERFORMANCE

Cognitive ability was evaluated by applying the Withers and Hinton test battery (Withers & Hinton 1971; Hinton & Withers 1971) (Appendix II). This provides an assessment of current awareness, concentration and attention, recall and abstract reasoning, and summates to provide a total numerical score. As no time limits apply, every encouragement can be afforded even very withdrawn patients, and its succinct format ensures the maximum likelihood of co-operation being maintained until the test is completed. Previous experience with patients similar to the subjects of the present study had shown that most could attempt the questions and could achieve some score at the end.

2:2:3. NEUROLOGICAL STATUS

The neurological status was assessed only in terms of motor functioning, with no attempt at evaluation of aspects of sensation. It was felt that the value of any sensory findings would be offset by loss of patient co-operation.

The examination technique adopted was based on that described by Renfrew (Renfrew 1967) and consisted of a general assessment of motor function - namely cranial nerves, tone and power, co-ordination and limb reflexes. An additional assessment was made of the presence and gross regional distribution of any spontaneous involuntary movement disorder the patient exhibited at any time during the routine examination. Any abnormalities of gait were also noted. These data were recorded on a schedule devised for the project (Appendix III).

These three assessments were conducted one ward at a time, the patients being seen in random order. The examinations were performed before the case notes of the subjects concerned had been scrutinised and before the nurses had been interviewed in detail about patient behaviour. Thus they were performed in the absence of any information about the individual's past or present status, especially drug treatments administered at any time.

2:2:4. BEHAVIOURAL PERFORMANCE

It was realised that information resulting from examinations conducted on a single occasion provides only a cross-sectional picture and in particular gives little impression of the patients' behaviour over time. While a number of scales are available for recording behaviour in long-stay patients, there are major problems

associated with many of these (Hall 1980). Furthermore in this aspect of the present study it was intended to record the views of those in close contact with the patients regarding various psychopathological features and their relation to behaviour, in addition to seeking their descriptions of the patients' behaviour itself.

The Current Behavioural Schedule (Appendix IV) was devised for this purpose, although it is based partly on the scale of Wing (1961). This schedule was completed by the examiner on the basis of a semi-structured interview with the nurse in charge of the ward where the patient resided. Although allowing the possibility of considering behavioural deficits under separate headings - such as social behaviour, activities, manifest abnormality, incontinence - the separate items could be summated to provide a total score (maximum 50) indicative of overall behavioural functioning. This scale has been shown to have good inter-rater reliability (total scores .99 - unpublished data).

2.3 RECORDED INFORMATION

After the patients had been examined, the case notes of the study sample were scrutinised in detail.

2.3.1 PERSONAL HISTORICAL DATA

Details of the patients' early lives were recorded on the first part of an In-patient Schizophrenia Survey Form (Appendix V) constructed for the survey. This form was based on the original questions which made up the Enquiry Form contained in the case records, which relatives had, since the hospital's inception,

been required to complete immediately after the patient's admission.

In recording these data definite statements were required to make a positive notation. For 'past academic record', the term 'higher' was applied to those subjects matriculating into or graduating from an institution of higher education, 'average' to those completing basic education without stated difficulty, and 'poor' to those noted as experiencing educational 'backwardness' or who had attended an institution for the educationally subnormal.

2.3.2. PAST PHYSICAL TREATMENTS

The second section of this form was designed to record details of past physical treatments to which the patient had been exposed. This included, where appropriate, the number of treatments, if such information could be found.

This section also contained a global impression rating of the course of the illness since the patients' admission.

The final section of this form was reserved for additional noteworthy comments, including details of additional drug ingestion, for example anticholinergics.

2.3.3. THE FEATURES OF THE PSYCHOSIS AT ITS WORST

A psychopathological picture of the patient's psychosis at its most florid was constructed using the Syndrome Check List (S.C.L.) of the Present State Examination for recording salient features (Wing et al 1974). This adaptation of the P.S.E. was devised for use in retrospective case note studies. When the data are submitted to computer analysis (the Catego program), the patient is allocated to one of 50 Catego sub-classes which, although not intended as substitutes for diagnosis, do, in broad terms bear a

close relationship to clinical diagnoses. Standardisation of the description of the mental states of patients included in clinical investigations is one of the major recommended uses of this system (Wing et al 1974).

In application of the Check List, items were only recorded positively in the situations where a clear description of the feature under consideration was present in the notes. Thus statements that the patient was felt to be "incoherent" or "hallucinated" did not qualify for positive rating.

For the purposes of storing and analysing data, and to maintain blindness to such variables as past neuroleptic treatment, each patient was assigned a code number from the start, by which he/she was identified subsequently.

2.4 STATISTICAL NOTE

Except where specified in analysis of data, the following principles were applied :

If two variables were continuous and likely to be normally distributed, then they were correlated, using Pearson's product moment correlation.

If one variable was continuous and likely to be approximately normally distributed, and the other categorical, the population was divided into groups on the basis of the categorical variable and the means of the groups on the continuous variable compared using ANOVA.

If both variables were categorical, X^2 analysis was calculated.

Analysis of examination variables - in particular 'positive'

and 'negative' totals - is more problematical than these stark rules suggest. In this initial analysis the examination variables were, for consistency, all treated as continuous, as it was felt that there were sufficient points in the range for each to permit this approach. However, it is accepted that the distribution poses a problem for this assumption, although the tests applied are considered sufficiently robust to absorb this difficulty. (In later analyses (Parts II and III) a more cautious approach is adopted by dividing the examination variables into present/absent and degrees of severity categories).

Chapter 3 - Results

3.1 GENERAL

Recorded Information was obtained from the case notes of all 510 cases. Interviews with nurses provided behavioural data on 501, the remainder being known inadequately for ward staff to comment in detail. Clinical examinations of the three other Assessed Abnormalities were conducted on fewer subjects. The reasons for omissions are shown in TABLE 1:3:1.

Although patients were examined before information was extracted from their notes, for reasons of logical presentation, data subsumed under 'Recorded Information' will be presented first, followed by those from the examinations (Assessed Abnormalities). The final part will concern correlations within and between these categories.

3.2 RECORDED INFORMATION

3:2:1 ITEMS ANALYSED

Certain items in the Schizophrenia Survey Form were not used in this analysis. These were :

i) Item on Febrile Illness : Very few patients were recorded as having had no febrile illnesses. Either a long list of illnesses was given, or the patient was said to have had "usual childhood illnesses", not further specified. It was felt that no meaningful comparisons could be made on the basis of such information.

ii) Item on Regularity of Employment : The sample was admitted to long-term care over half a century, during which time social circumstances and employment prospects had varied greatly. Such

TABLE 1:3:1

THE CLINICAL DEFICITS: REASONS FOR NON-ASSESSMENT

	CASES ASSESSED	LACK OF CONSULTANT PERMISSION	PATIENT REFUSAL	NON-COOPERATION (INCL. DEAF, POOR ENGLISH)	MUTENESS	INCOHERENCE	FRAILTY	ABSENCE (WORK, LONG LEAVE ETC)	DISCHARGE	DEATH
MENTAL STATE (KRAWIECKA)	458	8	19	4				12	5	4
COGNITION (WITHERS & HINTON)	407	8	24	14	25	11		12	5	4
NEUROLOGICAL	456	8	21				4	12	5	4
BEHAVIOURAL PERFORMANCE	501							4	5	

factors are difficult to evaluate at a distance and it was felt that patients' pre-admission work records might have reflected other than illness-related factors. Thus, comparisons made on the basis of premorbid employment appeared to be of dubious validity and were excluded.

iii) Items on Premorbid Personality and Alcohol Consumption : Almost all index patients were said by their relatives to have had an 'abnormal' personality before the admission illness was suspected, in that most were described as shy, withdrawn and with few interests. Likewise the vast majority of subjects were stated to have been total or relative abstainers from alcohol. It is likely that the predominance of such features in the histories to some extent reflects the fact that poor premorbid adjustment and absence of evidence of alcohol abuse are two of the features comprising the Feighner Criteria for Schizophrenia, so their inclusion in the Schizophrenia Survey Form probably represents a degree of duplication. For whatever reasons these statements were made, it was clear that the population could not be usefully sub-divided on the basis of these variables.

Other data which were collected but not used in the present analysis included treatment with barbiturates used as hypnotics, and paraldehyde, as there was no evidence that, in the way these drugs had been administered, they would be of relevance in promoting neurological or other deficits. Also excluded were treatments which at some time had enjoyed a brief vogue, such as T.A.B. vaccine, amphetamines and chemical convulsants.

The items of Recorded Information which were therefore considered, are shown in TABLE 1:3:2. With regard to those items

TABLE 1:3:2

ITEMS OF RECORDED INFORMATION ANALYSED

	SEX
TIME FACTORS	AGE
	AGE AT FIRST ADMISSION
	LENGTH OF TIME SINCE FIRST ADMISSION
	DURATION OF PRESENT ADMISSION
HISTORICAL FACTORS	FAMILY HISTORY OF SCHIZOPHRENIA
	HISTORY OF BIRTH TRAUMA/HEAD INJURY
	HISTORY OF FITS
	EDUCATIONAL ATTAINMENT
	P.S.E. SUBCLASS
PAST PHYSICAL TREATMENTS	LEUCOTOMY
	INSULIN COMA
	ECT
	NEUROLEPTIC EXPOSURE

which reflect the passage of time, the use of the term 'length of time since first admission' requires some qualification. In the calculation of results this term is taken as equivalent to 'length of illness'. While recognising that this is only an approximation, it has been used (in common with other studies) as the firmest temporal landmark against which the duration of illness can be gauged. To have accepted hearsay statements from relatives as an alternative would have been to introduce considerable imprecision.

Past treatment items (except leucotomy) were sub-divided to provide more detailed information, and in particular, to attempt an evaluation of the effects of varying degrees of exposure. All subjects were assigned to categories of exposure designated 'none', 'some' and 'much'. For insulin coma and electro-convulsive therapy the demarkation between 'some' and 'much' was taken as the mean number of treatments for the group who had received stated amounts of that therapy. For insulin coma, the mean was 61 treatments (range 1 - 206) and for ECT, the mean was 23 (range 1 - 234). Only the precise number of treatments recorded in the notes was used. If a patient was recorded as having had " a course" of either, this was noted but the sample was large enough to allow for exclusion of these cases in analysing the results.

It was impossible to be precise about absolute amounts of neuroleptic exposure in extracting data from the drug cards. In recognition of this problem no attempt has been made to quantify total neuroleptic administration in terms such as chlorpromazine equivalents, which have recently been advocated (Wyatt & Torgow 1976;Davis 1976). To have done so would have implied undue confidence in the accuracy

TABLE 1:3:3

CONVENTIONS FOR RATING NEUROLEPTIC EXPOSURE

NONE	NEVER GIVEN	
SOME FOR 1 YEAR OR LESS	CHLORPROMAZINE	100 mgs TID
	THIORIDAZINE	100 mgs TID
	TRIFLUOPERAZINE	5 mgs TID
	PERPHENAZINE	4 mgs BD
	DEPOT FLUPHENAZINE	25 mgs 2 WKLY
	DEPOT FLUPHENTHIXOL	40 mgs 2 WKLY
MUCH	MORE THAN THE ABOVE	

of information on this very important variable. Thus arbitrary criteria were adopted for 'some' and 'much' neuroleptic exposure which reflected the trends in treatment in a relative fashion. These criteria are shown in TABLE 1:3:3.

The basic descriptive data on Recorded Information variables (excluding P.S.E. categories) are shown in TABLE 1:3:4.

3.2.2 BASIC HISTORICAL AND PAST TREATMENT DATA

The sample consisted of 270 males and 240 females. The age distribution of the group is illustrated in Fig 1:3:1. As TABLE 1:3:4 shows the women were older than the men. While the length of time since their first admission was likewise greater, as was the duration of their current admission the major difference lay in the fact that the females were older when they first required hospitalisation. For 40.7 % of the males, and for 46.3 % of females, the current admission was their first and only one. The distribution of the durations of current hospitalisation for the sample as a whole is shown in Fig 1:3:2. Although the majority of this elderly population was admitted to long-term care many years ago, 29 % were admitted after 1960.

Fewer females than males fell into the category of 'higher' past academic attainment (3 % and 8.5 % respectively). Such sex differences as did emerge on past physical treatment items (TABLE 1:3:4) most probably reflect the treatment biases of different consultants. This was certainly the case for past neuroleptic exposure, as those consultants who advocated a dynamic treatment approach, had mainly commitments to male patients. Hence these

TABLE 1:3:4

RECORDED INFORMATION* (EXCLUDING P.S.E. SUBCLASSES)

HISTORICAL DATA

	AGE (YRS)	AGE AT 1st ADMISSION (YRS)	LENGTH OF TIME SINCE 1st ADMISSION (YRS)	DURATION OF PRESENT ADMISSION (YRS)	FAMILY HISTORY OF SCHIZOPHRENIA		
					NEGATIVE	POSSIBLE	POSITIVE
TOTAL SAMPLE (510)	59.2 ± SD 13.9	28.2 ± SD 8.9	31 ± SD 11.1	26.5 ± SD 13.1	217	67	65
MALES (270)	56 ± SD 13.4	26.5 ± SD 7.85	29.6 ± SD 10.7	25.2 ± SD 12.4	116	31	34
FEMALES (240)	62.8 ± SD 13.6	30.1 ± SD 9.7	32.7 ± SD 11.3	27.8 ± SD 13.7	101	36	31

	BIRTH TRAUMA/ HEAD INJURY		FITS(+)		PAST ACADEMIC ATTAINMENT			COURSE OF ILLNESS			
	NO	YES	NO	YES	HIGHER	AVERAGE	POOR	BETTER	SAME	WORSE	FLUCTUATING
TOTAL SAMPLE (510)	232	69	323	56	31	314	46	76	298	43	81
MALES (270)	117	45	169	33	23	164	28	31	159	32	41
FEMALES (240)	115	24	154	23	8	150	18	45	139	11	40

PAST PHYSICAL TREATMENT DATA

	LEUCOTOMY		INSULIN COMA			ELECTROCONVULSIVE THERAPY			NEUROLEPTIC MEDICATION		
	NO	YES	NONE	SOME	MUCH	NONE	SOME	MUCH	NONE	SOME	MUCH
TOTAL SAMPLE (510)	425	42	310	81	57	281	119	41	65	140	305
MALES (270)	229	16	154	40	46	150	69	14	49	67	155
FEMALES (240)	196	26	156	41	11	131	50	27	16	73	150

* TOTALS VARIABLE BECAUSE OF SUBJECTS WITH MISSING DATA ON DIFFERENT ITEMS

+ FITS: EXCLUSIVE OF 5 PATIENTS RECORDED AS TRANSIENTLY FITTING POST-LEUCOTOMY

FIG 1:3:1

Distribution of ages

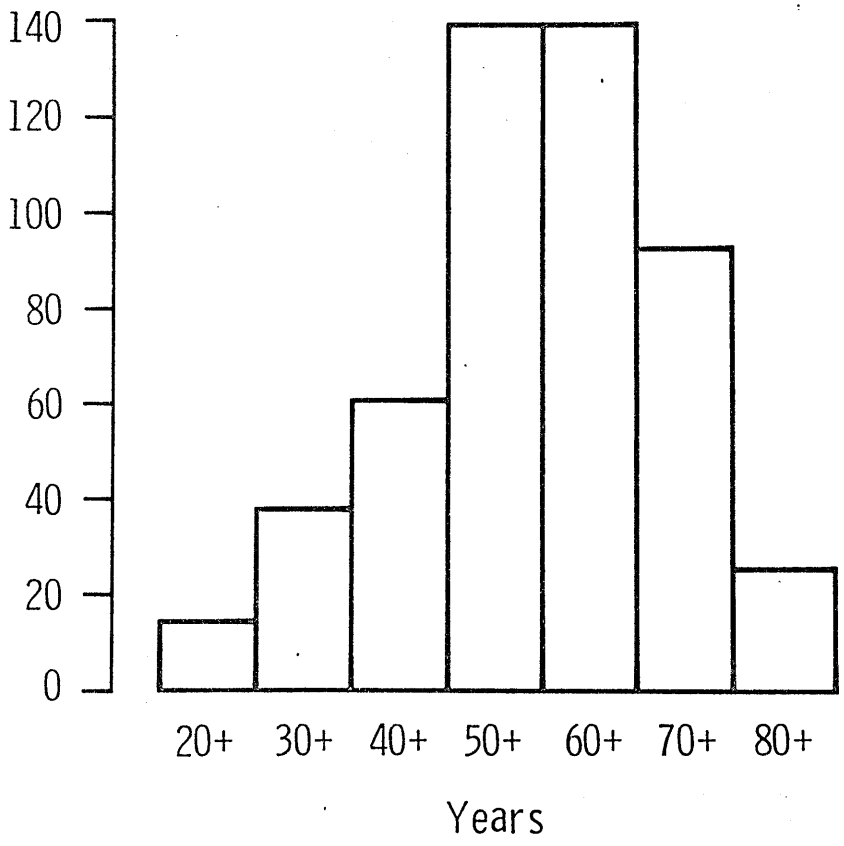
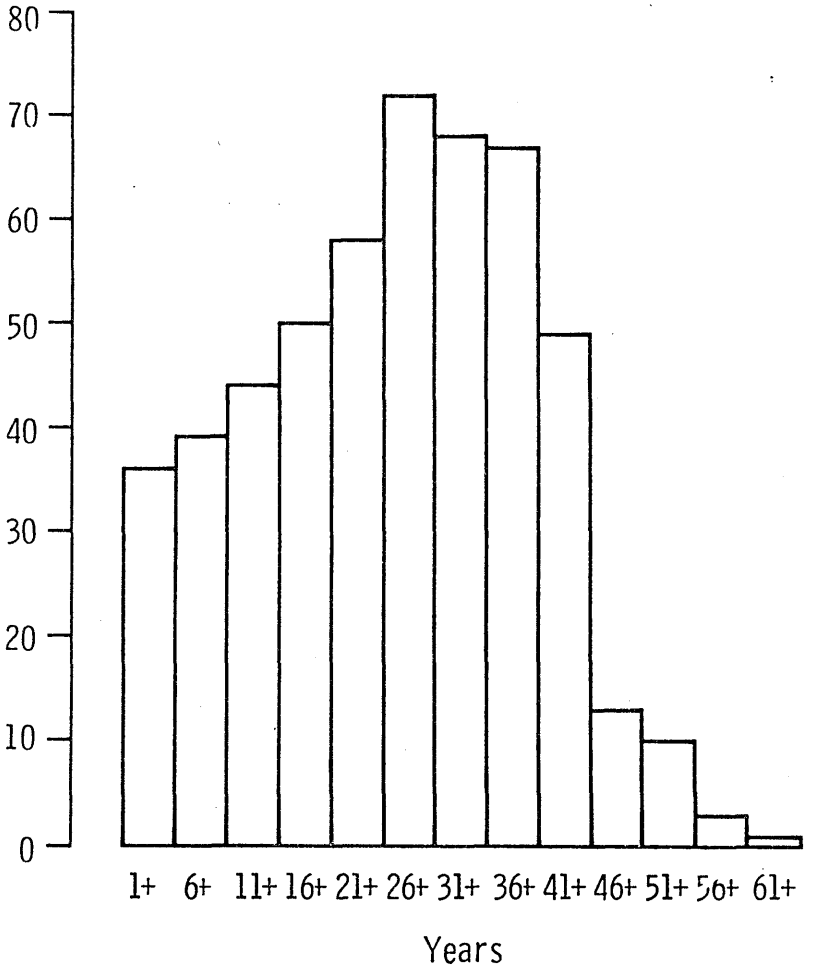


FIG 1:3:2

Distribution of durations of hospitalisation



findings probably reflect administrative idiosyncrasies which cannot be generalised, and so were not formally analysed.

3.2.3 THE CATEGO SUBCLASSES

The Catego subclasses into which the patients fell, based on the P.S.E. Syndrome Check List data, are shown in Fig 1:3:3. The vast majority of subjects (83.5 %) fell into one of the four main subclasses : NS + (nuclear syndrome), DS + (schizophrenia without first rank features), DP + (delusional (paranoid) psychosis), and CS + (catatonic syndrome). In this sample, 'NS' and 'DS' cannot really be separated, as the fact that nuclear features were not recorded in the case notes does not mean that they were not present. With two-thirds of the sample being admitted prior to Schneider's classification in 1959 (Schneider 1959), it is likely that in many instances they were not particularly sought.

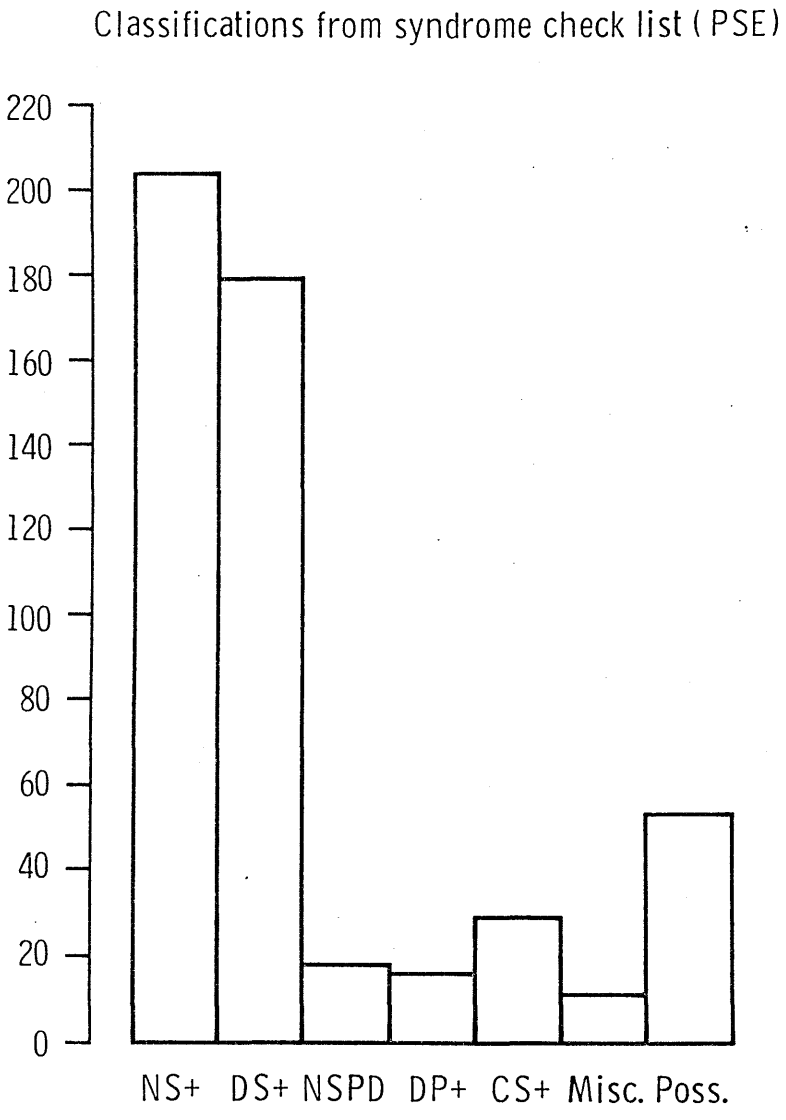
Those cases illustrated in Fig 1:3:3 as 'possible' include ones with residual psychoses and combination psychoses as well as those with suggestive, but not categorical, schizophrenic ratings on the Syndrome Check List. The 'miscellaneous' group of 12 patients, in fact all fell into affective classes, though in only 5 of these was the classification definite. Thus in less than 1 % of cases only was there a definite disagreement between Feighner and P.S.E. criteria.

3.3. ASSESSED ABNORMALITIES

3.3.1 MENTAL STATE

In considering the mental state data, results were calculated for the'positive', and 'negative' and 'non-specific' schizophrenic

FIG 1:3:3


Classifications from syndrome check list (PSE)
220
200
180
160
140
120
100
80
60
40
20
0
NS+
DS+
NSPD
DP+
CS+
Misc.
Poss.

subtotals separately.

The distributions of Krawiecka 'positive' and 'negative' subtotals in the sample are shown in Fig 1:3:4 and 1:3:5 respectively. The maximal total obtainable for 'positive' features is 15 (as clearly a rating of 4 on incoherence precludes the coherent expression of delusions) and for 'negative' features is 8. In this sample the mean 'positive' score was 3.6 ($\pm$ S.D. 3.45) and the mean 'negative' score 2.4 ($\pm$ S.D. 2.27).

Using total or subtotal scores from multi-item rating scales where one of the categories of severity allows for noteworthy but normal features to be recorded i.e. item rating of 1, presents major problems regarding the cut-offs for normality adopted. This problem will be discussed in detail in the following section (Part II - Movement Disorders). However, with regard to 'positive' features of the mental state, only one patient obtained a total of 2 that comprised two single scores of 1. Thus a total score of zero or 1 on the 'positive' schizophrenic items was taken as indicative of no abnormality. Adopting this criterion only 31.5 % of patients exhibited no 'positive' mental state phenomena.

For the 'negative' features, eight patients obtained a subtotal score of 2 comprising two single ratings of 1. However, 78 patients obtained this total on one single 'negative' item rated mildly, but nonetheless unequivocally, abnormal. It was thus deemed justifiable to adopt the same criteria of zero and 1 for normality, as the degree of contamination would be comparatively slight. By this standard, 39 % had no 'negative' features.

FIG 1:3:4

Distribution of positive scores on Krawiecka scale

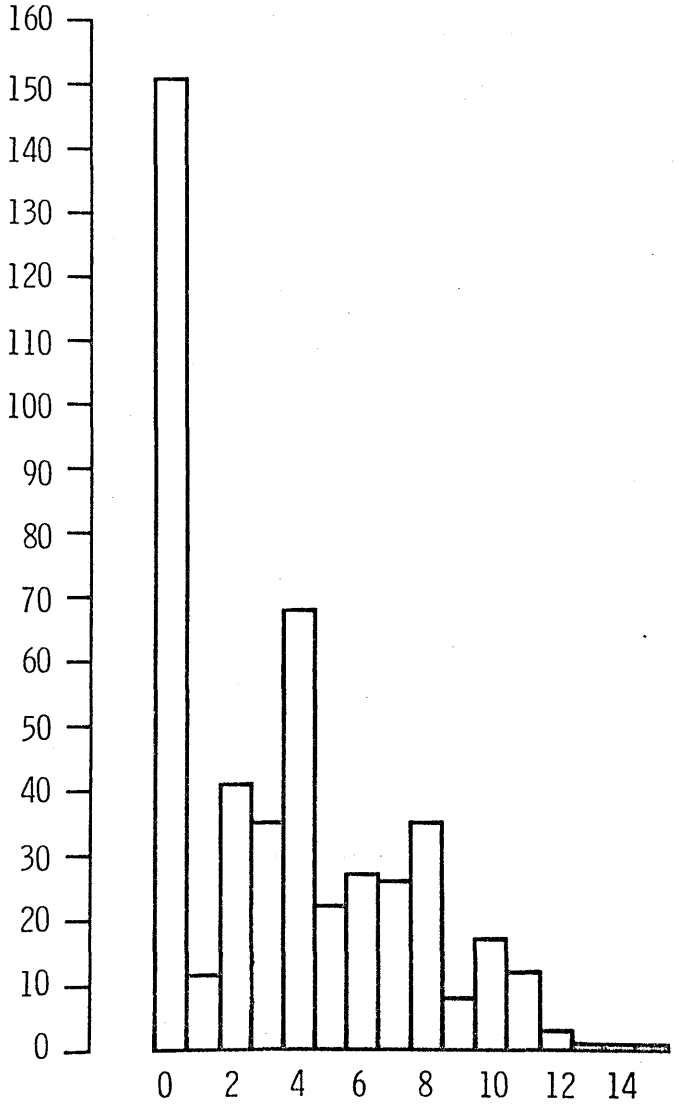
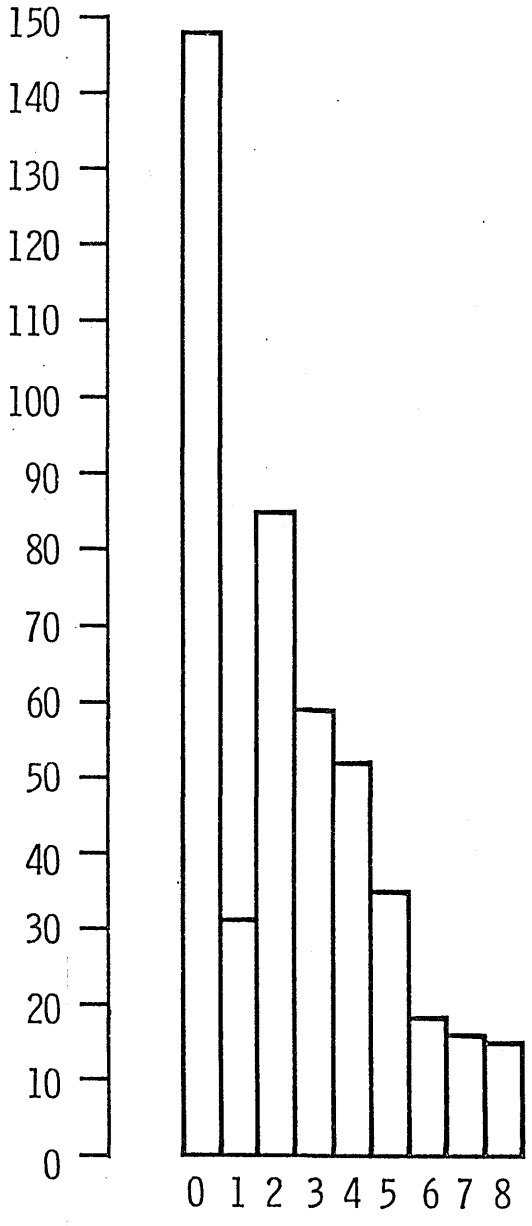


FIG 1:3:5

Distribution of negative scores
on Krawiecka scale



Using an overall normality criterion of zero and 1 for both 'positive' and 'negative' subscore totals, only 37 subjects (18 males and 19 females) or 8.1 % of the sample demonstrated no abnormality in these areas of the mental state.

Applying the same criterion for normality to the non-specific items, 112 (24.5 %) received positive ratings. This figure comprised16 % scoring 2 or more on depression and 15.1 % scoring 2 or more on anxiety. Of these patients, 30 were rated on both depression and anxiety. Thus for the 'non-specific' items on the Krawiecka Scale 9.4 % of subjects scored on depression alone, 8.5 % on anxiety alone, with 6.6. % scoring for both.

Although retardation was recorded in 128 patients (27.9 %), it never occured as the only abnormality. Only one patient was rated for psychomotor retardation in the presence of neurotic - type symptoms alone (i.e. anxiety and depression). Overwhelmingly this rating was confined to subjects who also demonstrated abnormality on items considered, for the purposes of the present study, to be indicative of a 'negative' schizophrenic state. Thus, of the 128 patients rating on retardation 117 (or 91.4 %) also obtained a score of 2 or more on affective flattening and/or poverty of speech/muteness. The associations of abnormal retardation scores and other mental state phenomena are shown in TABLE 1:3:5.

The prevalence of 'non-specific' abnormality is of interest but, as the present work is concerned with the more specific features of schizophrenia, they will not be considered further.

TABLE 1:3:5

ASSOCIATIONS OF PSYCHOMOTOR RETARDATION WITH OTHER FEATURES OF THE MENTAL STATE (NOS. OF PATIENTS)

WITH SPECIFIC* FEATURES ONLY						
Affective flattening plus poverty of speech	43					
Affective flattening alone	9	Poverty of speech alone	3			
Affective flattening plus 'positive' mental state features	15	Poverty of speech plus 'positive' mental state features	8			
Affective flattening plus poverty of speech plus 'positive' mental state features	21					
Positive mental state features only	9					
WITH NON-SPECIFIC* FEATURES ONLY						
Depression plus anxiety	1					
WITH BOTH SPECIFIC* AND NON-SPECIFIC* FEATURES						
Depression plus 'negative' mental state features	4	Anxiety plus 'negative' mental state features	2	Depression and anxiety plus 'negative' mental state features	1	
Depression plus 'positive' mental state features	0	Anxiety plus 'positive' mental state features	1	Depression and anxiety plus 'positive' mental state features	0	
Depression plus both 'negative' and 'positive' mental state features	10	Anxiety plus 'positive' and 'negative' mental state features	1	Depression and anxiety plus 'negative' and 'positive' mental state features	0	

* Specific features refers to those items of Krawiecka scale designated as 'positive' and 'negative' schizophrenic features in this study.
Non-specific features are those not so designated (i.e. anxiety and depression).

3.3.2 COGNITIVE PERFORMANCE

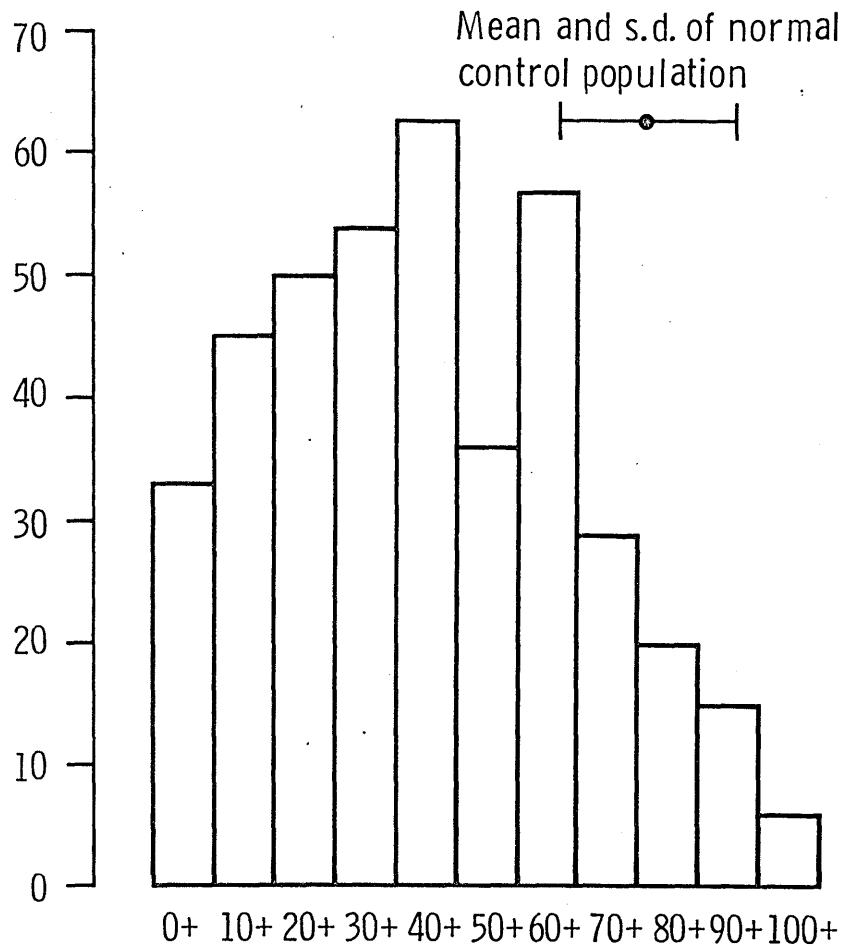
The total score obtainable on the Withers and Hinton test battery is 140. However the results to be presented here are based on a possible maximum of 131, as the Babcock Sentence was excluded. This was because a large number of these patients found the test difficult even after several attempts. To proceed further (to a maximum of 9 attempts as recommended) often produced frustration and irritability and hence in some cases the sentence was abandoned prematurely in order to maintain co-operation for the rest of the battery.

The range of performance on the Withers and Hinton battery was wide, the distribution of total scores being shown in Fig 1:3:6. The mean value and standard deviation illustrated on the figure refer to the mean scores obtained by two groups of patients used as controls when the test battery was applied in a previous study at Northwick Park Hospital (Johnstone et al 1976: Johnstone et al 1978b). One control group comprised volunteers from the normal male ancillary staff of the hospital (mean age 56 years) while the other was a sample of patients hospitalised for many years in the Royal Home and Hospital for Incurables, Putney, because of chronic physical disease (mean age 63.1 years). The mean score obtained by both these groups, with the Babcock Sentence score excluded, was 81 $\pm$ S.D. 14.

As Fig 1:3:6 shows, the majority of the present sample did very badly on this test, the mean for the study group being 44.6 $\pm$ S.D. 25.3. Indeed 62.5 % of the patients scored less than 2 standard deviations below the mean for the control group (i.e.53),

FIG 1:3:6

Distribution of Withers and Hinton scores



and none obtained more than 2 standard deviations above the mean control groups'score (i.e. 109). Thus, for whatever reason, the ability of most of the patients to perform tests of this type was substantially impaired.

3.3.3 NEUROLOGICAL STATUS

The initial breakdown of findings from the neurological examinations is shown in Fig 1:3:7. One hundred and one subjects demonstrated no motor abnormality whatsoever. Thus in 77.9 % of the population, at least one neurological sign could be demonstrated. These signs can be roughly divided into two main groups :

i) Those of a type conventionally referred to as extrapyramidal. The major qualifying criteria for this classification were the presence of rigidity in agonist/antagonist limb musculature and/or the presence of a spontaneous involuntary disorder of movement, other than simple, fine tremor, in any body part. Both these signs are generally held to reflect disruption of activity in so-called extrapyramidal brain systems.

ii) Those not conventionally designated as extrapyramidal. This group presented mainly abnormalities of pyramidal tract and lower motor neurone function (i.e. those usually called gross or localising neurological signs), but included a number of patients with miscellaneous disorders of motor activity. For this reason these patients will be referred to as the 'other' neurology group (i.e. 'other' = non-extrapyramidal). The presence of 'other' neurological features would preferentially allocate a subject to this group, but would not of course exclude the possibility of that patient at the same time having extrapyramidal signs.

A total of 263 patients demonstrated clinically an increase in muscle tone. Four of these, however, had additional clear signs that this abnormality was due to pyramidal dysfunction, and are included in the 'other' neurology group. Thus 259 patients showed

FIG 1:3:7

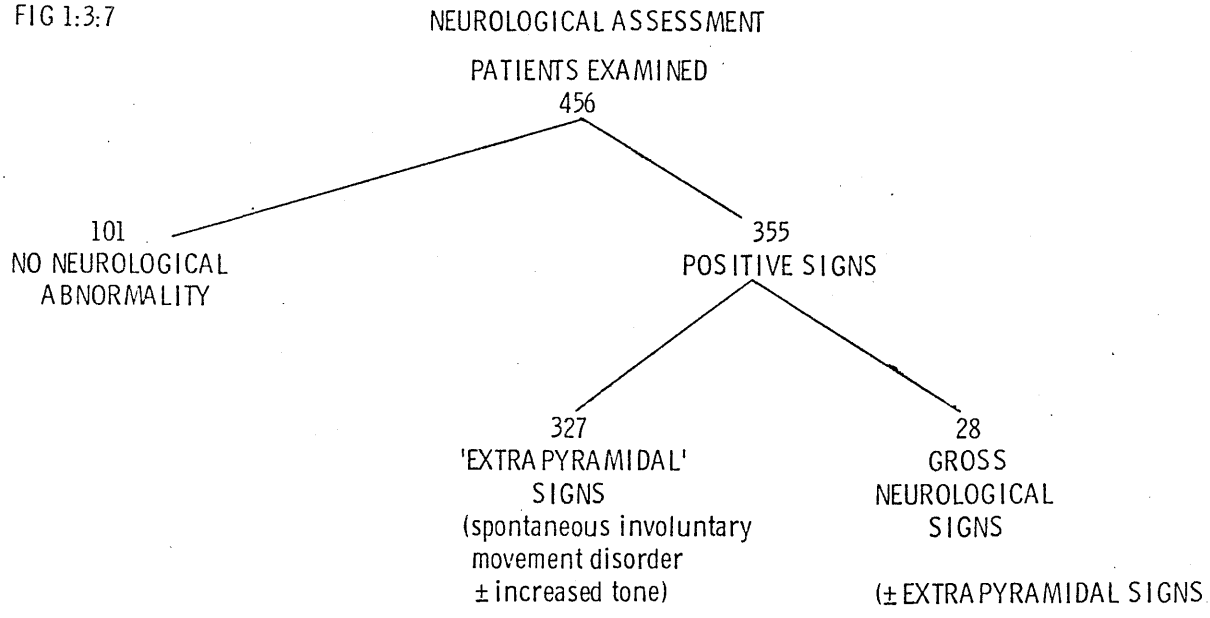

NEUROLOGICAL ASSESSMENT
PATIENTS EXAMINED
456
101
NO NEUROLOGICAL ABNORMALITY
355
POSITIVE SIGNS
327
'EXTRA PYRAMIDAL' SIGNS
(spontaneous involuntary movement disorder ± increased tone)
28
GROSS NEUROLOGICAL SIGNS
(± EXTRA PYRAMIDAL SIGNS

TABLE 1:3:6

MOVEMENT DISORDER IN NEUROLEPTIC-FREE PATIENTS

	MEAN AGE YEARS	TOTAL NO. OF CASES	NUMBER OF CASES WITH INDIVIDUAL PART AFFECTED				
			GAIT	FACE	UPPER LIMBS	TRUNK	LOWER LIMBS
MOVEMENT DISORDER	68	27	6	18	9	9	10
NO MOVEMENT DISORDER	72.8	25					

TABLE 1:3:7

'OTHER' NEUROLOGY - THE NATURE OF THE GROSS SIGNS

L.T. (UMN) SIGNS		S.T. (LMN) SIGNS		PTOSIS		NYSTAGMUS		MISCELLANEOUS	
Congenital hemiparesis	1	Bell's palsy	1	Unilateral (incl 1 leuc)	4	Slight (incl 1 leuc)	5	Optic atrophy (Tobacco amblyopia)	1
Diplegia	1	(R) Masseter atrophy	1						
Cerebrovascular accident	2	Partial ulnar palsy (old elbow fracture)	1	Bilateral (incl 1 leuc)	5	Moderate	2[D]	Fixed dilated pupil	1
Cervical spondylitis	1	Partial ulnar/median palsy (self-inflicted)	1			Gross	1[B]	Pupillary inequality	1
Isolated partial VII nerve (incl 2 leuc)	7[A]	Dorsal interosseous atrophy	1					Intermittent facial hemispasm	1
		Generalised interosseous atrophy	2					Bilateral quadraceps wasting (? IV neurological)	1
Hyperreflexia with lower limb clonus	1[C]	(R) Upper limb (indeterminate aetiology)	2					Pes Cavus	12ABC
								Pes Cavus (doubtful)	1
Disseminated sclerosis	1[D]	(L) Upper limb (leuc)	1					Catalepsy with flexabilitas cerea	2
		(R) Lower limb (indeterminate aetiology)	1					Negativism	1

A,B,C,D represent three patients with 2 abnormalities each

Leuc - patients who have been leucotomised

rigidity believed to represent extrapyramidal abnormality. Of these 103 (22.6 %) had rigidity without coincident involuntary movements, while in 156 (34.2 %) both rigidity and movement disorder were found. Spontaneous involuntary movements in the absence of rigidity were present in 68 patients (14.9 %).

Spontaneous involuntary movements in at least one body part were noted in 229 subjects (49.8 %). Of the 65 subjects whose case notes revealed no evidence of past neuroleptic treatment, 52 were available for examination. Twenty seven of these (51.9 % of neuroleptic-free patients) had involuntary movements. (TABLE 1:3:6). Thus the prevalence of abnormality, in terms of only the presence/absence of involuntary movements, was comparable in those with no history of neuroleptic treatment to that in the sample as a whole.

'Other' neurology is shown in TABLE 1:3:7. For the most part of these abnormalities were not striking. In particular, features indicative of serious CNS disorder were uncommon.

Therefore, most patients had some neurological abnormality and in the majority this was a disorder of movement and/or tone.

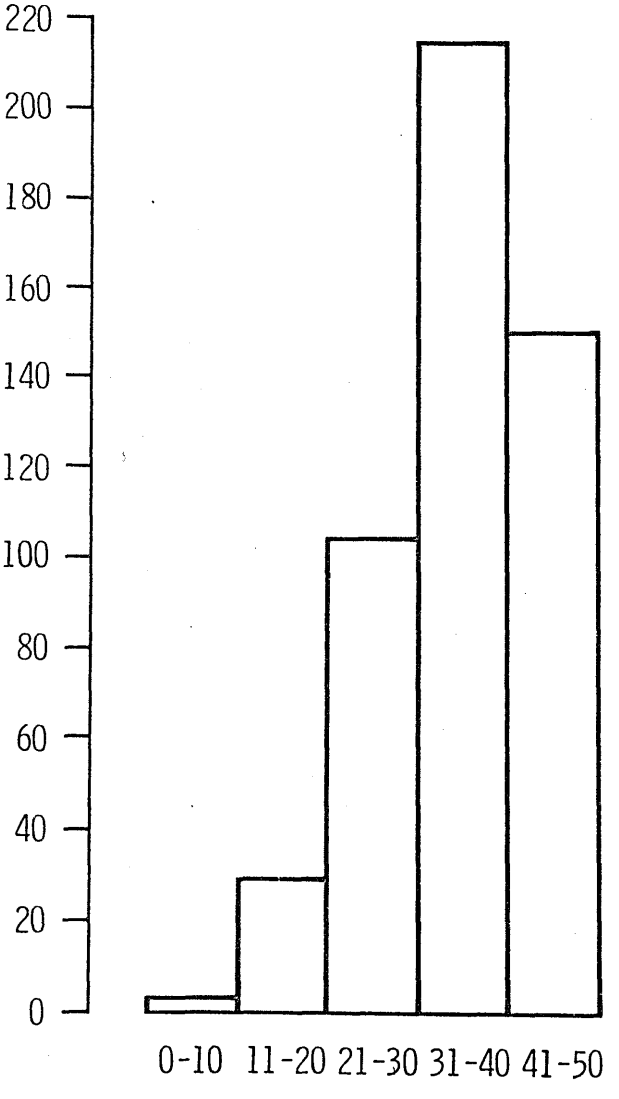
3.3.4 BEHAVIOURAL PERFORMANCE

While the Current Behavioural Schedule considered behaviour under different headings (Appendix IV), only total scores will be considered here.

It must be emphasised that this schedule was designed to record in standardised form only the rudiments of behavioural competence. Thus, obtaining a maximum score of 50 means no more than that the patient could converse at an elementary and general level, both

FIG 1:3:8

Distribution of scores on current behavioural schedule



spontaneously and if approached, that they could occupy themselves in a routine and have some limited leisure pursuit, that the more bizarre outward manifestations of their illness were controlled, and that they were not incontinent. Maximal attainment therefore implies a far from sophisticated level of behavioural performance.

The distribution of total scores on the Current Behavioural Schedule is shown in Fig 1:3:8. The mean score for the group was 34.7 $\pm$ S.D. 8.26. These findings demonstrate a striking degree of behavioural abnormality in this population. Of note is the fact that 97 patients were reported by the nursing staff as being incontinent.

3.4 RELATIONSHIPS WITHIN AND BETWEEN CATEGORIES

3.4.1 RELATIONSHIPS BETWEEN DIFFERENT ITEMS OF RECORDED INFORMATION

The correlations between different items of Recorded Information that attained statistical significance all related to the age of onset of the illness (as assessed from the time of first admission to hospital).

Firstly, age of onset was significantly related to PSE subclasses. The comparisons are shown in TABLE 1:3:8. No distinctions emerged between the 'NS' and 'DS' subclasses with regard to age of onset, but both these groups had a significantly earlier age of onset than the 'DP' group. Each of these in their turn had later onsets than those classified as 'CS'. PSE subclasses were not related to any other Recorded Information items, including other variables concerning the passage of time (TABLE 1:3:8).

TABLE 1:3:8

RELATIONSHIPS BETWEEN THE PASSAGE OF TIME AND PSE SUBCLASSES

	NS	DS	DP	CS	COMPARISONS	PROBABILIT
NUMBER	203	178	17	29		
AGE OF ONSET (YEARS)	29.3	27.8	34.8	22.8	NS < DP NS > CS DS < DP DS > CS DP > CS	p < 0.05 p < 0.001 p < 0.01 p < 0.02 p < 0.001
CURRENT HOSPITAL (YEARS)	25	26.8	23.6	30		
DURATION OF TOTAL ILLNESS	29.5	31.3	30	33.1		

ALL OTHER COMPARISONS NON-SIGNIFICANT

TABLE 1:3:9

RELATIONSHIPS BETWEEN AGE OF ONSET, FAMILY HISTORY AND PAST ACADEMIC RECORD

	NO FAMILY HISTORY (a)	POSSIBLE FAMILY HISTORY (b)	DEFINITE FAMILY HISTORY (c)	COMPARISON AND PROBABILITY	HIGHER ACADEMIC (a)	AVERAGE ACADEMIC (b)	POOR ACADEMIC (c)	COMPARISON AND PROBABILITY
AGE OF ONSET (YEARS)	28.6	28.1	25	$c < a$ $p < 0.01$	29	28.1	23.4	$c < a$ $p < 0.01$ $c < b$ $p < 0.001$
NUMBER	271	67	65		31	414	46	

ALL OTHER COMPARISONS NON-SIGNIFICANT

Secondly, age of onset was significantly correlated with family history, in that those with a definite family history of schizophrenia had a significantly earlier age of onset than those with no such history (TABLE 1:3:9).

Thirdly, there was a significant association between age of onset and the subject's academic attainment. Those of 'poor' past academic record (as defined previously - p 63) had an earlier onset than both those with a history of 'higher' ability and those of 'average' ability (TABLE 1:3:9).

There were no other significant relationships between items of Recorded Information.

3.4.2 RELATIONSHIPS BETWEEN DIFFERENT ITEMS OF ASSESSED ABNORMALITY

There were no significant relationships between the presence of 'positive' mental state features or those neurological features classified as 'other' neurology, and the remaining items of Assessed Abnormality. There were, however, striking correlations between the presence of 'negative' mental state features, cognitive impairment, neurological signs of extrapyramidal type and behavioural deterioration. These relationships are shown in Fig 1:3:9.

3.4.3 RELATIONSHIPS BETWEEN ASSESSED ABNORMALITIES AND ITEMS OF RECORDED INFORMATION

a) Mental state

The relationships between the 'positive' and 'negative' features of the mental state and Recorded Information variables reflecting the effects of the passage of time are shown in TABLE 1:3:10.

FIG 1:3:9 RELATIONSHIPS BETWEEN ITEMS OF ASSESSED ABNORMALITY

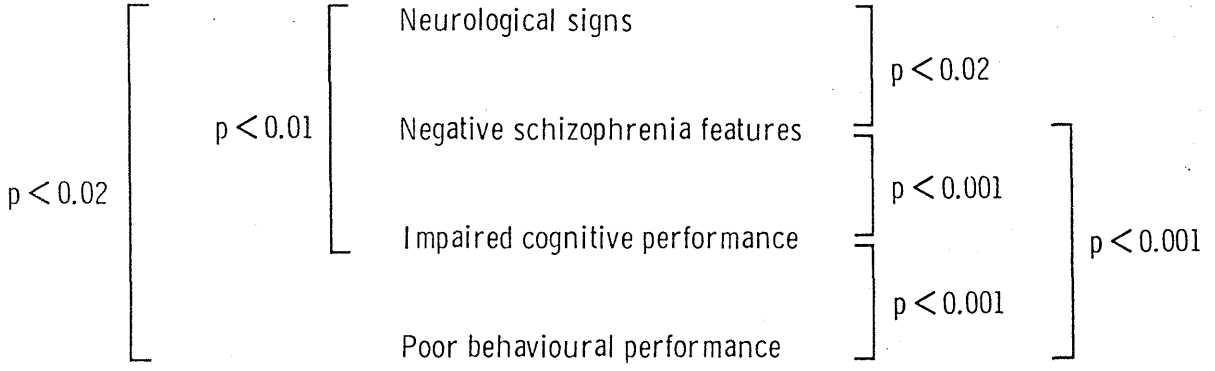


TABLE 1:3:10

CORRELATIONS BETWEEN MENTAL STATE, COGNITIVE AND BEHAVIOURAL VARIABLES OF ASSESSED ABNORMALITIES AND RECORDED INFORMATION VARIABLES REFLECTING THE PASSAGE OF TIME

	POSITIVE FEATURES SCORE	NEGATIVE FEATURES SCORE	WITHERS & HINTON SCORE	WARD BEHAVIOUR SCORE
PRESENT AGE	-0.04	0.03	-0.21**	-0.05
AGE AT FIRST ADMISSION	0.06	-0.19**	-0.01	0.06
LENGTH OF ILLNESS	-0.09	0.19**	-0.26***	-0.11
DURATION OF CURRENT HOSPITALISATION	-0.07	0.25***	-0.31***	-0.15*

* $p < 0.05$
** $p < 0.01$
*** $p < 0.001$

'Positive' features are not related to any time variables, while the presence of 'negative' features is associated with an earlier age of onset, a longer length of illness and longer duration of current hospitalisation, but not with present age.

The only other correlations between mental state features and Recorded Information variables to attain significance concern the PSE subclasses reflecting the features of the illness at its worst. These are shown in TABLE 1:3:11. Thus 'positive' phenomena in the current mental state are more associated with past events giving rise to 'NS' and 'DS' Catego subclasses than with a past history compatible with a 'CS' grouping, while the 'NS' subclass was also more associated with present 'positive' features than those defined as 'DP'. The presence of current 'negative' features was more associated with 'CS' types than any of the other main subclasses ('NS', 'DS', 'DP'), though 'negative' features were found more with 'DS' than 'NS', and with 'DS' than 'DP' classifications.

The present mental state deficits therefore were determined only by the form the illness took at its worst and by events reflecting the passage of time since its onset. In particular, no past treatment variables were of significance in determining the present abnormalities in terms of 'positive' and 'negative' mental state phenomena.

b) Cognitive Performance

Relationships between the passage of time and cognitive performance are shown in TABLE 1:3:10. Present age, the length of

TABLE 1:3:11

RELATIONSHIPS BETWEEN MENTAL STATE, COGNITIVE AND BEHAVIOURAL PERFORMANCE AND FEATURES OF THE ILLNESS AT ITS WORST (PSE SUBCLASSES)

POSITIVE FEATURES (KRAWIECKA)	NS > CS $p < 0.01$	DS > CS $p < 0.05$	NS > DP $p < 0.05$		
NEGATIVE FEATURES (KRAWIECKA)	NS < CS $p < 0.01$	DS < CS $p < 0.001$	NS < DS $p < 0.01$	DP < CS $p < 0.001$	DS > DP $p < 0.05$
WITHERS AND HINTON	NS > CS $p < 0.01$	DS > CS $p < 0.01$	DP > CS $p < 0.05$		
BEHAVIOURAL PERFORMANCE	NS > CS $p < 0.001$	DS > CS $p < 0.01$	DP > CS $p < 0.01$		

the illness and the duration of the present admission were all associated with adverse effects on cognitive performance. Similarly, intellectual impairment was more associated with a 'CS' grouping than any other subclass (TABLE 1:3:11).

Past academic attainment had a significant and predictable bearing on Withers and Hinton test scores. Those of 'higher' past attainment did better than those of 'average' ($P < 0.001$) and those of 'poor' ability ($P < 0.001$), while those with an 'average' history in this regard also performed better than those in the 'poor' academic group ($P < 0.01$).

Only one past treatment variable significantly correlated with present cognitive functioning. Those in the category of 'much' treatment with past insulin coma (i.e. more treatments than the mean for the treated group) performed significantly <u>better</u> on the Withers and Hinton test when compared to those with no history of insulin treatment ($P < 0.05$).

Thus cognitive impairment was associated to some extent with the type of the basic illness, to certain factors reflecting its duration and to an early history of intellectual disadvantage. Insulin therapy was the only past treatment variable associated with present cognition, and this association was opposite to what might have been predicted. In particular, the gross destructive procedure of leucotomy, and ECT, reputedly a cause of intellectual impairment, were not associated with cognitive deficit in this sample.

c) Neurological Status

No significant relationships emerged between the presence

of 'other' neurology and items of Recorded Information. This applied to past leucotomy also.

In analysing the extrapyramidal abnormalities the population was divided into those receiving neuroleptics ('ON' group) and those not receiving them ('OFF' group) when examined. The significant relationships that emerged between extrapyramidal abnormality and Recorded Information variables concerned only age and length of illness as shown in TABLE 1:3:12. It is noteworthy that none of the past treatment variables, including exposure to neuroleptic drugs, correlated with present extrapyramidal signs as assessed here.

The regional percentage prevalences of involuntary movement and postural abnormality (face, limbs and also gait) by history of past neuroleptic exposure are shown in TABLE 1:3:13, where the currently 'ON' and currently 'OFF' distinctions have been maintained. In only one comparison did a past history of heavy neuroleptic treatment increase the prevalence of abnormality - namely those 'OFF' neuroleptics when seen, but with a history of 'much' past treatment, had a significantly higher prevalence of gait abnormality (73 %) as opposed to those in the 'some' (33 %) and 'none' (20 %) categories ($x^2 = 13.84, df = 2, P = <0.001$).

d) Behavioural performance

Current Behavioural Schedule total scores were inversely correlated with the duration of hospitalisation (TABLE 1:3:10), but there were no other relationships with time factors.

The only other significant relationships between behavioural

TABLE 1:3:12

SIGNIFICANT RELATIONSHIPS BETWEEN NEUROLOGICAL VARIABLES AND ITEMS OF RECORDED INFORMATION

	AGE		TIME SINCE FIRST ADMISSION	
CURRENT NEUROLEPTIC STATUS	ON	OFF	ON	OFF
MOVEMENT DISORDERS	$p < 0.001$	N/S	$p < 0.001$	N/S
INCREASED TONE	$p < 0.01$	N/S	$p < 0.05$	$p < 0.05$

TABLE 1:3:13

PREVALENCE OF INVOLUNTARY MOVEMENTS AND POSTURAL ABNORMALITY IN RELATION TO NEUROLEPTIC EXPOSURE

PAST NEUROLEPTIC STATUS \ CURRENT NEUROLEPTIC STATUS	ON			OFF		
	FACE	TRUNK AND LIMBS	GAIT	FACE	TRUNK AND LIMBS	GAI
'NONE'	30	30	36	35	27	20
'SOME'	34	31	41	40	33	33
'MUCH'	29	35	39	47	29	73

performance and items of Recorded Information concerned the PSE subclasses (TABLE 1:3:11). Those in the 'CS' subclass were more associated with behavioural disability than those in any of the other major groupings.

Chapter 4 - 'The Defect State'

4.1 INTRODUCTION

As has previously been discussed (p 40), English - language psychiatry appears to consider the sequelae of an acute schizophrenic illness in terms of attributes of normal mental activity that are lost or deficient, and tends to use the term 'defect state' in a restricted sense. This study has confirmed that such patterns of deficit are not the only ones that can be demonstrated, in that many subjects exhibited clinical features of a florid, productive type. The results have also indicated however that patients whose mental state is characterised by 'negative' features are more likely to experience deficits in other areas. The usage of English - language practice does appear to have merit in the sense of inferring a particular set of sequelae to an acute schizophrenic illness. In view of this finding, an attempt was made to identify the historical correlates of the 'defect state' clearly and specifically defined.

4.2 DEFINITION - GENERAL PROBLEMS

Two of the major constituents of 'defect state' as applied in English-language psychiatry (Jilek 1968) have been utilised in the present work - namely affective flattening and poverty of speech/muteness. It must be acknowledged that these features are difficult to assess reliably, especially when rating severity as demanded by ordinal scales.

The problem however is more fundamental than one of grading severity, having adjudged definite abnormality to be present.

The difficulty centres on the subjective, and hence unquantifiable, judgements used by clinicians to determine what is normal in a given personality, of a given age, in a given set of environmental circumstances. For example, a certain taciturn reserve may be deemed acceptable and normal in an 80 year old, but considered to reflect mild 'negative' deficit in a younger subject. Related to this is the assumption implicit in rating 'negative' features, that the signs being noted do indeed primarily reflect mental state phenomena and not neurological abnormality, in particular parkinsonism.

In the present state of knowledge it is unavoidable that judgements regarding the presence of 'negative' features are largely impressionistic (especially since such decisions are usually made in full knowledge of the basic diagnosis). However, in view of the interest of the 'defect state' concept in the light of findings presented here, it was felt important to apply more strict criteria for defining the term before seeking historical correlates.

4.3 DEFINITION - PROPOSED CRITERIA

Two different but complimentary approaches were adopted in an attempt to define the 'defect state' more tightly.

The first was to increase the severity criterion on 'negative' features scores for inclusion of subjects in the 'defect state' category. This is the obvious choice, as clearly contamination of the 'negative' scores by factors such as age - related appearance, awkwardness in an interview situation, mild parkinsonism etc. is more likely when 'negative' scores are low and reflect only mild putative

abnormality. Higher 'negative' scores are likely to reflect an increased confidence that abnormality is present and is essentially one of mental state.

The second approach involved the introduction of another mental state criterion whose assessment was separate from that of 'negative' features. The addition of a second assessment criterion would increase the homogeneity of the group thus defined. As reviewed earlier (p 43) other workers have indicated that long-standing schizophrenic patients may operate at an impaired level of cognitive performance - findings confirmed here. The present study allowed for evaluation of cognitive ability by means of a numerical score obtained on formal testing. It thus seemed appropriate to incorporate the principle of cognitive impairment into the criteria for 'defect state'.

The cut - offs adopted for 'negative' features and cognitive impairment are arbitrary, and were chosen to reflect a balance between confidence in the presence of mental state abnormality and adequate numbers. TABLE 1:4:1 shows the distribution of patients with increasing Withers and Hinton total scores and increasing totals for Krawiecka 'negative' features, from a minimum of 4, to a maximum of 7. Four was taken as the minimum score acceptable for reflecting essentially mental state abnormality with reasonable confidence. Clearly with marked poverty of speech, inferences regarding cognitive ability become less valid, and no confident conclusions can be drawn in someone who is mute. In this type of patient profound intellectual impairment is a reasonable assumption from the general statistical association between 'negative' features

TABLE 1:4:1

DISTRIBUTION OF PATIENTS IN TERMS OF WITHERS & HINTON AND KRAWIECKA 'NEGATIVE' FEATURES SCORES

KRAWIECKA 'NEGATIVE' TOTAL / WITHERS & HINTON TOTAL	4 OR MORE	5 OR MORE	6 OR MORE	7 OR MORE
1-10	15	10	9	9
11-20	22	17	10	4
21-30	21	15	7	3
31-40	18	9	2	1
41-50	9	5	1	
51-60	5	1		
61-70	4	1		
71-80	1	1	1	
81-90	2	2		
91-100	2	2		
MUTES	27	16	15	11
TOTAL	126	79	45	28

and cognitive scores reported earlier. The distributions in TABLE 1:4:1 are however restricted to those who retain some verbal ability. A Withers and Hinton cut - off of less than the mean for the total sample was chosen as indicating evidence of cognitive impairment.

A Withers and Hinton total of 40 or less, and a Krawiecka 'negative' total of 7 or more and 6 or more yielded too few subjects for reliable analysis, especially in view of the higher proportion of these groupings made up of mute patients. With 'negative' totals of 4 or more and 5 or more, application of the proposed Withers and Hinton criterion excluded approximately the same proportion of subjects (18.2 % and 15.2 % respectively), while in both these groups, 20 % of patients were mute. Clearly the first Krawiecka grouping (4 or more) secured the largest number of subjects.

Thus, in this study, patients having a schizophrenic 'defect state' were defined as those obtaining a total score of 4 or more from the two 'negative' mental state items of the Krawiecka scale and a score of 40 or less on the Withers and Hinton tests of cognitive ability.

4.4 HISTORICAL CORRELATIONS

Analyses were performed to elicit relationships between the 'defect state' as defined and items of Recorded Information. TABLE 1:3:10 shows that both 'negative' mental state features and cognition are correlated with time factors, which have thus to be accounted for. Also however, those time factors to which each relates are slightly different. To rationalise analysis, one time factor relating

to the patient per se and one relating to the illness were selected. Age was chosen as the obvious patient variable. With length of illness and duration of current hospitalisation being the same in almost half the sample, these two variables are clearly highly correlated. Other parts of this work utilised the length of illness variable and, for consistency, this was chosen in the present context.

The technique of maximum likelihood analysis was used to assess whether the likelihood of having a 'defect state' as defined was determined by age or length of illness, or by any of the other Recorded Information variables analysed in this section (TABLE 1:3:2). This analysis (Plackett 1974) is based on a log - linear model which gives a maximum likelihood X^2 analysis for each of the effects of interest. It provides a test of the partial association of the factors - for example, the association between 'defect state' and length of illness, with the effect of age removed. The results of this analysis are shown in TABLE 1:4:2.

The likelihood of having a 'defect state' is determined by the length of illness and not by age. The only other Recorded Information item of definite significance was past academic attainment, those in the 'poor' group having a highly significantly increased likelihood of showing a 'defect state'. Of the four items demonstrating a non - significant trend ($P<0.1$), birth trauma/ head injury/fits combined, and PSE subclass had P - values that just missed the 5 % level of significance. The former item, being a combined one, should not be over-emphasised. However, it is of interest that being placed in the PSE subclass for catatonic syndrome

TABLE 1:4:2

MAXIMUM LIKELIHOOD ANALYSES: VARIABLES INFLUENCING THE PRESENCE OF THE 'DEFECT STATE'

MAIN EFFECTS MODELS	X^2	df	P	ELIMINATIONS FROM MODELS	X^2	df	P
AGE, LENGTH OF ILLNESS, SEX	31.28	25	N/S	AGE	3.34	4	N/S
				LENGTH OF ILLNESS	24.43	3	<0.001
				SEX	0.29	1	N/S
LENGTH OF ILLNESS, FAMILY HISTORY, SEX	24.62	17	N/S	LENGTH OF ILLNESS	11.63	3	<0.01
				FAMILY HISTORY	4.56	2	N/S
				SEX	1.12	1	N/S
LENGTH OF ILLNESS, BIRTH TRAUMA/HEAD INJURY/FITS*, SEX	8.38	10	N/S	LENGTH OF ILLNESS	19.94	3	<0.001
				BIRTH TRAUMA/HEAD INJURY/FITS	3.48	1	<0.1
				SEX	0.9	1	N/S
LENGTH OF ILLNESS, PAST ACADEMIC ATTAINMENT, SEX	10.19	7	N/S	LENGTH OF ILLNESS	7.65	2	<0.025
				PAST ACADEMIC ATTAINMENT	19.09	2	<0.001
				SEX	0.47	1	N/S
LENGTH OF ILLNESS, P.S.E.(*), SEX	17.47	22	N/S	LENGTH OF ILLNESS	31.85	3	<0.001
				PSE SUBCLASS	7.46	3	<0.1
				SEX	0.1	1	N/S
LENGTH OF ILLNESS, LEUCOTOMY, SEX	14.76	13	N/S	LENGTH OF ILLNESS	35.04	3	<0.001
				LEUCOTOMY	3.35	1	<0.1
				SEX	0.22	1	N/S
LENGTH OF ILLNESS, INSULIN COMA, SEX	13.93	19	N/S	LENGTH OF ILLNESS	9.91	3	<0.05
				INSULIN COMA	1.07	2	N/S
				SEX	0.13	1	N/S
LENGTH OF ILLNESS, ECT, SEX	3.14	3	N/S	LENGTH OF ILLNESS	8.5	3	<0.05
				ECT	1.01	1	N/S
				SEX	0.84	1	N/S
LENGTH OF ILLNESS, HISTORY OF NEUROLEPTIC TREATMENT°, SEX	11.35	10	N/S	LENGTH OF ILLNESS	20.61	2	<0.001
				HISTORY OF NEUROLEPTIC TREATMENT	4.8	2	<0.1
				SEX	1.54	1	N/S

* THOSE WITH A HISTORY OF BIRTH TRAUMA/HEAD INJURY OR A HISTORY OF FITS TAKEN TOGETHER

(*) MAJOR SUBCLASSES ONLY - 'NS', 'DS', 'DP', 'CS'

° 'NONE', 'SOME', 'MUCH'

('CS') increased the likelihood of developing a 'defect state' over those in the three other major subclasses.

Thus those historical factors which significantly determine the likelihood of developing a 'defect state' as defined in this study are a long duration of illness, a history of academic difficulty and possibly a catatonic diagnosis. A history of brain damage based on evidence of birth trauma, head injury or fits may also be relevant. Past physical treatments are not relevant.

Chapter 5 - Discussion

5.1 GENERAL COMMENTS

This section was based on the standardised recording of historical and examination data. The validity of the findings however rests heavily on firstly, accounts provided by relatives and secondly, the accuracy and comprehensiveness of case note records.

Relatives' accounts were given in close temporal proximity to the admission of the patient, when certain factual errors are less probable. This was however also likely to be a period of great stress for relatives, many of whom may have been participating in the patient's commital. This in its turn could influence the recall of emotionally laden information. The amount of historical data available regarding the patients' mental states and progress, was greatly facilitated by statutory requirements under the mental health legislation that pertained prior to 1959. At that time, the physician in charge of the case was required to provide a written statement of the patient's condition at regular intervals. As a result, older case notes were usually a bountiful source of information.

In addition to general caveats to the interpretation of results in all studies involving the retrospective collection of data, some comments specific to this study require emphasis.

The prevalence of a family history of definite schizophrenia is certainly an underestimate, which has bearing on the correlations reported. There are three reasons for this.

a) This item on the Schizophrenia Survey Form was rated conservatively. If any vagueness entered the relatives' answer to this question on the Enquiry Form, the item was rated 'possible'.

b) The information was obtained by the case - note method, which has been shown to produce lower prevalences for family history than direct questioning of the relatives themselves (Thompson et al 1982).

c) Enquiry Forms were completed, in general, when the patients were young and hence at a time when the lifetime expectancy of illness in other family members, especially siblings, remained high.

For these reasons, the real frequency of schizophrenia in the families of the index patients is now likely to be considerably higher.

The data on birth trauma which are not based on obstetric records, and head injury, must be considered 'soft'. Essentially they depend on what the relatives could, or chose to, remember. Likewise qualification must be exercised in interpreting correlations with a history of fits. This is, in effect, a compound item. Although all patients in this category were described as having had a seizure or seizures of grand mal (major convulsive) type, this may have represented anything from a febrile convulsion of childhood to idiopathic epilepsy or a reduction in seizure threshold by medication, particularly neuroleptics. In a handful of cases, the seizures followed leucotomy.

The credibility of a history of no exposure to neuroleptic drugs, and the reasons for accepting this, are discussed at length in Part II. It must be emphasised at this stage, however, that whether

or not a patient was managed along psychotherapeutic lines depended essentially on where he/she lived. With few exceptions, it is unlikely that factors of social class bias were operating here as what is now the London Borough of Brent was divided for the purpose of consultant responsibility, along geographical, not primarily class, lines. As Shenley was the only institution providing psychiatric care to this population, selective referral elsewhere was unlikely to have occurred often and would not be an issue with long - stay patients. Although a small number of patients remain who were admitted from the rest of Britain or abroad because of the hospital's erstwhile reputation in the psychotherapy of schizophrenia, these are now few and all have received neuroleptics.

The only identifiable bias to operate in determining treatment was sex. By chance most of those interested in psychotherapeutic approaches had responsibility for male wards. This was of course at a time when the accepted practice was to maintain sexual segregation. Hence most of those who now remain free from exposure to neuroleptic drugs are males.

Whether or not a patient received neuroleptics was largely - with the exception of sex - a matter of chance and those who remained neuroleptic - free are not considered to be otherwise different from the rest of the sample. There is no reason to believe that this sample as a whole differs from the generality of long - stay schizophrenic patients in the United Kingdom.

One year of continuous hospitalisation was one of the two initial inclusion criteria for the present work. Criteria based on time - be it duration of illness or of hospitalisation - are to some

extent arbitrary, and little agreement exists in the literature on which is the more appropriate (Strauss 1973; Serban & Gidynski 1975). Evidence exists that with modern adminstrative and treatment policies the likelihood of discharge decreases substantially after 6 - 12 months continuous in-patient stay (Gorwitz et al 1966; Yolles & Kramer 1969). Hence, in an attempt to increase the homogeneity of the hospital based population studied here, one year of continuous hospitalisation was adopted as the cut-off for inclusion.

5.2 THE FINDINGS

5.2.1 THE DEFICITS

The findings presented here show these patients to be an extremely impaired group. Their disabilities extend through many activities affecting mental state, cognitive performance, motor functioning and the subjects' overall ability to behave in a manner adequate to satisfy basic personal and social needs.

The mental state abnormalities did not merely consist of the characteristic features of schizophrenia. Affective symptomatology was found in a substantial minority of patients. This is in agreement with Huber's view that this type of abnormality can be a part of the long - standing schizophrenic picture (Huber 1966), but as no formal analysis of 'non-specific' features was conducted here, the relationship of these to any particular pattern of long - term deficit cannot be evaluated. However, in the present sample affective symptoms (anxiety and/or depression) were the sole abnormality in only 9 patients (2 % of those examined). Cheadle et al

found a much higher prevalence of "neurotic" symptoms in their large schizophrenic out-patient group (Cheadle et al 1978). They reported this to be the only type of abnormality in 30 % of the sample. This study however used the PSE, which lists a very extensive range of 'neurotic' symptoms as opposed to the two features rated on the Krawiecka scale, and had looser diagnostic criteria ("current British criteria") than those employed here.

' Other ' (i.e. gross localising) neurological signs were uncommon and varied, and partly reflected an aging and behaviourally disturbed population. They formed no overall pattern. The prevalence of gross neurological abnormality was lower than that found in earlier work (Mettler & Crandall 1959), which may reflect the strict diagnostic criteria applied to the present sample and also improved investigative techniques at the time of admission and since.

Pes cavus was found in 12 patients, 10 of whom were female. This sign was present bilaterally in 10 and unilaterally in 2 cases. Pes cavus is uncommon, but has been described as a marker for neurological disorder in non - affected carriers of genetically transmitted conditions (Brain & Walton 1969; Harding 1981), and also as a permanent sequela to central nervous system disease (Brewerton et al 1962; Duthie & Bently 1983). Its significance in this sample is uncertain, the numbers being too small for reliable statistical analysis.

5.2.2 PHYSICAL TREATMENTS

The current deficits exhibited by the patients in this study

bore no relationship to past physical treatments. Only one examination variable (cognitive performance) was related to one past physical treatment variable (insulin coma). The fact that patients who had received 'much' insulin coma performed significantly better cognitively probably reflects the operation of an incidental selection factor. The impression was gained that this approach was more enthusiastically adopted in those of higher educational attainment and/or social class. The relationship between past insulin and relative cognitive preservation may reflect the fact that present cognitive ability relates to past cognitive ability, as was shown.

The lack of a relationship between present deficits and past physical treatment is worthy of emphasis, as these treatments are all actually, or by repute, damaging.

The behavioural and intellectual deficits resulting from profound and prolonged hypoglycaemia are well known (Marks& Rose 1965) and a syndrome referred to as insulin - induced hypoglycaemic encephalopathy was described in the older psychiatric literature (Spencer 1948; Halle & Ross 1951). Its features - paresis,confusion, EEG abnormalities especially the emergence of slow waves - may have been transitory but it appears that no long - term follow - up of such cases was performed. In the present sample it was not uncommon for hypoglycaemia to be of sufficient degree to cause major convulsions, and for some physicians at one point, this was the desired effect. Nonetheless, there is no evidence to suggest that controlled hypoglycaemia contributed to the deficits of those schizophrenics who received it.

When the leucotomies in the present sample were done, this was an unstandardised, essentially blind procedure which produced lesions of great variability, a point that will be illustrated in Part III. The sequelae of these 'free - hand' leucotomies could be dramatic in terms of brain destruction, yet in the areas studied here, the sequelae in terms of clinical deficits were striking by their absence.

Recently, Benson et al have studied a group of 16 leucotomised schizophrenics up to 25 years after their operation with a view to establishing by clinical and special techniques, the long - standing neuropsychiatric sequelae of the procedure in the context of schizophrenia (Benson et al 1981). These authors were likewise struck by the lack of gross clinical abnormality in the presence of clear destructive frontal lesions on C.T. Indeed, they go so far as to state that any major neurological deficit following prefrontal leucotomy (the operation carried out in all but 1 of the present sample) represents " a complication rather than a result of the procedure". On neuropsychological testing, their leucotomised patients performed less well than normals but better than non - leucotomised schizophrenics. Without proper controlled studies, evaluation of such findings is extremely difficult. Benson et al interpreted this as reflecting illness or basic IQ factors rather than factors associated with the operation itself. In the older literature leucotomy was reported to result in an increment in IQ after 12 months compared to pre-operation values (Struckett 1953). However, selection factors of the type mentioned earlier in relation to insulin coma are likely to operate with regard to leucotomy as well,

and any interpretation of the correlation, or lack of it, between leucotomy and cognition must be cautious.

The sample of Benson et al is not comparable with the present one, as it contained both out-patients and in-patients and used a different - and more complex - evaluation of cognitive ability, but in the much larger sample reported here no cognitive differentials could be established between leucotomised patients and the rest. However, both studies are in agreement in concluding that, when set against the deficits of the basic, long - standing schizophrenic illness, post - leucotomy residuae are difficult if not impossible to detect.

Electroconvulsive therapy continues to be a controversial form of management, with persistent assertions that its use results in brain damage, which is reflected especially in subtle impairments of memory (Friedberg 1977). The investigation of this question is confounded by the fact that such impairment may emanate from residual features of the condition for which the treatment was given rather than from effects produced by the treatment itself. One recent study into the efficacy of ECT in the treatment of depressive illness (Johnstone et al 1980) compared aspects of memory in two groups of depressed patients, one of which received standard ECT, the other "simulated ECT" (anaesthetic without electrically induced convulsion). During a course of 8 treatments, definite but short - lived impairments were detected in those receiving the electrical shock, but no differences between the two groups could be found 6 months after the end of the course.

In the present sample, 8 ECT's would represent minimal

exposure to this modality (one patient received 234 treatments in a single, uninterrupted course), and the effects on the brain - if any - of extensive or repeated courses are as yet unknown. In the present sample however, past ECT did not relate to any of the present deficits, including cognitive performance.

One of the most interesting findings was the lack of a relationship between past neuroleptic exposure and neurological abnormality of extrapyramidal type. The only factors that did relate to these neurological features were those which are to do with the passage of time - i.e. age and length of illness. The fact that these associations are, with one exception, found only in those actually receiving neuroleptics when examined may reflect an equalising process of age on drug - effects, with neuroleptics being stopped because of the effects of increasing age/disability.

The precise relationship between involuntary movements and past neuroleptic administration - both in terms of cumulative exposure and duration of exposure - remains unclear. The literature relevant to this question will be reviewed in detail in Part II. Many reasons undoubtedly contribute to the lack of clarity on this fundamental point - such as differing criteria for abnormality, diagnostic heterogeneity, inaccuracy in drug histories, different fashions in prescribing both geographically and over time - but few authors have considered the possibility that some of the disorder being studied may actually be intrinsic to the patient's psychiatric condition itself. This has been particularly overlooked with regard to schizophrenia, the major area of concern with 'tardive dyskinesia'. The whole question of the prevalence of

spontaneous involuntary movement disorders in long-standing schizophrenics, and the correlations with these is the subject of detailed investigation forming the substance of Part II.

Taking an overview of the findings, the present deficits exhibited by the patients appear to relate to firstly, the features of the illness at its worst, and secondly to factors reflecting the passage of time (age of onset and past academic record each influenced deficits in particular areas only). Thus the clinical picture presenting now seems determined largely by the clinical picture of the basic schizophrenic disease process itself, by the operation of some additional influences occurring over time, or possibly by a combination of both. While it is not possible to say how much benefit, if any, past physical treatments effected, they do not appear to have made the patients worse, at least in terms of the areas of functioning examined in this study.

5.2.3 DETERMINANTS OF THE PRESENT PICTURE

In the present work, the features of the illness at its worst represented in PSE subclasses give a profile of the symptomatology inherent in the basic illness and can be considered as associated with various measures of severity. Consistently the 'CS' group emerged as particularly disadvantaged. They had a significantly earlier age of onset and the longest periods in hospital. They had significantly more prominent 'negative' features in the mental state, performed significantly less well on cognitive testing and had the worst behavioural capabilities. The 'NS'/'DS' patients in general adopted an intermediate position between 'CS'

and 'DP' groups. The 'DP' subjects had the latest age of onset, had fewer 'positive' features than the 'NS'/'DS' patients (which may merely reflect the paranoid's reticence in proferring symptoms), and also had significantly fewer 'negative' features than those in all other categories. Behaviourally and intellectually it was not possible to separate 'NS'/'DS' and 'DP' patients.

The Catego subclasses are strictly defined, patients being allocated in a rigid hierarchical fashion (Wing et al 1974). They do not therefore correspond exactly to the more loosely applied conventional diagnostic subgroups of schizophrenia, which makes comparison with the published literature difficult. However, certain facts regarding subgroups were confirmed. Paranoid patients ('DP') had a much later onset than others and had a mental state less coloured by apparant, obvious psychopathology. They were a small group in the population, which reflects the tight Catego definition, the fact that application of the St. Louis criteria militates against their inclusion (Feighner et al 1972), and the reduced likelihood that such subjects will require long - term care. Furthermore the reduced proportion of 'chronic' samples which are made up of paranoid patients even when this is more widely defined has been noted by others (Depue & Woodburn 1975; Klorman et al 1977).

The idea that the pattern of the original presentation has echoes in the long - established defect symptomatology was noted in the older literature. Kant, for example, studying patients ill for at least 10 years, stated that "the three original basic subtypes * ..... are still very definitely recognisable in the end stages", and that " transitions between the various subtypes are very few"

* Kant's sample included no simple schizophrenics.

(Kant 1943). This was for him a general conclusion on consistency of syndromes, not of symptoms as advocated by Leonhard, whose views he criticised. Insofar as they refer to syndromes, Kant's findings are in accord with those of the present work.

It is of interest that even within a sample who, because of their failure to be discharged may be said to have done badly, the PSE is able to identify a group whose illness appears to have run a particularly malignant course (CS +).* Kant likewise found in his sample of long - standing schizophrenics that catatonic patients were small in number but represented the most severely deteriorated individuals (Kant 1943). One must however be cautious of generalising this finding. Catatonic schizophrenia is a confusing condition - especially in its historical context - and one which is now infrequently seen. Only 5.7 % of the present sample came out as CS +. At its height catatonic schizophrenia was recognised as being associated with two widely divergent prognoses. As Kant put it, catatonics were "destined either to recover completely or to deteriorate"(Kant 1941). This good outcome/poor outcome dichotomy has recently been equated with the clinical patterns of excitation and retardation respectively (Morrison 1973). This population of CS + patients

* PSE subclasses only approximate to clinical diagnoses (p 98). Catatonic Syndrome, is derived from the major Catego class of 'Other Psychoses' and not from the specifically 'Schizophrenic' class. Thus the presence of catatonic features alone would be sufficient for a subject to qualify. In the present context, where all subjects also conformed to St. Louis criteria for schizophrenia, the CS + subclass is likely to be equivalent to a clinical diagnosis of catatonic schizophrenia.

cannot therefore be considered representative of all schizophrenics who would initially be classified as catatonic. It is possible that the good prognosis patients without deficit or recurrence did not actually have schizophrenia as currently conceived (and would in any case have been excluded from the present sample), whereas the very bad prognosis patients described by Kant are of the type represented as CS + in the population described here.

The effects of the passage of time on patients' deficits could reflect two factors :

- the cummulative effects of institutional environment on a damaged individual.

- the relentless progression of a disease process.

The work of Wing and Brown and their colleagues referred to earlier, suggests that both may be of relevance, although their finding of only a limited amelioration of 'negative' characteristics with the enrichment of the environment, indicates that the "biological component" reputedly underlying these deficits (Wing 1963; Wind & Brown 1970) is substantial.

The present study was not designed to unravel fully the relative contributions of illness and environment in producing the clinical deficits reported. However, certain points are worthy of note. The hospital providing care for this study sample would be considered 'good' by Wing & Brown's standards. All

patients were encouraged where possible to attend industrial and occupational therapy units on a regular basis and sheltered and open employment outside the hospital was fostered. All were encouraged to keep personal possessions and the wards often had a homely, domestic atmosphere. Outings and holidays were regularly organised. Such a social ambience is stated as militating against the development of the 'clinical poverty syndrome' (Wing & Brown 1970).

Two pieces of evidence support the view that 'negative' features described here are primarily illness - related phenomena likely to be minimally determined by environment. The first is the strong correlations that were established between 'negative' features and two organic, illness - related features - cognitive impairment and involuntary movement disorder. Even if the former is interpreted as reflecting poor attention, decreased motivation etc., there is no question that environment can cause involuntary movements, especially when a very determined effort was made to ensure that only involuntary and not manneristic/ stereotypic movement was recorded. The strong correlation between 'negative' features and movement disorder in particular, make it unlikely that environment was making a major contribution to the presence of the former.

Secondly, and more importantly, Johnstone et al have reported the findings of a parallel study to the present one, where schizophrenics who had not come to long - term care but had been discharged from the same hospital formed the study group (Johnstone et al 1981). In this investigation, 201 patients were

found to have been discharged from Shenley hospital during the years 1970 - 1974 inclusive with a case note diagnosis of schizophrenia. Of these, 120 were Feighner positive, 105 of whom were traced and 77 examined by the same techniques as were used with the in-patient group reported on here.

The authors found that taking age, sex and length of illness into account, both groups were equally impaired in terms of 'positive' and 'negative' mental state features and behavioural ratings. However, the institutionalised group were significantly worse on cognitive testing than the out-patients. This study indicates that the deficits of established schizophrenia may well be continuing features of the illness, regardless of whether the setting is one of long - term institutional care or not. Further, it suggests that prolonged hospitalisation may be the consequence of cognitive disability rather than vice versa.

The strong relationships that emerged between the separate items of Assessed Abnormality are probably the most striking findings of the present section and argue in favour of the predominantly biological nature of the deficits described. Two explanations of these relationships are possible. Firstly, such strong correlations could be generated if the various assessments overlapped in what they were measuring. 'Negative' features, poor cognitive performance and behavioural deterioration could all reflect the presence of some single underlying deficit, as for example, impairment of motivation. This argument could not however apply to the presence of extrapyramidal neurological

abnormality, such as hyperkinetic involuntary movement disorder. While mental state or other non-specific factors may be of relevance in modifying the severity of this type of clinical sign, they could not be primarily implicated in cause.

The second explanation is preferred - namely that the deficits detected in this sample represent, in general, limitations in separate areas of functioning, which develop together and which may represent the clinical manifestations of common or related pathophysiological processes.

5.2.4 PATTERNS OF DEFICIT

It has long been realised that some schizophrenics do well in terms of outcome, while others do badly, many studies going back to the pre-neuroleptic era showing this common finding (for review, see Stephens 1978).

The present study was restricted to the worst prognosis patients, yet it is of interest that even within this group, two 'patterns' of deficit also appear to emerge. In the one, 'positive' mental state features do not correlate with any other type of deficit, while in the other, 'negative' features of the mental state correlate with extrapyramidal neurological abnormality, cognitive impairment and behavioural disorganisation.

Such a distinction is relative, not absolute. Although 'positive' and 'negative' features were not positively correlated with one another, neither were they negatively related. The presence of one type of abnormality did not exclude the presence of features of the other. The overlap was considerable.

Thus, conclusions can only be general - namely, that patients in whom 'negative' features are prominent are more likely to exhibit related deficits in other areas of functioning, while patients in whom the mental state is coloured by prominent 'positive' features are not.

Recently, Crow has suggested a classification of schizophrenia into what he calls a Type I syndrome and a Type II syndrome, based on hypothesised pharmacological and structural differences (Crow 1980). The former is characterised by productive 'positive' mental state features probably mediated by dopaminergic mechanisms, while the latter is characterised by 'negative' features and structural brain change and is not primarily associated with disruption of dopaminergic systems. The limited nature of the present sample does not allow comment on such a hypothesis for the generality of schizophrenia, but the theory does present major conceptual problems such as the reported resolution of 'negative' symptomatology, the question of long-established productive symptomatology not responsive to dopamine blockade by neuroleptics, etc. The present study has shown that no sharp distinction exists between 'positive' and 'negative' features. In view of the implications of irreversibility and structural brain change in the Type II syndrome, it would appear that Crow's system would require classification to be hierarchical, with 'negative' features always taking precedence over 'positive' features when both coexist in the same patient. This runs the risk of mild abnormality of 'negative' type - or even of contaminating,

extraneous clinical features - being given classificatory priority over 'positive' features unequivocally morbid and of marked degree. At the level of our present knowledge, this may be in error.

Exactly what clinical features should be used in attempts to subclassify long - established schizophrenic illnesses remains unclear. Although different authors appear to describe features, on the face of it, similar, this is usually not the case, and comparisons based on the assumption of similarity are misleading. Even when the same general terminology is used, the specific constituent features may differ.

The confusion in this area can be readily illustrated. Both Wing and Brown (cf p 42) and the present study refer to 'negative' features, but the constituent psychopathology is different. Wing's poverty of speech item refers to poverty of content of speech on 4 of its 5 severity points (Wing 1961) while the present work was essentially rating reduced amount of talk or words used, both spontaneously and on questioning. Only at the most extreme severity point (muteness) do both studies concur. Likewise, Wing's affective item incorporates both restricted affect and incongruity of affect, while the present work separated these and considered only the former to be a 'negative' feature.

Depue and his colleagues have utilised a simple split based on Venable's behavioural axis of activity - withdrawal (Venables 1957), and have found important differences in patients grouped this way (Depue & Dubicki 1974; Depue et al

1975; Depue 1976). Psychomotor activity was not assessed in the present study and for this reason alone comparisons would be unjustified, but the need for caution is emphasised by the realisation that Depue's withdrawn patients have more hallucinations and delusions than those in the active group (Depue & Dubicki 1974). Hence the reasonable assumption of a general similarity between 'withdrawn' and 'negative' patients is inaccurate.

Andreasen has published a number of detailed studies of what she refers to as "positive and negative symptoms" (Andreasen 1979; 1982; Andreasen & Olsen 1982). Despite the similarity in name to 'positive' and 'negative' features described throughout the present work, they are fundamentally different. Andreasen's "positive symptoms" comprise hallucinations, delusions and positive formal thought disorder in common with 'positive' features used here, plus two behavioural items - "bizarre behaviour" and "catatonic motor behaviour". Her "negative symptoms" comprise alogia, avolition, anhedonia, affective flattening and attention deficit, some of which are compound items. For example alogia is used to rate poverty of speech and poverty of content as well as "blocking", while "affective flattening" is also recommended for the rating of incongruity. Hence Andreasen's "symptoms" (which are strictly speaking mainly clinical signs) bear little resemblance to the 'features' employed here.

In advocacy of Crow's two syndromes theory Angrist et al utilised withdrawal as one of the constituents of their negative

state (Angrist et al 1980), although Crow had not included this behavioural characteristic in his original definition of the syndromes (Crow 1980). Although 'withdrawal' was not used in the present dichotomy based on mental state variables, it could be argued from the findings that 'psychomotor retardation' should not be considered as a non-specific item but should be included in the definition of 'negative' features. Over 90 % of those rating 2 or more on psychomotor retardation also obtained a score of 2 or more on affective flattening and/or poverty of speech/muteness.

Exclusion of retardation was arbitrary but had it been reclassified 'negative' this would not have altered the basic findings. No subject scored on this item alone and only 11 had a retardation rating in the absence of either or both of the other two components of 'negative' features. It is important to note however that confident elucidation of psychomotor retardation as an independent feature distinct from flattening of affect and, especially, poverty of speech/muteness, is difficult. Although the fact that half (64) of those who rated on retardation did so only in the presence of both flattening and poverty of speech could be seen as indicative of a relationship between the three, equally this may merely reflect the difficulty in separating them, and the examiner's consequent tendency to rate retardation automatically when the others are present.

Almost all these proposed systems are derived theoretically and confusion will continue until features are defined whose

validity can be shown in experimental settings.

The pattern of deficit referred to here as 'defect state' was defined as part of the present work and is not comparable to similar terms applied elsewhere. It is hence open to the charge of idiosyncrasy of the type illustrated earlier from the literature. Its justification lies in an attempt to create a degree of homogeneity within those patients with 'negative' type deficits in their mental state who have been shown by the results to represent an interesting subgroup of the total population.

Two points of note emerged in analysis of those conforming to 'defect state' criteria :

i) the positive association with length of illness.

ii) the absence of a relationship with past neuroleptic treatment.

These relationships certainly reflect in large part the basic findings with regard to 'negative' mental state features and cognitive performance analysed independently, and the relationship between impairment in these two areas - both of which were referred to earlier. They do however serve to underline those basic findings, especially as the literature gives little guidance on these two important questions.

Using "deterioration" or other broad terminology, some authors state that such deficits progress throughout the course of the illness (Kraepelin 1919; Tsujino 1966), while others believe they reach a plateau in the years immediately following an acute episode (Shakow 1946; Huber et al 1975), while others

yet again refer to their unpredictable resolution (M Bleuler 1978). That 'defect state' in the present work related to length of illness is compatible with the idea of progressive evolution. However, it must be borne in mind that this finding refers to a progressive fulfilling of the criteria over time, and not to a subsequent increase in severity, once established. It is possible that more specific defect patterns of the type defined here bear a more predictable relationship to the duration of illness than looser, impressionistic concepts.

It is striking that the 'defect state' was not determined by age. Thus it would appear that the deficits evaluated were not being contaminated by the non-specific changes of advancing years. Age and length of illness are of course closely related in this sample and it must be stated that while separation of the effects of each may be statistically meritorious this may in actuality represent a somewhat spurious distinction. Nonetheless in statistical terms at least, the contribution of length of illness to the defects was highly significant while that of age did not even approach significance.

Although it has been claimed that the introduction of neuroleptic drugs has modified the post - acute schizophrenic picture (Van Epen 1969; Pasnik-Kisiel 1970; Huber et al 1975) the evidence for this remains unclear. Fish (1964) has however reported that groups of schizophrenics classified into Leonhard subtypes show differential improvements with neuroleptic treatment. With the present population of severely ill patients it could not

be demonstrated that neuroleptics made any contribution to the presence of the 'defect state' as specifically defined or indeed to its individual components.

Following from the findings discussed here, some comments are justified on terminology. The results indicate that maintaining a distinction between the terms 'chronic' and 'defect state' is useful even within a population who have all experienced personal decline as a specific criterion of their diagnosis. 'Chronic' is probably most appropriately applied in a purely descriptive sense, to infer the presence of persisting, post - acute abnormalities without any implication as to their form or duration. 'Defect state' would then be reserved for that situation where a particular pattern of 'negative' type abnormality is implied. As has been shown, such a specific usage can identify a type of patient with multiple deficits. In association with 'negative' features in their mental state, they are likely to have cognitive impairment (evidenced on formal testing as well as in a history of academic difficulty), behavioural deterioration and extra-pyramidal signs. They may also exhibit, or have exhibited, catatonic features. Such deficits are likely to relate to the duration of the illness rather than the patients' age, and will not be associated with any forms of physical treatment administered in the past. By this usage all 'defect state' patients would also be 'chronic' but the corrollary would not be the case.

These proposals, based on experimental data have much

in common with Huber's theoretical views referred to earlier (p 40). They recognise the variability of post-acute states while reserving specific terminology for a pattern of deficit that may allow specific inferences of aetiology based on brain dysfunction.

Not all psychiatrists would espouse such views however. Manfred Bleuler, for example has written :

> "the term 'defect state' itself does not fully correspond any longer to present day concepts. It indicates too strongly something unchangeable and irrevocable and ignores the fact that behind the pathological condition, healthy life lies concealed. These conditions do not indicate that anything has been permanently destroyed: pathological behaviour simply replaces healthy behaviour."
> (M. Bleuler 1978 p 191).

The present work provides no support for such an assumption, and indeed suggests that 'defect state', as defined here, is a valid clinical entity with correlations which make it highly likely that it is mediated by some abnormality of cerebral functioning.

Dichotomisation of established schizophrenics on the basis of some variant of the 'positive'/'negative' distinction has been advocated by a number of workers. The distinction based on mental state suggested here has the advantage of simplicity, is derived from present evaluations and not assessments of distant, historical information which may be unreliable, and has been shown empirically to have potential relevance.

The ultimate worth of any classificatory system depends on its usefulness in making valid predictions about some major aspect of a condition. The 'positive'/'negative' feature distinction

will be applied in Part II and Part III in the analysis of movement disorder and C.T. scan data. The likelihood of 'negative' features being based on brain disorder will be explored in these contexts.

PART II

SPONTANEOUS INVOLUNTARY DISORDERS OF MOVEMENT

"It is natural that the central nervous system should have been the object of much research in schizophrenia. Emil Kraepelin ... always hoped that science would one day duplicate for dementia praecox the triumphant actualisation of the medical model, as it took place in reference to general paresis. Such hope has not been realised"

SILVANO ARIETI
INTERPRETATION OF SCHIZOPHRENIA

PART II

SPONTANEOUS INVOLUNTARY DISORDERS OF MOVEMENT

Chapter 1 - Literature Review

1.1 INTRODUCTION

> "Tardive dyskinesia (TD) is not now considered rare or controversial and may be the most frequently diagnosed iatrogenic disease of the nervous system. Diagnosis of TD in individual cases can occasionally be difficult, but in contrast to a decade ago the existence of TD is unquestioned. There is no serious effort at this time to attribute tardive dyskinesia to tics or to habits, nor to the 'stereotypes' of schizophrenia nor even to voluntary mannerisms in edentulous or senile patients" (Paulson 1981)

Few psychiatrists would challenge the above statement though lingering doubts as to the validity of the concept of 'tardive dyskinesia', expressed over the past 20 years, still persist. However, Paulson's outwardly dogmatic view is carefully worded, and two points are striking by their omission. Firstly, the concept of 'tardive dyskinesia' rests on epidemiological evidence of a statistical association. The transposition of this statistical relationship within populations to the individual case is the major conceptual difficulty in diagnosis. Secondly, while Paulson rightly refers to all the things that 'tardive dyskinesia' would not be attributed to, especially "the 'stereotypes' of schizophrenia", he makes no reference to authentic involuntary movements, that it was suggested earlier, may be a part of the schizophrenic illness per se.

1.2 THE CONCEPT OF TARDIVE DYSKINESIA

The term 'neuroleptic' was used by Delay and Deniker shortly after the introduction of chlorpromazine, to emphasise that drugs of this type appeared to act directly on the central nervous system (Delay & Deniker 1968). Acute postural and movement abnormalities and a parkinson-like syndrome were soon recognised as features associated with treatment (Hall et al 1956; Deniker 1961; Melvin 1962; American College of Neuropsychopharmacology Task Force, 1973). As side-effects, these manifestations were rarely thought of as serious and never as permanent. In particular, it was not thought that they could be indicative of an irreversible neurotoxic effect of the drugs.

In 1957, Schonecker described a syndrome of abnormal involuntary movements in 3 elderly chronic psychiatric patients with cerebral arteriosclerosis (Schonecker 1957). The abnormalities consisted of " automatisms with licking and smacking movements of the lips " - that is, they were complex and orofacial - and occured in subjects who had all been on chlorpromazine. Although often accredited as the first report of 'tardive dyskinesia', it must be doubtful if Schonecker's patients had this condition as subsequently conceived. Two of the 3 had severe parkinsonism develop concomitantly and duration of exposure ranged from " the first days of treatment " to a maximum of only 8 weeks.

Three years after this Uhrbrand and Faurbye described an apparently similar appearance in 33, mainly psychotic long-stay patients treated by a variety of physical means (Uhrbrand and Faurbye

1960) Nonetheless, they concluded that the outstanding factor in their patients was prolonged exposure to what they referred to as "psychopharmaca". In fact what these authors were proposing was the concept of 'neuroleptic - caused ' involuntary movement disorder, where the spontaneous motor activity was "bucco-linguo-masticatory" in distribution, though whole body movements were mentioned in passing. This syndrome was subsequently designated 'tardive dyskinesia' - 'tardive' representing the view that onset occurred late in the course of neuroleptic treatment compared to the other known neurological sequelae (Faurbye et al 1964). Since that time the concept has widened in its essentials.

The term 'dyskinesia' was not commonly used prior to its introduction in the present context. Strictly speaking, 'dyskinesia' in neurological context is a generic term for any abnormal kinesis. Applied thus, it would cover choreiform, athetoid and myoclonic movements, tics etc, and would even include tremor (Marsden - Personal communication). As a generic term there is no specific implication of cause involved in its usage.

Many of the early authors, including Uhrbrand and Faurbye, focused on the bucco-linguo-masticatory triad of features, presumably as these were the most striking and conspicuous abnormalities. Other movements such as "rocking and torsionary body movements" were briefly mentioned in "the most serious cases" (Uhrbrand and Faurbye 1960), as was tremor, but the emphasis was overwhelmingly orofacial. In the psychiatric literature, the general descriptive term 'orofacial dyskinesia', where dykinesia meant only 'abnormal kinesis', became synonymous with 'tardive dyskinesia' involving an implication

of neuroleptic causation. Such conceptual confusion was facilitated by the fact that the movements being described not only had an apparently specific distribution but were also slow, complex and even co-ordinated, setting them apart from movements of the choreic, athetoid, myolonic or tic-type more familiar to psychiatrists. Thus Crane and Naranjo could write :

> "Complex dyskinesias are the most common disorders observed in long-term patients and are often referred to as tardive dyskinesias".
> (Crane & Naranjo 1971)

Crane and Naranjo do mention that peripheral movements could be found in psychiatric patients but their description gives clear emphasis to slow, "complex" repetitive orofacial activity. In particular they separately define and describe chorea, athetosis, tics etc from "complex" or "tardive" dyskinesias.

For many of the descriptive writers, therefore, 'dyskinesia' was a special word implying neuroleptic causation, complexity of form, and a distribution of abnormality largely restricted to the orofacial region. This would perhaps have been acceptable had it been convincingly shown that drug history - and specifically that of neuroleptic exposure - could be used as the validating criterion of this syndrome. The widespread use of neuroleptics and the resultant lack of satisfactory non-treated control groups, made this difficult to demonstrate.

With the introduction of standardised rating scales and their demands for a more comprehensive examination covering all body areas, it has become clear that movements in all body parts can be found in long-standing 'chronic' schizphrenic patients.

Abnormalities of movement are not just restricted to orofacial areas and may not be complex or co-ordinated. Most workers would now accept that the term 'dyskinesia' can be applied widely to virtually any abnormal movement regardless of its characteristics or distribution, though there remains a strong tendancy to confuse the definition of the term with the implications of its use in specific situations. When it is used with an implication of neuroleptic cause, it has still not widened to its generic sense however. Marsden et al, for example have stated that "tremor is not a part of tardive dyskinesia" (Marsden et al 1975).

The second point of diversification in the concept relates to the drugs implicated in causation. Uhrbrand and Faurbye referred only to neuroleptics and reserpine though since that time a number of different categories of drug have become involved, such as tricyclic antidepressants (Fann et al 1967; Dekret et al 1977), antihistamines (Thach et al 1975), and even benzodiazepines (Kaplan and Murkovsky 1978). Thus, 'neuroleptic-caused' dyskinesia has widened to dyskinesia produced by psychoactive drugs. Even the word 'psychoactive' must be used selectively as not all drugs which can affect mental functioning and can 'cause' orofacial or other involuntary movements would be included, a noteable exception being L-dopa. The hyperkinetic syndrome sometimes associated with its adminstration (Barbeau et al 1971) is not referred to under the 'tardive dyskinesia' heading.

Likewise a change has occurred in the duration of treatment required before involuntary movements can be considered 'tardive'. Originally it was suggested that 2 years or more was necessary

(Sigwald et al 1959; Faurbye 1964; Crane 1973) but more recently this limit has been revised downwards considerably. Movements have been labelled 'tardive' after only a few months of treatment (Degkwitz 1969; Moline 1975; Stimmel 1976; Chouinard & Jones 1979).

It therefore seems the original concept of tardive dyskinesia has been extended and now has a more general meaning. It appears to be applied to most, although not all, forms of spontaneous involuntary movement activity occurring in the setting of treatment with most psychoactive drugs for a period of more than a few weeks.

1.3 THE CLINICAL FEATURES

Review of the literature on the clinical features of involuntary movements attributed to psychotropic drugs reveals a variable mixture of orofacial and lingual dyskinesias, chorea, athetosis, dystonia, tics and complex facial grimacing. Detailed descriptions have been published elsewhere (Marsden et al 1975; APA Task Force 1979) and only a brief resumé will be presented here.

Coarse vermicular movements of the tongue without its displacement (lingual myokymia) may be the earliest manifestation (Crane & Naranjo 1971), though such movements are easily missed. Alternatively, it has been suggested that tic-like movements of the lips or face, or increased frequency of blinking may be the earliest signs (Karson 1979).

Traditionally however, lingual dyskinesias are considered the most characteristic features. These movements may be of the

slow, sustained dystonic type, but are usually described as being of the course, irregular, choreoathetoid kind, producing varying degrees of displacement of the tongue inside and outside the mouth. Clinically, descriptive terms such as snail-like contractions, bon-bon sign and fly-catcher sign are often applied to these abnormalities. An inability to sustain voluntary lingual protrusion for 30 seconds has been described as characteristic of severe cases (Pi and Simpson 1981). While descriptions in the literature imply that different varieties of tongue abnormality represent step-wise progressions in severity, this remains to be established. Pursing, puckering, smacking and bridling lip and perioral movements can occur, separately or in combination, as can chewing, grinding jaw movements. Elevation or frowning of the brows, upward deviation of the eyes, increased blinking or blepherospasm can result from involvement of periorbital muscles while co-ordinated expressive abnormality produces complex grimacing.

In addition to these typical orofacial dyskinesias, restless choreiform and athetoid limb movements can occur not infrequently, especially in a distal distribution, and the postural antigravity muscles may be affected either locally (e.g. neck) or generally. Whole body involvement gives rise to a striking writhing, restlessness with disturbance of both posture and gait. Finally dyskinesias of the respiratory and pharyngeal musculature can give rise to periodic tachypnoea or irregularity of respiratory rhythm, difficulty in swallowing occasionally reported as life-threatening (Casey & Rabins 1978) and forced spontaneous vocalisations.

Thus the range of involuntary motor activity attributed to psychotropic (particularly neuroleptic) ingestion is extensive, and the variability of the clinical picture between cases remains one of the major problems in diagnosis. It has been suggested that age may have a bearing on the pattern of abnormality in that older subjects (i.e. over 50) may be more likely to develop orofacial dyskinesias, while in younger patients, especially children and young adults, peripheral movements may predominate (Marsden et al 1975; Polizos & Englehardt 1980)

1.4 CHARACTERISTICS OF THE DYSKINESIAS

The conspicuous distribution has often been taken as characteristic of so-called 'tardive dyskinesia'. As was mentioned earlier however, (and as the aforegoing descriptive account illustrates) this is not the case. Peripheral dyskinesias have been described as the only abnormalities detectable, especially in younger subjects (McAndrew et al 1972; Polzios et al 1973). Syndromes of involuntary movement attributed to L - dopa can feature predominantly orofacial dyskinesias (Yahr 1970), though Gerlach has suggested that peripheral movements make proportionately a greater contribution to total abnormality in this situation than when neuroleptics are the putative cause (Gerlach 1977).

However, spontaneous movements attributed to drugs share characteristics common to all extrapyramidal, choreoathetoid syndromes. They are typically responsive to features of the mental state, being exacerbated by anxiety and emotional stress and alleviated - at least partially - in a setting of composure. They

diminish with decreasing states of arousal and so ease with drowsiness or sedation and disappear during sleep. They can be suppressed for varying periods of time by conscious effort at least in the initial or milder stages, though this effect is often unpredictable. On the other hand attempts to inhibit one portion of a complex dyskinesia can produce exacerbation in other portions. Related to this, a repetitive voluntary motor activity in distant body parts or concentration on fine motor tasks may enhance the movements. Spontaneous motor activity may first become manifest when neuroleptics are stopped or the dose reduced, while increasing the dosage may, temporarily at least, suppress it.

Patients are not infrequently unaware of their movements the reasons for which are unclear. It has been suggested that affectively ill patients may be more likely to complain than those with more serious conditions such as schizophrenia (Simpson & Lee 1977). On the other hand, subjective awareness may partly reflect the distribution in that peripheral and truncal movements are more likely to be disabling and recognised as abnormal than dyskinesias of the face - an area which in anyone can be characterised by considerable motor activity, even at rest. Only rarely do orofacial movements interfere with speech, eating, or respiration, or produce oral ulceration (APA Task Force 1979).

1.5 THE EVIDENCE IN SUPPORT OF THE CONCEPT - THE ROLE OF NEUROLEPTIC DRUGS IN ESTIMATES OF PREVALENCE

Although, as was mentioned earlier, a range of drugs other than neuroleptics have been implicated in the production of involuntary

movements, the evidence is largely anecdotal (APA Task Force 1979). For this reason, the following review will restrict the concept of tardive dyskinesia to one of 'neuroleptic - caused movement disorder'.

The concept of neuroleptic - caused movement disorder is based on epidemiological evidence of a statistical association between the two. Assessments of this evidence range from "thoroughly convincing" (Marsden et al 1975) through "compelling" (Kane & Smith 1982) to sceptical (Crow et al 1983). In general, the scientific quality of the evidence is poor, with reports covering heterogeneous patient groups studied by unstandardised methods. Even now, there are no universally accepted criteria for establishing the diagnosis and mild or doubtful cases, which may be highly relevant pointers to the establishment of more serious disorder (Kane et al 1980), are easily missed.

Notwithstanding, Kane and Smith (1982) have calculated the mean prevalence of abnormality from 56 sets of data published in 49 studies of neuroleptic treated subjects from 1960 to 1979. They arrived at a figure of 20 % ($\pm$ 14 %) based on almost 35,000 patients. These authors also calculated that the prevalence in neuroleptic-free subjects was 5 % ($\pm$ 9 %) from 19 sets of data in 14 studies encompassing 11,000 subjects published over the same period. The statistical difference in the prevalences is highly significant ($P < 10^{-5}$).

Jeste and Wyatt (1981) reviewed those 12 "major studies" which compared the prevalence of involuntary movements in neuroleptic-treated and neuroleptic-free samples and calculated that the

prevalence in the former group was 3 $\frac{1}{4}$ times that reported in the latter group.

Both sets of reviewers agree on a prevalence attributable to neuroleptic drugs of 13 - 15 % with pooled data, and in suggesting that about 5 % is attributable to spontaneous disorder.

Reviews of this kind present striking data. However, the comparisons they make are not strictly justified, as subjects differ on many important variables other than exposure to neuroleptics. For example, while most of the figures for prevalence in those on neuroleptics are derived from long-stay psychiatric patients especially schizophrenics, data on spontanous rates are often based on nursing home residents or other non-psychiatric subjects. Furthermore, pooled data from studies using different assessment and recording techniques cannot take account of the important variable of severity criterion. These major criticisms apply to both the comprehensive review of Kane and Smith, and also to the more limited contrasts between treated and untreated samples within the same study evaluated by Jeste and Wyatt.

Ideally, proving the validity of the concept of 'neuroleptic-caused movement disorder' would require to account not only for the fact that clinically similar conditions can occur spontaneously, as is attempted in comparing pooled data. It would also be necessary to take account of diagnosis as a possible interposing aetiological factor. Schizophrenia, the major indication for long-term neuroleptic administration, is a condition which may itself be associated with the development of abnormal motor activity (cf Part I).

The literature is surprisingly lacking in reports of putative TD in non-psychotic and non-psychiatric patients. This undoubtedly reflects the relatively infrequent use of neuroleptics, and possibly the smaller doses employed, in these situations. Klawans et al (1974) reported 7 cases aged 41 - 69 years, all of whom had developed involuntary movements after "prolonged" neuroleptic treatment. Five had diagnoses of "anxiety neurosis" and 2 of "chronic gastritis". All developed lingual-facial-buccal movements but in 6, other abnormalities were also detectable. Kataria et al (1978) reported 3 elderly subjects with "chronic tardive dyskinesia" associated with metaclopramide, which although not conventionally classed as a neuroleptic, does exhibit dopamine blocking activity. Such reports are however isolated. Recently, several publications have suggested that patients with affective disorder may be at higher risk of developing 'TD' than those with other psychiatric diagnoses (Davis et al 1976; Rosenbaum et al 1977), though the evidence is anecdotal.

Thus while data on the prevalence, severity and distribution of movement disorder developing in non-psychiatric and non-schizophrenic psychiatric patients could provide valuable evidence in support of a primary role for neuroleptics in the aetiology of involuntary movements and on the role of diagnosis, systematic investigation in these areas has not been undertaken to date and no suitable figures are available for comparison.

One study has looked at matched groups of schizophrenics varying on neuroleptic exposure. Crane, using his own criteria, studied the prevalence of "dyskinesia" in "two fairly typical

populations" of young and middle aged chronic psychiatric in-patients (Crane 1968b). One group, in the U.S.A., had been heavily exposed to neuroleptics, while the other, in Turkey, consisted of "minimally" and "moderately" treated patients. He found no dyskinesia in the minimally treated patients and significantly more in the heavily than moderately treated subjects. This finding persisted when only schizophrenics matched for age and sex were compared. The difference between those heavily treated and the rest with regard to dyskinesia was highly significant ($P < 0.001$).

This study provides compelling evidence for a direct role of neuroleptics in the production of involuntary movements in schizophrenics, but has been criticised on administrative grounds, in that in Turkey, patients exhibiting neurological signs are segregated from the rest, rendering the Turkish sample less "typical" of Western patients than was thought (Turek 1975).

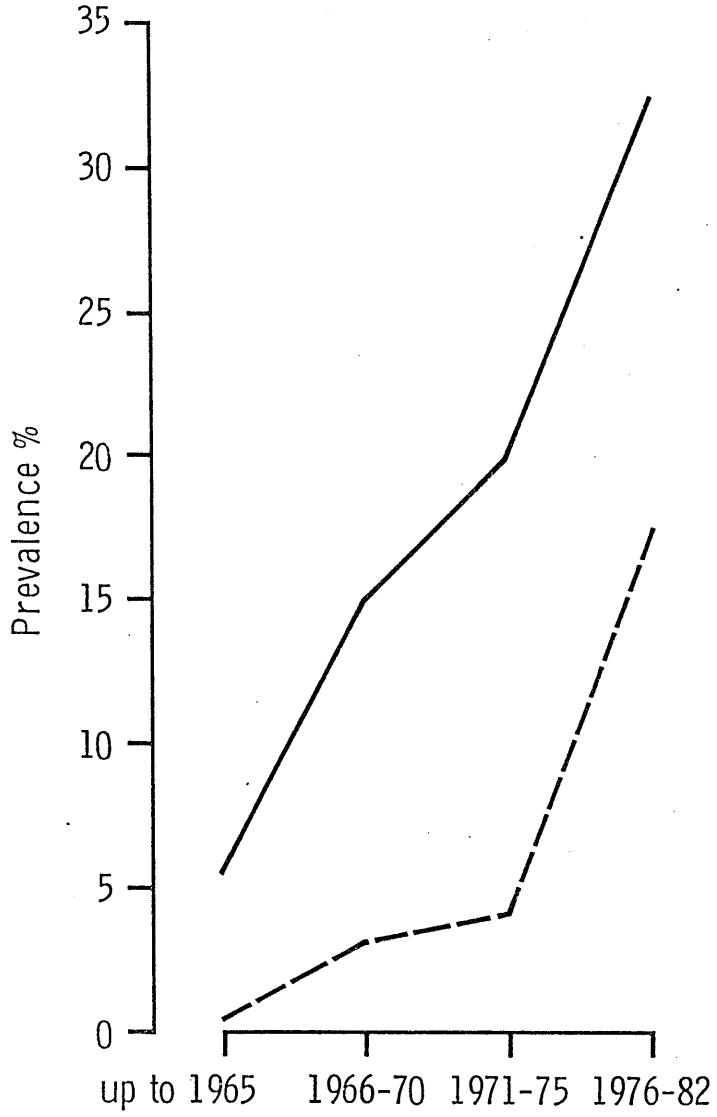
1.6 PREVALENCE OVER TIME

It is clear that the reported prevalence of putative TD has increased in the past two decades (Fig 2:1:1).

Originally, nominal present/absent ratings or crude clinical impressions were the basis of recording findings, leaving individual authors to establish what was significant enough to warrent recording. More recently, standardised ordinal scales which take account of differing severities of abnormality have been introduced and the question arises as to whether this increased prevalence is apparant or real.

Kane and Smith concluded that this phenomenon was "not entirely"

FIG 2:1:1 The mean prevalence of 'tardive dyskinesia' (continuous line) in neuroleptic treated patients, and 'spontaneous' dyskinesias (broken line) in neuroleptic-free patients over time



attributable to the increasing use of rating scales, because ratings based on nominal categorisation showed no significant increase in reported prevalence (Kane & Smith 1982). Equally however, it is possible this means only that the prevalence of severe abnormality, more likely to be considered noteworthy in nominal categorisations, has not changed. It still allows the interpretation that milder degrees of severity are more likely to be increasingly sought and recorded in fulfillment of the demands of multi-item rating scales.

Jeste and Wyatt also concluded that this phenomenon was unlikely to reflect solely over-diagnosis consequent upon increasing awareness of the condition (though they did not specifically discuss the role of increasingly comprehensive recording techniques), an aging study population, or emphasis on particularly disadvantaged in-patient groups (Jeste & Wyatt 1981).

In confirmation of the fact that the reported increase in prevalence over time is to some extent apparent, is the point that a similar phenomenon can be demonstrated using data from studies of patients never exposed to neuroleptics (Fig 2:1:1). There is no evidence that the earlier of these investigations studied younger subject and that the prevalence of later ones reflects the 'cumulative' effects of some incidental factor such as age.

The trend appears to be continuing. Studies published between 1980 - 1982 are summarised in TABLE 2:1:1. Of these, the study of Kane et al is striking in the low prevalence it reports. This is likely to reflect the authors' more stringent

TABLE 2:1:1 RECENT STUDIES OF THE PREVALENCE OF 'TARDIVE DYSKINESIA'

STUDY	DIAGNOSIS	N STATUS	MEAN AGE	RATING SCHEDULE	SEVERITY CRITERION	PREVALENCE	COMMENT.
GARDOS et al 1980	76% SCHIZOPHRENIC 15% SCHIZOAFFECTIVE	122 OUTPATIENTS	37.2	AIMS R.S.	MILD	44% (16% BY AUTHORS OWN CRITERIA)	NO SEVERE CASES
KANE et al 1980	MIXED 54% SCHIZOPHRENIC	271 120 INPATIENTS 151 OUTPATIENTS	31.8	AIMS R.S.	MILD (BY TWO RATERS)	4%	COMPARABLE PREVALENCE IN NEUROLEPTIC TREATED AND NON-TREATED
WOJCIK et al 1980	MIXED	210 25 INPATIENTS 185 OUTPATIENTS	42.7	AIMS	MILD	19.5%	
EZRIN-WATERS et al 1981	SCHIZOPHRENICS	94 OUTPATIENTS	37	R.C. SMITH	MILD	44%	
ITAL et al 1981	MIXED 80% SCHIZOPHRENIC	200 INPATIENTS	71.5	CRANE/ NARANJO	SEVERE CASES ONLY	12%	
RICHARDSON AND CRAIG 1982	MIXED	132 INPATIENTS	40	R.S. (ABBR)	MILD	45.4%	
MUKHERJEE et al 1982	MIXED	153 OUTPATIENTS	49.8	AIMS	MILD	30.7%	34% NEVER IN HOSPITAL
McCREADIE et al 1982	SCHIZOPHRENIC	117 IN/OUT-PATIENTS	75	AIMS	MILD	31%	
CHOUINARD et al 1982	SCHIZOPHRENIC	48 OUTPATIENTS	?	CGI OF CHOUINARD et al	MILD	50%	NOT PRIMARILY A PREVALENCE STUDY

requirements, in that the prevalence illustrated is that from two raters assessing independently. Including any rating by either examiner increases the prevalence to 22.2 %.

Using the criterion 'mild or more', the mean prevalence of abnormality from 8 of these studies (that of Ital et al is excluded as they were only considering "severe" abnormality) encompasing 1147 patients, is 33.6 % though using Kane et al's more liberal figure it becomes 35.9 %. All these studies used standardised recording techniques.

Thus, it is concluded that a statistical association can be demonstrated between a history of neuroleptic exposure and the prevalence of spontaneous involuntary disorders of movement. This association is on the basis of pooled data from studies over 25 years, where different diagnostic criteria and recording methodologies have been used and is calculated without consideration of other potentially relevant variables.

1.7 INCIDENCE

There are no reliable data on the incidence of neuroleptic-caused dyskinesia. Gibson (1978) followed 374 schizophrenic out-patients for 3 years and noted a progressive increase from 7 % to 22 % in the number of patients with at least mild oral dyskinesia - an annual incidence of approximately 5 %. Severe dyskinesia remained constant at 1.6 % throughout. However, all his patients had been receiving neuroleptics for many years (mean 13 years) prior to commencement of the study. Nonetheless

Gibson's figure is comparable to the 4 - 5 % annual incidence calculated by Gardos and Cole in Boston (Gardos & Cole 1980), and to the 12 % over 4 years reported by Kane et al (1982 b).

1.8 PUTATIVE PREDISPOSING FACTORS

A number of risk factors were reported in the earlier literature based on uncontrolled observations, and many of these have gained widespread clinical acceptance. In the following evaluation of putative predisposing factors, investigations presenting comparisons between dyskinetic and non-dyskinetic groups will be considered. Studies for and against each variable are summarised in TABLE 2:1:2.

1.8.1 DRUG-RELATED FACTORS

a) TYPE OF NEUROLEPTIC

All currently available neuroleptic drugs have been implicated in the production of involuntary movements. Uhrbrand and Faurbye's original report noted that 15 patients had received trifluoperazine and a number of workers emphasised the potential role of the more potent neuroleptics. Despite theoretical merits, however, there is no clinical evidence to support the view that the more potent dopamine blocking drugs produce a greater risk of movement disorder (APA Task Force Summary 1980)(TABLE 2:1:2). In the United States, fluphenazine has been suggested as producing a greater risk (R.C. Smith et al 1978). This is however the only marketed depot neuroleptic in the U.S. and any implied risk may relate to non-specific factors inherent in depot

TABLE 2:1:2

STUDIES FOR AND AGAINST PROPOSED PREDISPOSING FACTORS IN TARDIVE DYSKINESIA

A. DRUG-RELATED FACTORS

PREDISPOSING FACTOR	FOR		AGAINST	
TYPE OF NEUROLEPTIC (POTENCY)	GARDOS et al	1977	HUNTER et al	1964
	R.C. SMITH et al	1978	PRYCE & EDWARDS	1966
	FAMUYIWA et al	1979	DEMARS	1966
	JESTE et al	1979a	DEGKWITZ et al	1967
	CHOUINARD et al	1979	DYNES	1968
	KANE et al	1980	HEINRICH et al	1968
	EZRIN-WATERS et al	1981	HIPPIUS & LANGE	1970
	MUKHERJEE et al	1982	JUS et al	1976a
			SIMPSON et al	1978
			PERRIS et al	1979
			GARDOS et al	1980
MAXIMUM DAILY DOSAGE	CRANE	1974	JUS et al	1976b
	R.C. SMITH et al	1978	GARDOS et al	1977
	GARDOS et al	1980	EZRIN-WATERS et al	1981
	MUKHERJEE et al	1982	RICHARDSON & CRAIG	1982
DURATION OF EXPOSURE	PRYCE & EDWARDS	1966	DEMARS	1966
	HEINRICH et al	1968	DEGKWITZ et al	1967
	CRANE & SMEETS	1974	LEHMANN et al	1970
	CRANE	1974	HIPPIUS & LANGE	1970
	GARDOS et al	1977	KENNEDY et al	1971
	JESTE et al	1979a	BRANDON et al	1971
	EZRIN-WATERS et al	1981	JUS et al	1976a
			GARDOS et al	1977
			SIMPSON et al	1978
			GIBSON	1978
			JOSE et al	1979
			CHOUINARD et al	1979
			PERRIS et al	1979
			FAMUYIWA et al	1979
			MALLYA et al	1979
CUMULATIVE EXPOSURE	HEINRICH et al	1968	DEGKWITZ et al	1967
	CRANE & SMEETS	1974	SIEDE & MULLER	1967
	GARDOS et al	1977	CRANE	1970
	JESTE et al	1979a	LEHMANN et al	1970
			HIPPIUS & LANGE	1970
			KENNEDY et al	1971
			BRANDON et al	1971
			JUS et al	1976a
			SIMPSON et al	1978
			R.C. SMITH et al	1978
			JOSE et al	1979
			PERRIS et al	1979
			FAMUYIWA et al	1979
			MALLYA et al	1979

TABLE 2:1:2 continued

PREDISPOSING FACTOR	FOR		AGAINST	
EXPOSURE TO MULTIPLE NEUROLEPTICS	BELL & SMITH	1978	DEMARS CRANE & PAULSON JUS et al SIMPSON et al	1966 1967 1976b 1978
ANTI-CHOLINERGICS	CRANE PERRIS et al MALLYA et al EZRIN-WATERS et al ITAL et al	1974 1979 1979 1981 1981	KENNEDY et al JUS et al GARDOS et al ASNIS et al CHOUINARD et al SIMPSON et al JOSE et al PERRIS et al GARDOS et al	1971 1976b 1977 1977 1979 1978 1979 1979 1980
NEUROLEPTIC-FREE INTERVALS	JESTE et al	1979	CRANE GARDOS et al	1974 1980
B. NON-DRUG RELATED FACTORS				
AGE	DEGKWITZ et al HIPPIUS & LANGE BRANDON et al CRANE OGITA et al JUS et al J.M. SMITH et al SIMPSON et al BELL & SMITH SMITH et al JOSE et al CHOUINARD et al EZRIN-WATERS et al RICHARDSON & CRAIG MUKHERJEE et al McCREADIE et al	1967 1970 1971 1974 1975 1976a 1978 1978 1978 1979a/b 1979 1979 1981 1982 1982 1982	HUNTER et al CRANE & PAULSON TURUNEN & ACHTE CRANE HEINRICH et al LEHMANN et al KENNEDY et al FANN et al GARDOS et al	1964 1967 1967 1968a 1968 1970 1971 1972 1980
SEX (F > M)	HUNTER et al DEMARS TURUNEN & ACHTE DEGKWITZ & WENZEL HEINRICH et al JONES & HUNTER LEHMANN et al BRANDON et al KENNEDY/HERSHON et al J.M. SMITH et al FAMUYIWA et al PERRIS et al	1964 1966 1967 1967 1968 1969 1970 1971 1971/ 1972 1978 1979 1979	CRANE & PAULSON CRANE CRANE HIPPIUS & LANGE OGITA et al JESTE et al GARDOS et al EZRIN-WATERS et al MUKHERJEE et al	1967 1968b 1970 1970 1975 1979a 1980 1981 1982

TABLE 2:1:2 continued.

PREDISPOSING FACTOR	FOR	AGAINST
'ORGANICITY' (VARIOUS PARAMETERS)	EDWARDS 1970 FAMUYIWA et al 1979 WEGNER et al 1979 ITAL et al 1981	HUNTER et al 1964 PRYCE & EDWARDS 1966 DEMARS 1966 DEGKWITZ & WENZEL 1967 SIEDE & MULLER 1967 GREENBLATT et al 1968 HEINRICH et al 1968 EDWARDS 1970 BRANDON et al 1971 FANN et al 1972 CRANE 1973 CRANE 1974 JUS et al 1976a GELLENBERG 1976 GARDOS et al 1977 ASNIS et al 1977 SIMPSON et al 1978 BELL & SMITH 1978 JOSE et al 1979 CHOUINARD et al 1979 FAMUYIWA et al 1979 JESTE et al 1980 GARDOS et al 1980
PAST PHYSICAL TREATMENTS: INSULIN		DEGKWITZ & WENZEL 1967 HEINRICH et al 1968 BRANDON et al 1971 JUS et al 1976a
ECT	HUNTER et al 1964	DEGKWITZ & WENZEL 1967 DEMARS 1966 HEINRICH et al 1968 EDWARDS 1970 BRANDON et al 1971 JUS et al 1976a ASNIS et al 1977 GARDOS et al 1977 CHOUINARD et al 1979 GARDOS et al 1980
LEUCOTOMY		HUNTER et al 1964 DEMARS 1966 EDWARDS 1970 BRANDON et al 1971 JUS et al 1976a
"SOMATIC THERAPIES"	ITAL et al 1981	
FEATURES OF THE MENTAL STATE	CHOUINARD et al 1979 ITAL et al 1981 McCREADIE et al 1982	

preparations, such as differing bioavailability and compliance.

b) MAXIMUM DAILY DOSE

There is no evidence of a relationship between higher maximal daily doses and frequency of movement disorder.

c) DURATION OF EXPOSURE

The bulk of the literature is against this being of relevance.

d) CUMULATIVE EXPOSURE

The assumption that cumulative neuroleptic exposure is relevant in predisposing to involuntary movements is not borne out in the literature.

e) EXPOSURE TO MULTIPLE NEUROLEPTICS

This has not been shown to be relevant.

f) NEUROLEPTIC - FREE INTERVALS

Jeste et al (1979a) found that the variable which maximally distinguished between dyskinetic and non-dyskinetic patients was the number of drug-free intervals of 2 months or more, which were reported to be significantly more frequent in the former group. This has not been replicated, but remains of interest as its practical implications are quite contrary to those of the widely advocated 'drug holidays'.

g) ANTICHOLINERGIC MEDICATION

There is no clinical substantiation for the view, however theoretically plausible, that anticholinergic medication promotes the development of involuntary movements.

1.8.2 NON - DRUG - RELATED FACTORS

a) AGE

Age remains one of the most striking positive associations reported in literature on involuntary movements. A number of studies which did not find a relationship with age examined patients within relatively narrow age ranges. Kane and Smith (1982) suggest a minimum of 3 decades of age range in a study sample, with patients under 50 represented. Applying these criteria, the bulk of the literature is in favour of a relationship between age and the presence of involuntary movements. Jeste and Wyatt (1981)calculated an overall unweighted mean prevalence of abnormality in patients over 40 that was three times that in younger subjects.

Although age can be quite consistently shown to be a significant correlate of involuntary movements the exact nature of this relationship remains unclear. Smith and Baldessarini (1980) reviewed 9 studies and found that strong correlations existed between age and both prevalence and severity of movement disorder. In addition they concluded that there was a strong negative relationship between age and spontaneous remission of involuntary movements attributed to neuroleptics. Both increased severity and low spontaneous remission rates could contribute to

higher prevalence rates in older subjects even if incidence were not affected by age per se. Furthermore, sex may complicate evaluation of the effects of age. It has been reported that middle aged males may show slightly more severe dyskinesia (Chouinard et al 1979) though it has also been suggested that elderly females may have especially severe abnormal movements (Smith et al 1979b). Such discrepancies may reflect the differing age ranges of subjects who form the cohorts of different investigations (Smith & Dunn 1979).

A further complication in evaluating this question is the suggestion, mentioned earlier, that the distribution of abnormal movements may differ in different age groups. Thus, younger patients, especially males, may be more prone to develop generalised dystonic and choreoathetoid syndromes while in older patients, especially females, orofacial movements may be more likely (APA Task Force 1979). Using blanket descriptive terms such as 'dyskinesia' or basing evaluations on multi-item rating scale total scores or global impressions may mask regional body variations.

The exact nature of the association between age and involuntary movement disorders remains to be determined.

b) SEX

One of the earliest suggestions was that 'TD' was more common in women. A number of the pioneering descriptive studies were, however, confined to female wards, and others did not examine the role of sex independent of age.

A recent review of the subject (quoted by Kane and Smith 1982) calculated that the average unweighted F:M prevalence was 1.68 : 1 from a total of 31 studies. This is a comparable finding to that of Jeste and Wyatt (1981) who calculated an overall weighted mean prevalence for women that was 41 % higher than for men, using a more selective series of 19 studies.

However, a number of studies have failed to show a significant relationship between female sex and neuroleptic - related movement disorder (TABLE 2:1:2), and as Jeste and Wyatt (1981) have pointed out, there are as yet too few studies to allow the determination of the differential effects of age on males and females with regard to the production of 'TD'. A further difficulty relates to the suggestion of Smith et al (1979b) that the sexes may differ in prevalence only at the highest criterion of severity. In view of the relative rarity of 'severe' cases this finding could be secondary to sampling fluctuations, as the number of subjects on whom analysis was conducted was small.

Despite the above statistical association from pooled data, it remains unclear whether sex differences are consequent upon the intruding effect of some secondary factor such as age, or whether they reflect some biological variant such as brain neurotransmitter differences, the effect of sex hormones on central systems or merely different patterns of neuroleptic treatment. In this regard, several authors have noted that women tend to receive longer or higher dose treatments than do men (Degkwitz & Wenzel 1967; Jones & Hunter 1969; Fann et al 1972; Simpson et al 1978).

c) ORGANICITY

As with sex, one of the earliest anecdotal associations with dyskinesia was organic brain disorder. Despite this early impression, this is a question that remains remarkably poorly investigated. A variety of parameters of organicity have been adopted, from the conventional such as a diagnosis of organic brain syndrome, to the more controversial such as a history of ECT.

Pryce and Edwards could not distinguish between an experimental group of 21 dyskinetic subjects and a group of matched controls in terms of "organicity". This term however encompassed a variety of parameters, many of doubtful validity. Although no differences emerged between the groups on Walton's Modified Word-Learning Test, this could not be performed in over 25 % of the sample. Subsequently, Edwards assessed 34 matched pairs drawn from a larger pool of 184, using the same parameters. Significantly more of the experimental group had a diagnosis of dementia and fulfilled "organicity" criteria in general. Despite a large group who once again could not be tested, significantly more dyskinetic patients were impaired on the Word-Learning Test than patients free from dyskinesia. Edwards concluded that his findings were not just the result of a preponderance of dementing cases in his experimental (dyskinetic) group, as more patients with a functional diagnosis and dyskinesia showed evidence of "brain damage" than functional subjects without dyskinesia. More recently, Ital et al showed significant impairment on items of the Goldfarb scale (of

orientation and memory) in a severely dyskinetic group compared to a matched, non-dyskinetic group.

Three other studies using different neuropsychological tests have been reported. Famuyiwa et al found no difference on Withers and Hinton totals in their dyskinetic patients compared to dyskinesia-free controls, though both were significantly impaired in comparison to normals. The groups studied in this work were however relatively young and had short durations of illness. The degree of their cognitive impairment was slight compared to that reported with other schizophrenics using this test (e.g. Johnstone et al 1978b). However, the authors did report significant impairment on the Inglis Paired Associate Learning Test in the dyskinetic group compared to controls.

José et al found a relationship between impaired "orientation/memory" on the Missouri Mental State Examination and "tardive dyskinesia", though this was certainly due in large part to the fact that those comprising their small sample with involuntary movements (6/76) were older than the rest.

Asnis et al reported no differences in a group of dyskinetic out-patients compared to dyskinesia-free patients using both the Mental Status Questionnaire and the Face-Hand Test of Kahn et al, though the study sample was again relatively young and the latter test in particular was devised for use with elderly subjects.

No association has been reported between involuntary movement disorder and a positive neurological history (other than dementia) or with leucotomy, and although Wegner et al have

suggested an association with the B-mitten complex on EEG, two other studies have reported no association with EEG variants (Gardos et al 1977; Ital et al 1981). The CT scan data(which in general is negative) will be discussed subsequently (Part III).

Thus, although the idea is widespread that neuroleptic-caused movement disorder is associated with brain damage, the evidence to confirm it is equivocal (TABLE 2:1:2).

d) PAST PHYSICAL TREATMENTS

As mentioned above, no studies have found an association between dyskinesia and leucotomy. On the contrary, four studies have reported no association.

Nine of the 13 patients described by Hunter et al had received ECT, some in considerable amounts (from 14 - 212 treatments), but apart from this uncontrolled observation there is no evidence to suggest an association with ECT. Indeed 10 studies have reported no association (TABLE 2:1:2).

Brandon et al (1971) reported significantly <u>less</u> orofacial abnormality in patients with a history of insulin coma therapy than in patients who had not received this, though believed the explanation lay in the relatively lower age of the insulin-treated patients. Four other studies found no relationship (TABLE 2:1:2).

Thus there is no evidence to implicate past physical treatments in the production of movement disorders.

e) FEATURES OF THE MENTAL STATE

This area is probably the most neglected with regard to predisposing factors in neuroleptic-related movement disorder. Chouinard et al (1979) found that among schizophrenics of the same age, those for whom neuroleptic treatment was producing little therapeutic effect were more likely to have a greater prevalence and severity of abnormal movements. Unfortunately the mental state features on which this finding was based are not described.

Ital et al (1981), using the 28 item Expanded BPRS, found significant relationships between movement disorder and a number of items of the type associated with 'negative' or 'defect' states (e.g. impaired communication, emotional withdrawal, blunted affect, apathy or disinterest etc.). These authors note that no relationships were established with the so-called 'productive' symptomatology of psychosis. As their dyskinetic and non-dyskinetic samples were closely matched for age and sex these two variables could not account for the finding.

Recently, McCreadie et al reported similar results in a study of schizophrenics within a defined geographical area. Movement disorder was significantly related to affective flattening (Krawiecka Scale) and social withdrawal (Wing Scale).

Thus, although there is some evidence to suggest that involuntary movements may be more prevalent in patients with persisting mental state abnormality - especially that of the 'negative' or 'defect' type - insufficient work has been published in this area to allow definite conclusions.

1.9 COURSE AND PROGNOSIS

This remains a controversial area. While early reports were concerned with the "apparent" irreversibility of the syndrome, more recent work has sought to establish the role of reversibility in the course and prognosis.

Earlier reports were not encouraging with regard to the resolution of dyskinesia on neuroleptic withdrawal, but more recent studies since the mid-70's have reported increasing proportions of patients whose symptoms resolve or significantly improve. This probably reflects the fact that newer studies with higher prevalences included milder abnormality in patients treated for shorter periods, and also the longer follow-up intervals employed.

The American Psychiatric Association Task Force Report on Tardive Dyskinesia, calculated an average remission rate of 22 % from 12 studies from 1960 - 1980 (APA Task Force Summary 1980). The rate rises to 30 % if only studies from 1970 are considered, and to 64 % for those after 1976. Jeste and Wyatt, reviewing the literature up to 1980, concluded that the syndrome is reversible in slightly more than one-third of patients (Jeste & Wyatt 1981).

Recently, Seeman reported a 2 year follow-up of out-patient schizophrenics diagnosed as having TD, and who had either been on "prolonged" drug holidays or had their neuroleptic dosage reduced (Seeman 1981). She noted disappearance or marked reduction in dyskinesia ratings in 56 % of subjects. This is in line with more recent published remission rates. In addition,

Seeman found the signs had disappeared or reduced markedly in 76 % of those under 40 years of age, but in only 37 % of those older than 40. This may reflect the view mentioned earlier, that such movements are more severe in older patients.

Systematic studies which have so far looked at this question have used total rating scale scores so there is as yet no information on which distributions of abnormality may be most susceptible to improvement or on shifts of distribution that may follow dose reductions.

Underlining the confusion about the question of reversibility/irreversibility, is the finding of Gardos and Cole who sent questionnaires to 20 investigators specialising in the area of 'tardive dyskinesia' (Gardos & Cole 1980). They asked for opinions regarding the frequency with which dyskinesia persisted in patients whose drugs had been withdrawn for 3 - 24 months. The experts' reported figures ranged from 0 % to 100 %. Such striking variability is likely to reflect more than variation in symptomatology and treatment policies, but probably reflects profound differences in understanding of 'tardive dyskinesia'. It would appear that for some, irreversibility is becoming incorporated in the concept of the syndrome.

1.10 PROPOSED PATHOPHYSIOLOGY

The similarity between involuntary movements associated with neuroleptic administration and other choreoathetoid syndromes has suggested a common biochemical basis. It is beyond the scope of the present work to review the substantial literature

that has been generated in this area. Comprehensive reviews have been published elsewhere (Tarsy & Baldessarini 1977; Baldessarini & Tarsy 1979; Marsden & Jenner 1980; De Veaugh - Geiss 1982). In summary, evidence has accrued to support the view that the pathogenesis of 'tardive dyskinesia' relates to chronic dopamine receptor site blockade, which may be considered as a form of chemical denervation, and that the pathophysiology resides in the resultant receptor site hypersensitivity, which develops in conformity with Cannon's Law.

While this view is in keeping with a number of clinical observations and has gained widespread acceptance, other facts cannot be readily accommodated within this model in its simplest form. Some of these difficulties have been reviewed by Klawans et al (1980). Recently Jeste and Wyatt (1981a) have suggested an alternative model implicating other amine systems.

The pathophysiology of movement disorder associated with neuroleptic intake is complex and, at present, poorly understood. Exploratory pharmacological investigations which do not take account of the non-specific modifying influences of the study drugs on factors such as mental state, and which necessitate the probing of central neurotransmitter systems in isolation, are likely to provide misleading, or at best, partial information. The question of the relationship between dopamine receptor change consequent upon neuroleptic administration and that which it has been suggested, may underline the schizophrenic process itself (Owen et al 1978), is of great interest but remains to be elucidated.

1.11 NEUROPATHOLOGY

No consistent neuropathological abnormality has been found in the brains of patients with neuroleptic-related movement disorder. In the only controlled study to date, Christensen et al (1970) did find nigral degeneration in 27 out of 28 brains from patients with dyskinesia, and mid-brain and brain-stem gliosis in 25. In control material from non-dyskinetic subjects the respective figures were 7 and 4. Although matched, the controls differed from subjects on variables other than the absence of dyskinesia (e.g. age, neuroleptic treatment etc).

1.12 SUMMARY OF THE LITERATURE

1) The statistical association between involuntary movements and neuroleptic administration rests on epidemiological data which in general are of poor quality, and require caution in their interpretation. Nevertheless, the strength of the association is striking.

2) The prevalence reported in the literature is increasing, which may partly reflect a genuine increase in frequency though is likely also to reflect apparant changes consequent upon greater recognition.

3) The reported annual incidence of 3 - 5 % requires confirmation.

4) No specific drug-related factors have been clearly demonstrated as increasing the risk of developing movement disorders.

5) Only age, of the non-drug related variables, has shown relative consistency of effect. Female sex, organic predisposition and features of the mental state remain either unclear or unconfirmed with regard to predisposition.

6) The course and prognosis of the involuntary movements remains controversial. This relates to the reversibility/irreversibility phenomenon with neuroleptic reduction or cessation.

7) The pathophysiology underlying involuntary movements in this context is ill-understood. Straightforward theories linking the features solely to post - synaptic dopamine receptor supersensitivity are likely to be over-simplifications.

8) No neuropathological lesion has yet been identified.

Chapter 2 - The Present Study

2.1 GENERAL

The review presented in this section has concentrated on the literature relevant to 'tardive dyskinesia'. This is now voluminous and swamps the few sketchy hints in the older, descriptive writings which suggested that schizophrenia itself may possibly be associated with the development of involuntary movements (Part I). The discrepant size of the two literatures should not justify the implications of the larger over-shadowing those of the smaller. As has been shown, the concept of 'tardive dyskinesia' rests on evidence open to quite basic methodological criticisms, and in those most at risk of developing abnormal movements - namely schizophrenics in whom the condition is established - aspects of the illness per se have not been systematically explored.

Ideally, for the role of neuroleptics and illness to be adequately evaluated, a large number of subjects with standardised diagnoses would require to be randomly allocated to neuroleptic or no neuroleptic and assessed, blind to treatment, over many years. The scale, complexity and ethics of such a study are against it ever being done. However, valuable information could still be obtained by investigating diagnostically homogeneous and symptomatologically defined schizophrenics who have and who have not been treated with neuroleptic drugs, and who have all in addition been managed in the same administrative environment. No such study has yet

been reported.

2.2 THE SPECIFIC QUESTIONS

The specific questions addressed in this part of the study have been laid out previously but will be re-stated for clarity.

1) Is established schizophrenia, unmodified by neuroleptic drugs, associated with the development of spontaneous involuntary movements ?

2) In established schizophrenia can the concept of tardive (neuroleptic-caused) dyskinesia be shown to have validity and if so what are its correlates ?

2.3 THERAPEUTIC BACKGROUND

The study population that is the basis of the present work was ideally suited for the evaluation of these questions, because of the widely differing treatment policies operated for many years, and which were briefly referred to earlier (Introduction 3 IV : Part I Chapter 5.1).

Shenley Hospital has, since it opened in 1934, provided psychiatric care for the adjacent London Boroughs of Brent and Harrow. From the administrative point of view, the two 'halves' of the hospital were separate. Admission either to the Harrow Division or the Brent Division depended entirely on what borough the patient resided in. From its early years the hospital's two Divisions began to diverge in treatment orientation with Brent Consultants adopting a more psychotherapeutic approach. By the time neuroleptics were introduced into the hospital in

1956 an essentially therapeutic community orientated programme was established for Brent patients. The Consultants concerned were particularly interested in the application of these principles to the management of schizophrenia. Intrinsic to this programme was the avoidance where possible of physical treatments of all kinds. In the 1960's when neuroleptics were becoming widely prescribed, this dynamic approach reached its zenith. Shenley acquired a considerable international reputation in the psychotherapeutic management of schizophrenia and one of the Brent Consultants, Dr. David Cooper, became a prominent member of the so-called 'anti-psychiatry' movement. His accounts of the work of his unit ('Villa 21')were widely read and influential.* This practice persisted well into the 1970's (the Senior Consultant only retired in 1975).

This philosophy of treatment was not imposed by medical staff but rather evolved over many years. Hence non-medical personnel (nurses, social workers, occupational therapists etc.) were attracted and recruited into the system because they shared the belief in its humaneness and efficacy.

For these reasons, it is felt that a history of no exposure to insulin coma, ECT, and especially neuroleptic drugs is reliable. In view of the staff's commitment, it is unlikely that neuroleptics were given without being recorded on drug sheets and certainly there is little question that this could have taken place regularly.

None of the aforegoing is meant to imply an absolute proscription on the use of physical treatments for Brent patients.

* see : Cooper D., "Psychiatry and Antipsychiatry" Tavistock London 1967.

It was merely that alternative methods of management were emphasised and the administration of physical treatments avoided. Medication was used. For example, barbiturate hypnotics were sometimes given and acute behavioural disturbance was occasionally managed with parenteral barbiturates or paraldehyde. Some patients were eventually given neuroleptics.

Because of these general principles it was possible for some patients to pass the greater part of their years without receiving physical forms of treatment and in particular without being managed with neuroleptic drugs. This has been confirmed in informal conversation with a number of nurses whose careers span many years at the hospital and who were in the past involved in psychotherapeutic programmes for schizophrenic patients.

Chapter 3 - Methods

3.1 EXAMINATION AND RECORDING TECHNIQUES

The population was re-examined between May and July 1980. This second neurological examination focused solely on spontaneous involuntary disorders of movement and abnormalities of gait and posture. The assessments were conducted according to a format which combined the procedural recommendations for the rating scales adopted for recording of findings.

Two different scales were chosen for recording purposes - the Abnormal Involuntary Movement Scale, or AIMS, (Guy 1976) and the Rockland (or Simpson Dyskinesia Rating) Scale (Simpson et al 1979). The AIMS, (Appendix VI) devised at the National Institute of Mental Health, is succinct, of proven reliability on its major items, and has been widely used. Its classification is, however, gross, all involuntary movements being subsumed under 7 regional headings each on a 5 point severity scale, and it has a strong facial bias. It specifically excludes tremor from its ratings. Hence the information it notes is compatable with a more restricted definition of 'dyskinesia'.

The scale devised by Simpson et al at the Rockland Institute, New York * (Appendix VII) is somewhat wider in its conceptualisation. It consists of 43 items each with a 6 point scale severity, 34 of which demand the evaluation of specific, named movements arranged systematically. The remaining 9 items are left for

* This scale was in preprint form when used in the present study and at that stage was referred to by the name of the Institute where it was devised. Since publication, it has become generally known by the name of its principal author and is usually called the Simpson Dyskinesia Rating Scale. The original designation has been retained in the present work.

the rating of non-specified movements felt to be present but not ratable on the specific items. The Rockland Scale (RS) includes tremor in its main items and there is nothing to preclude the examiner from using non-specific items to record tremor of different clinical types. This scale records abnormality compatable with a wider definition of 'dyskinesia'.

Patients were examined individually, one ward at a time and in random order. The assessments were conducted in a side room. Subjects were observed unobtrusively as they entered the room, sat down and were engaged in general conversation. Facial movements were assessed with mouth closed and open and tongue resting passively on the floor of the mouth and protruded. Distal upper limb and periorbital movements were evaluated with the patient standing upright, arms extended in front, both with fingers horizontal and abducted and with wrists limp. This stance was adopted with eyes open and closed.

Two 'activating' or 'reinforcement' techniques were employed to enhance dyskinetic activity - namely, rapid thumb and sequential finger opposition and alternate foot - tapping.

Posture, gait and associated arm movement were noted as the patient walked away from and toward the examiner in their normal walk in the open ward.

A final unobstrusive observation was made as the patient left, or if necessary, after the formal examination.

Both scales were completed at the time on the basis of

the definition of items and severity points required for each. For severity, the maximal abnormality at any time during the interview was taken. The AIMS requirement for movements "that occur upon activation to be rated one less than those observed spontaneously" was suspended. To have enforced this would have meant that the '1' rating, by definition for movements considered doubtfully abnormal in either type or degree, would have been contaminated by definitely abnormal activity (e.g. choreoathetosis) only detectable in certain circumstances. As it was felt that a number of such movements should always be considered abnormal, regardless of the circumstances in which they are elicited, the AIMS rule was regarded as conceptually unsound.

These examinations were conducted after completion of the initial assessments described in Part I. For this reason alone it would not have been possible for the examiner to recall the drug status of individual patients. In addition however, throughout the project patients were identified by code numbers, thus ensuring blindness as to treatment past and present.

Following the second examination, the patients' drug intake during the interim period was re-checked. Where individual records continued to indicate that the subject remained neuroleptic-free, confirmation was sought from the nursing staff and, where possible, from the patients themselves.

As neither the AIMS nor the RS makes provision for recording movement activity of a 'manneristic' or 'stereotyped'

variety, abnormalities of this type were not assessed and not knowingly rated.

3.2 STATISTICAL NOTE

3.2.1 ANALYSIS OF DATA

No entirely satisfactory method exists for the analysis of data recorded on multi-item rating scales. Three main methods have been advocated :

1) TOTAL SCORES: This is the obvious method, but the regional sensitivity of the scale is lost. Furthermore, it presents the major problem of adequately separating pathological from non-pathological ratings, which will be discussed below. With distributions of scores which are not bimodal, adoption of cut-offs in accounting for severity is of necessity arbitrary.

2) SINGLE SYMPTOM CRITERIA: This is based on the numbers attaining at least one rating at a defined point on the severity continuum on at least one item of the scale and is a straight-forward method of accounting for severity in prevalence estimates. It is obvious that a subject fulfilling a specified criterion must also fulfill all lower criteria. Thus prevalence based on a single symptom criterion of, say, '3', is the number of subjects who score at least one '3' on any item. It however, takes no account of the number of items rated at the specified criterion and consequently greatly compromises the scale's sensitivity.

3) GLOBAL IMPRESSIONS: It is possible on the basis of the number of items scored at each severity point to estimate

a global impression of the degree of abnormality, and to use this single numerical value in analysis. This has the advantage of simplicity and flexibility but this is gained at the total sacrifice of regional sensitivity. This method would appear to introduce a subjective quality into analysis which runs counter to the basic purpose of standardised multi-item recording techniques.

In the following analyses, both total scores and single symptom criteria will be used as stated. The global impression method was not utilised.

3.2.2 ADOPTING CUT - OFFS

The major part of the following analyses uses the total scores method. This necessitates the adoption of cut-offs to distinguish abnormality from normality, and to define varying degrees of severity.

In common with most multi-item rating scales in clinical psychiatry, both those used here reserve one point on the severity continuum ('1') for recording signs which are present but not considered to be abnormal in either type or degree. This means that totals represent all motor activity noted, not just that considered pathological. Injudicious use of total scores could result in someone scoring 4 on one item, and hence having an abnormality of note, being considered for analytical purposes the same as someone who scored '1' on four separate items who, by the definitions of the schedule, had no definite pathology. A low cut-off increases the likelihood of contamination

of the abnormal group this way, while raising it too high will exclude some subjects with mild but definite abnormality. In the present work cut-offs for normality were based on the minimal misclassification of subjects either way, while those for analyses involving severity were arbitrary.

a) AIMS DATA

Eleven subjects had a total AIMS score of '1'. Only three were rated '1' on more than one item, and of these, only one had a total (this was 2) comprising solely '1's. No totals of three arose from '1's. On the other hand, 38 patients had a total of 2 made up of single, mild ratings. Hence on the basis of minimal misclassification, an AIMS total of 0 or 1 is defined in the basic analyses as normal, while abnormality is taken as a total score of 2 or more.

Although based on the data, many would say this defines normality too conservatively, so some of the later analyses were repeated, defining normality by the higher cut-off of 0 - 2.

Ranges of totals reflecting the normal/mild-moderate/severe distinctions were mainly chosen on statistical considerations to provide roughly equal numbers in comparison cells. These are defined as they arise.

b) ROCKLAND DATA

Ten subjects had an RS total of '1'. Of 12 subjects with two single ratings of '1', these were the sole ratings in

just two and, as with the AIMS, no-one obtained a total of 3 from three '1's. Thirty two subjects had an RS of '2' comprising single, mild ratings while raising the cut-offs total to 3, misclassified 52 subjects. Hence in the initial analyses an RS total of 0 or 1 was taken as normal, 2 or more as abnormal.

While minimal misclassification occurred with this cut-off, a normality criteria of 0 - 1 on a 43 item scale is undoubtedly parsimonious. Raising the cut-off to account for both a wider concept of normality and the size of the scale is arbitrary. In the present work the higher normality criterion was fixed at an RS total of 4.

In addition to using grand totals from all 43 RS items, the regional pattern of relationships with past neuroleptic exposure was explored using Rockland subscore totals for Face, Neck and Trunk, Upper Limbs and Lower Limbs items. The low normality cut-off for these subscore totals was maintained at 0 - 1. The higher cut-off was arbitrarly taken as 0 - 3. This value, slightly lower than that chosen for use with grand totals, reflects the fewer number of items comprising the subscore totals and the fact that grand totals included the three whole body ratings of the RS (items 41 - 43) not included in any of the subscores.

Arbitrary ranges of totals in estimates involving severity are defined in the text.

3.2.3 STATISTICS

As was mentioned (Part I, Chap. 2.4.) in this detailed evaluation of involuntary movements a more cautious approach to the analysis of examination variables was adopted. In both this and the subsequent section they were treated as ordinal measures, distinctions being drawn between those not scoring and those scoring positively by defined cut-offs for normality, and between different ranges of scores to represent severity of abnormality. This recognises the patterns of distribution of the Assessed Abnormality scores and keeps the present analyses in line with the published literature.

Groups defined on this basis were compared using the X^2 statistic. Group mean score differences and mean number of movements were compared using t - tests, while the relative contributions of age and length of illness to the development of movement disorders were assessed using analysis of variance (ANOVA) and co-variance (ANCOVA).

The maximum likelihood/log linear technique referred to earlier (Part I Chap. 4.4) was used as stated.

The relationship of prevalence and severity of movement disorder to individual items of Recorded Information and Assessed Abnormality was investigated using unified analysis of variance by ranks (Meddis 1980). This technique requires only that the measures being evaluated are ordinal, but not that their distributions are normal.

The following data were subjected to a large number of analyses increasing the risk of significance being achieved by

chance. In view of the unique characteristics of the study sample and the importance of the questions being explored, a conservative approach to the interpretation of statistical significance was adopted. Thus, notwithstanding the hypotheses set out in the Introduction (3, iii), a 2 - tail interpretation was employed throughout Part II.

Chapter 4 - Results

4.1 GENERAL

Of the original sample of 510 subjects, 411 were available for the second examinations concentrating specifically on involuntary movement disorders. Of these, 364 had a history of exposure to neuroleptic drugs, and 47 had remained neuroleptic-free. The demographic and treatment details of this sample are shown in TABLE 2:4:1.

In the first examination, when only presence or absence of involuntary movements was considered, 50.4 % of the sample had demonstrable abnormality. On the second examination, using the AIMS scores (which, being free of tremor are more compatible with the initial assessments), this prevalence corresponds to a cut-off point of 3 (moderate) on the severity continuum (Fig 2:5:2). Adopting this 'moderate' criterion, a highly significant relationship was established between the way a patient was rated on the first and on the second examinations (Face: $X^2 = 51.03$, df = 1 : Limbs: $X^2 = 19.25$, df = 1).

Results of data recorded on AIMS and RS will be presented separately.

TABLE 2:4:1 DEMOGRAPHIC AND TREATMENT DATA IN STUDY SAMPLE (411 SUBJECTS) BY HISTORY OF NEUROLEPTIC EXPOSURE

	N	Sex	Age Mean ± SD	Length of Time since first Hospitalisation Mean ± SD	PAST PHYSICAL TREATMENTS				DRUG STATUS AT EXAMINATION			
					Leucotomy	Insulin*	ECT*	Neuro-leptics**	Neuro-leptics	Anti-cholinergics	Tricyclic Anti-depressants	Others
Neuroleptic Treated	364	M. 187 F. 177	56.9 ± 13.29 RANGE 21-91 yrs	29.8 ± 10.6 RANGE 2-60 yrs	NO 333 YES 31	NONE 261 SOME 56 MUCH 45 (+2 UNKNOWN)	NONE 242 SOME 94 MUCH 28	SOME 119 MUCH 245	OFF 77 ON 275 (+12 Indeterminate. Medication on PRN basis only)	OFF 188 ON 160 (+16 on PRN basis only)	OFF 352 ON 12	Lithium Carbonate ON: 4 Amantadine ON: 2
Neuroleptic Free	47	M. 40 F. 7	66.7 ± 11.66 RANGE 29-90 yrs	35.36 ± 10.06 RANGE 10-56 yrs	NO 44 YES 3	NONE 37 SOME 6 MUCH 4	NONE 37 SOME 8 MUCH 2	-	-	OFF 46 ON 1	OFF 47 ON 0	-

* SOME/MUCH = LESS/MORE THAN MEAN NUMBER OF TREATMENTS FOR ENTIRE SAMPLE

** SOME/MUCH = LESS/MORE THAN CHLOPROMAZINE 100 gms TID OR EQUIVALENT FOR AT LEAST ONE YEAR

5.1 THE TOTAL SAMPLE

5.1.1 PREVALENCE AND SEVERITY

Fig 2:5:1 shows the distribution of total scores of 2 or more in the sample of 411. The prevalence of abnormality by this criterion is 64.96 %.

The distribution of scores is roughly, though not precisely, exponential, and certainly offers no definite cut-off points for the division of abnormality by severity. The high prevalence of a score of 6, which is the major flaw in the exponentiality of the distribution, may reflect the central tendancy phenomenon - i.e. the examiner's tendancy to rate in the centre of the severity continuum - operating on facial items which, by the nature of the abnormalities in that region, are likely to be rated in pairs. Thus, of the 46 scores of 6, over half (24) arose from two ratings of '3' on facial items.

The skewed distribution shown in Fig 2:5:1, is reflected in the mean AIMS total for the group, which was 4.28 $\pm$ SD 4.68.

Fig 2:5:2 shows the prevalence of abnormality at increasing criteria of severity in all body regions together and in each separately using the single symptom criterion technique. This illustrates the crucial dependence of prevalence on the criterion of severity adopted.

In general, very high prevalences of involuntary movement disorder were found in this group of long-stay schizophrenics. With a single symptom criterion of 3 - that is a moderate degree of abnormality on at least one item - 50.6 % of patients had demonstrable

FIG 2:5:1

Distribution of pathological (>2) AIMS total scores (n = 267)

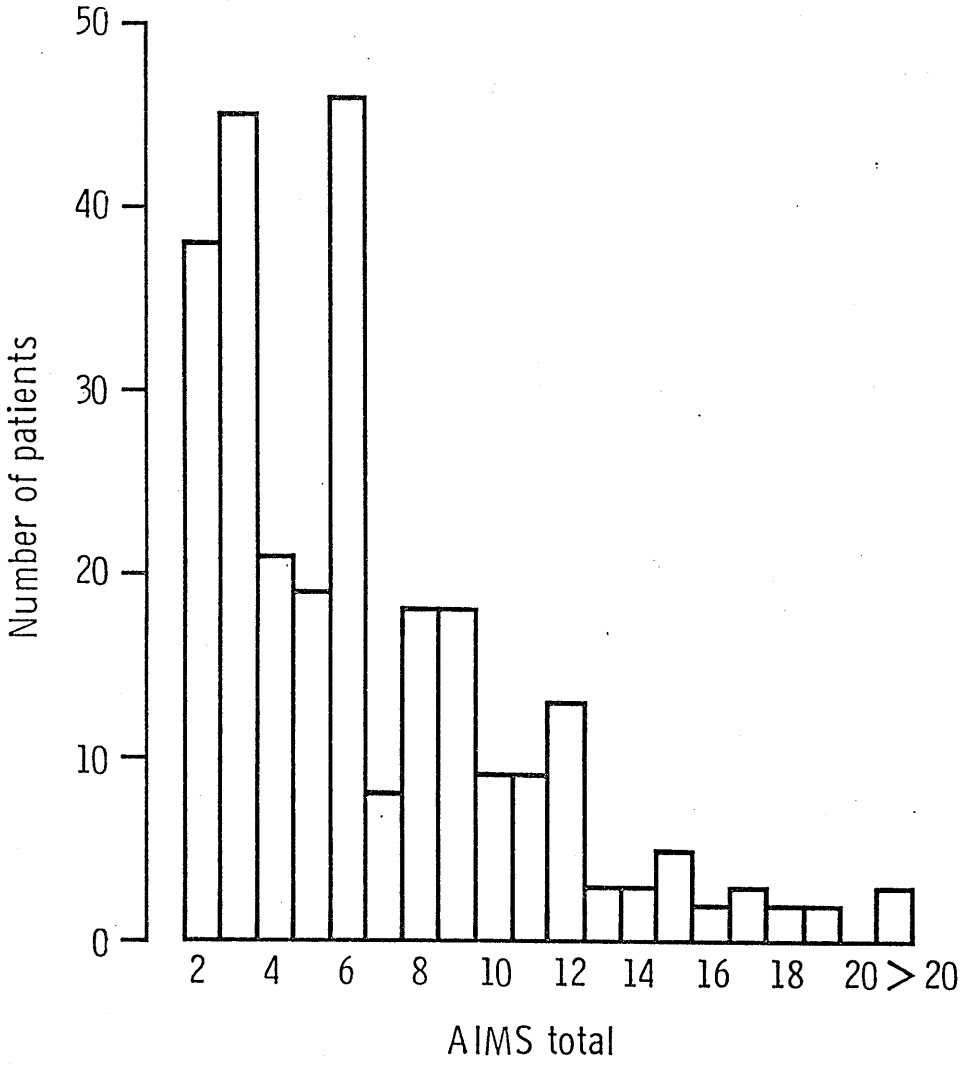
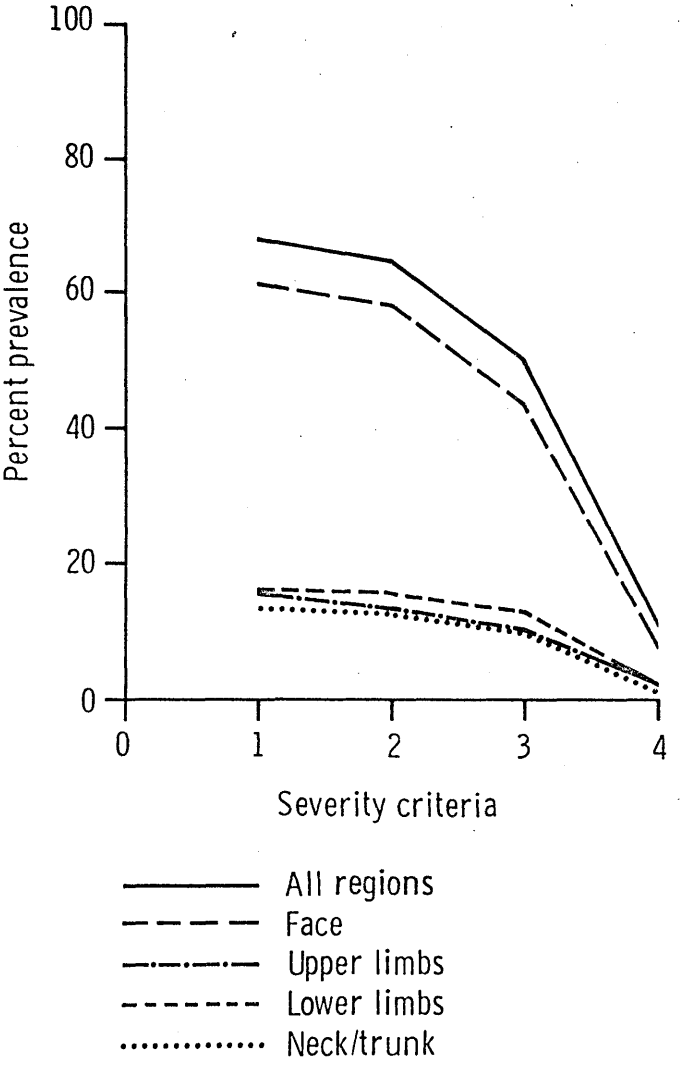


FIG 2:5:2

Regional prevalences at different severity criteria on A. I. M. S.



disorder. As Fig 2:5:2 shows, the major component of total abnormality was contributed by ratings of facial movements.

5.1.2 THE DISTRIBUTION OF MOVEMENT PATTERN

The percentage of the total sample who attained a pathological rating (i.e. at least a single rating of 2 or more) is shown for each AIMS item in order of frequency in TABLE 2:5:1.

This confirms that movements involving the tongue, lips and jaws, (the buccomasticatory lingual or BML, component) are the most prevalent dyskinesias in patients such as these, with movements of the axial/girdle musculature being least common.

5.2. COMPARISON OF NEUROLEPTIC TREATED and NEUROLEPTIC-FREE SUBGROUPS

As was mentioned earlier, the concept of 'tardive dyskinesia' rests on epidemiological data from comparisons of samples differing on many variables other than neuroleptic exposure. However, at a clinical level the diagnosis is essentially made on the basis of a history of exposure to neuroleptic drugs.

In its elementary form the concept of neuroleptic-caused movement disorder could be validated if diagnostically homogeneous groups who had and had not been exposed to neuroleptics could be shown to differ in the prevalence and/or severity and/or distribution of involuntary disorders of movement. The present population offered an ideal opportunity to test this simple form of the concept.

TABLE 2:5:1

DISTRIBUTION OF INVOLUNTARY MOVEMENTS ON AIMS IN ORDER OF FREQUENCY

AIMS AREA	% PREVALENCE (RATING 2 OR MORE)
TONGUE	35.4
LIPS	28.1
JAWS	23.7
FACIAL EXPRESSION	18.3
EXTREMITIES - LOWER	15.6
EXTREMITIES - UPPER	14.4
NECK, SHOULDER, HIPS	13.7

5.2.1 PREVALENCE AND SEVERITY

Of the 411 schizophrenics examined for the second time, 47 continued to be neuroleptic-free. (During the first part of the study 65 such patients had been identified - Part I).

The prevalences of abnormality at increasing criteria of severity, in patients with a history of neuroleptic treatment (364) and those who had remained neuroleptic-free (47) are shown in Fig 2:5:3, which considers all body regions together and each separately. No differences reaching conventional levels of statistical significance were found between the groups at any severity or in any region (X^2 analysis). The prevalence of abnormality is again high in those free from neuroleptic exposure. With a single symptom criterion of 2, 53.2 % of these patients had movement disorder.

5.2.2 MEAN SCORES

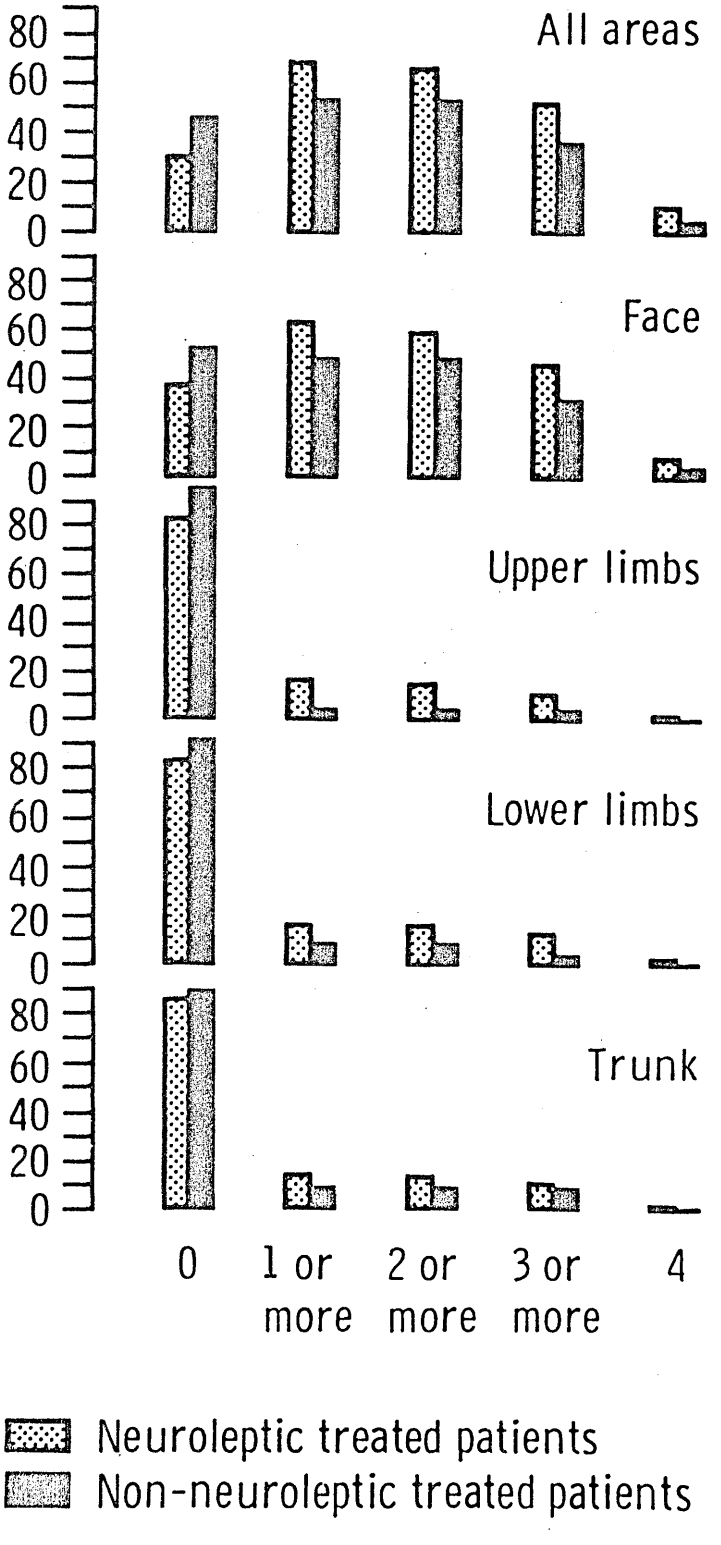
The mean total and regional scores for neuroleptic-treated and neuroleptic-free groups are illustrated in Fig 2:5:4. None of the differences between the groups attained statistical significance at the 5 % level, though there was a non-significant tendancy towards higher upper limb scores in the neuroleptic-treated group ($t = 1.93$, $df = 409$, $P < 0.1$).

5.2.3 MEAN NUMBER OF MOVEMENTS

As it is possible that one group might exhibit fewer movements of greater severity than the other, the mean number of movements was calculated for all regions together and face separately.

FIG 2:5:3

Prevalence (as percentage) of abnormality for increasing criteria of severity on A. I. M. S.



A. I.M.S. scores (means and standard errors)

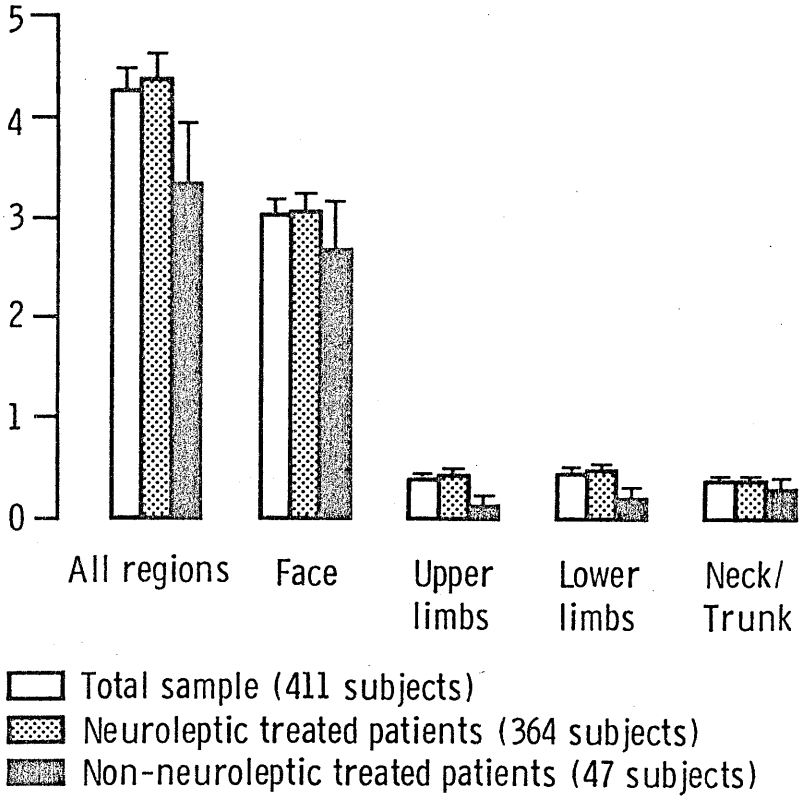
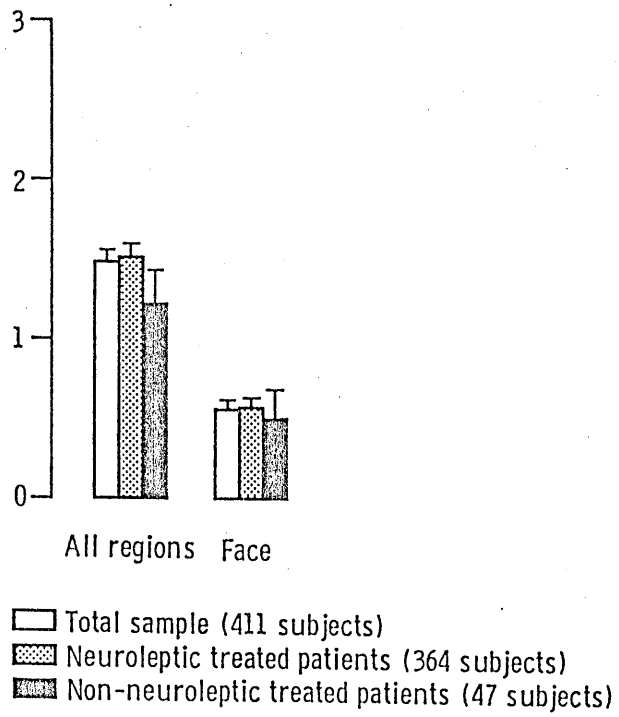


FIG 2:5:5

Mean number of movements rated 2 or more on A.I.M.S. (with standard errors)



(The corresponding value for the other separate body regions was too small to be of use). As Fig 2:5:5 shows, no significant differences emerged between the groups.

5.2.4 DISTRIBUTION OF MOVEMENT PATTERNS

To investigate possible differences in the distribution of abnormal movements between the groups, X^2 analysis was conducted on 2 x 2 contingency tables, those showing no pathological movements (0 and 1) being compared with those rating an involuntary movement in pathological degree (2 or more). This was performed for each of the 7 AIMS items.

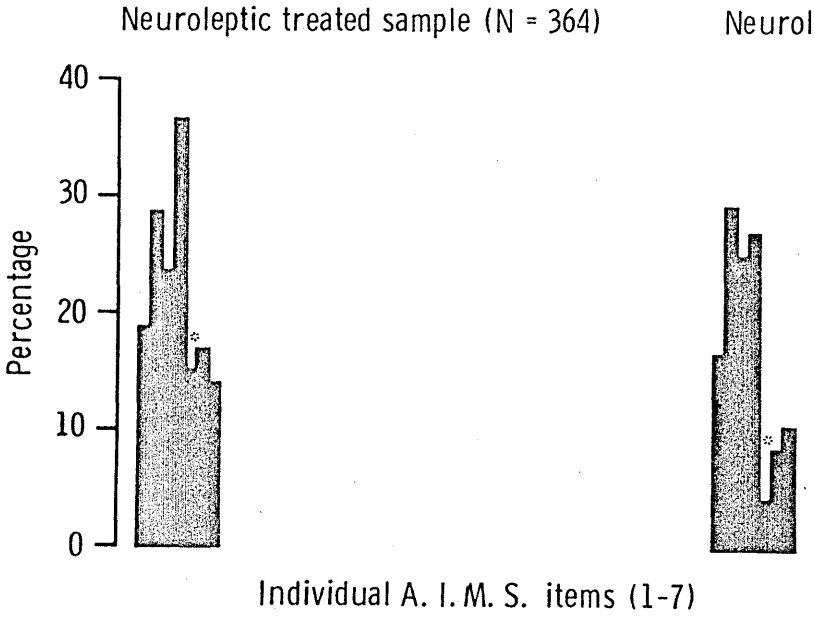
The distribution of abnormality for the neuroleptic-treated and free groups is shown in Fig 2:5:6. The only significant difference was that those exposed to neuroleptics exhibited upper limb abnormality more frequently than those in the neuroleptic-free group ($X^2 = 4.06$, $df = 1$, $P < 0.05$). When a similar comparison was performed taking severity into account, no significant differences emerged between the groups.

If those patients who attained a pathological rating (2 or more) in any one or more AIMS items are defined as the 'morbid' sample from the point of view of involuntary movements, 267 subjects can be identified. The distribution of abnormal movements within neuroleptic-treated and neuroleptic-free subgroups of this 'morbid' sample likewise showed no significant differences.

Thus, the distribution of abnormal movements within the total sample and also among 'morbid' patients considered separately was remarkably similar for those who had been exposed to neuroleptic

FIG 2:5:6

Distribution of pathological (2 or more) ratings on A. I. M. S. within total sample (N = 411)



* $p < 0.05$

medication and those who had not.

In summary, these results do not provide support for the view that in long-standing schizophrenic patients the concept of neuroleptic-caused involuntary movement disorder can be validated solely by the presence of a history of neuroleptic exposure. Involuntary movements with a predominantly orofacial distribution can be commonly found in patients such as these whose illnesses have remained unmodified by neuroleptic drugs.

However, in order to assess accurately a possible role for neuroleptics in relation to movement disorder, and to evaluate the relevance of involuntary movements to the schizophrenic illness per se, it is necessary to take account of the fact that the neuroleptic-free patients, with a mean age of 66.7 ($\pm$ SD 11.66 years), were considerably older than the neuroleptic-treated patients (mean age 56.9 $\pm$ SD 13.29 years).

5.3 THE ROLE OF TIME AND SEX

Total scores were used to evaluate the role of age and sex in the prevalence and severity of movement disorder in the total sample. A possible separate contribution from length of illness was sought with regard to severity. Although data on age using single symptom criteria are presented, this method was used mainly to explore the relationship with sex, in line with the published literature.

5.3.1 THE ROLE OF AGE AND SEX IN PREVALENCE

The relationship between an AIMS total score of 2 or more

and increasing age in the total sample and in females and males separately is shown in Fig 2:5:7, and the results of analysis by the maximum likelihood/log linear method, in TABLE 2:5:2.

As can be seen, a highly significant association between sex and age emerged, more of the females being older, and although a significant association between age and prevalence could be demonstrated no association between sex and prevalence could be established.

This lack of a role for sex in prevalence of abnormal movements in this sample is illustrated by the corrected F:M ratio for each age band. This is the ratio of the percentage of females to the percentage of males scoring 2 or more in each age group.

	CORRECTED F : M RATIO
< 40	1.19
40-49	0.93
50-59	1.2
60-69	0.89
> 70	1.08

This shows little apart from random variation.

Thus, while age was of importance in determining prevalence of abnormal movements in the present sample, sex per se could not be shown to be so. It is of interest, as Fig 2:5:7 shows, that although both sexes appear to plateau with age this occurred a decade earlier in the females than in the males.

FIG 2:5:7

Relationship of prevalence (AIMS total 2 or more) to age

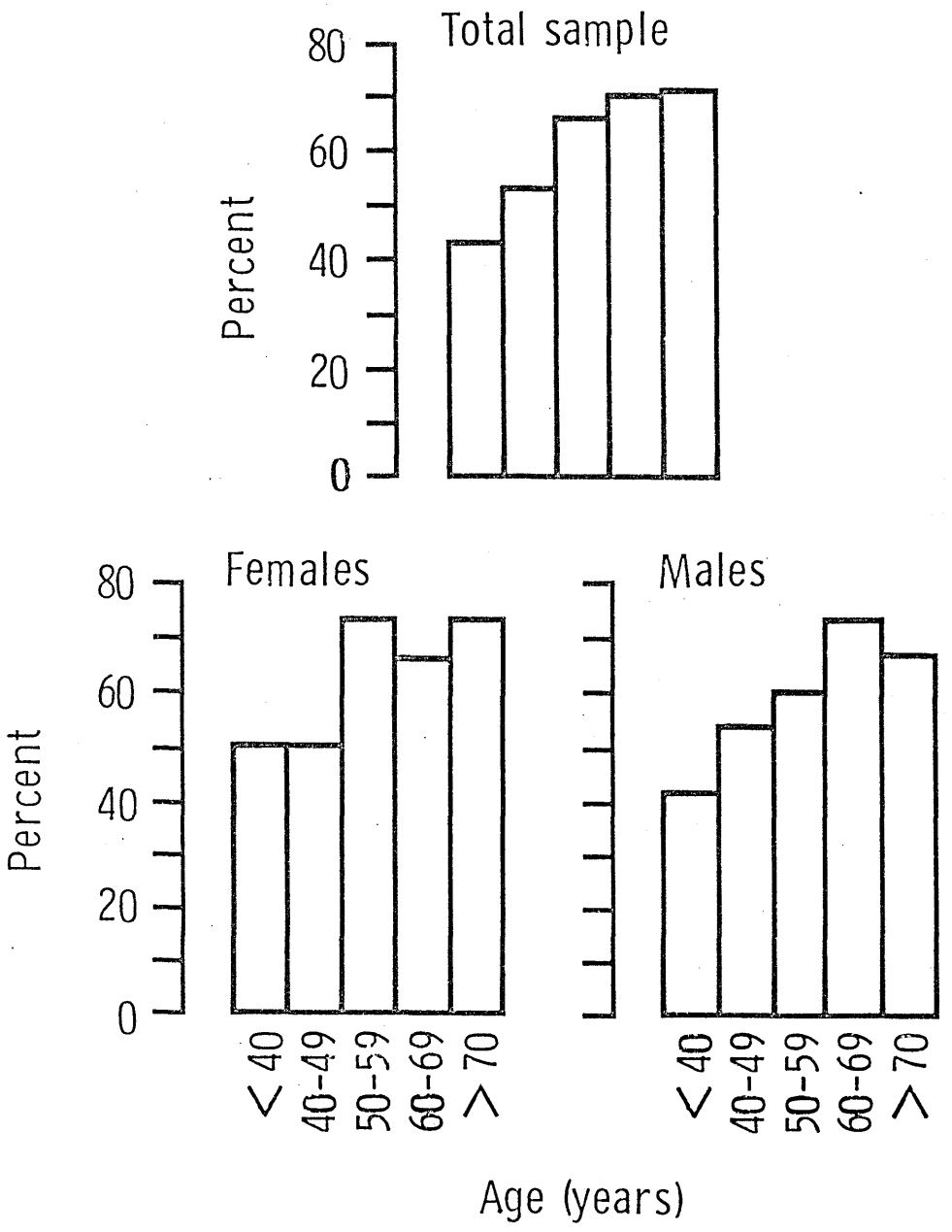


TABLE 2:5:2

ANALYSIS (MAXIMUM LIKELIHOOD/LOG LINEAR) OF THE RELATIONSHIP BETWEEN THE PREVALENCE OF MOVEMENT DISORDER, AGE AND SEX

EFFECT	D.F.	CHI-SQUARE	PROBABILITY
SEX	1	3.98	$p = 0.046$
AGE	4	70.71	$p < 0.0001$
PREVALENCE	1	37.5	$p < 0.0001$
SEX x AGE	4	35.06	$p < 0.0001$
SEX x PREVALENCE	1	0.26	$p = 0.61$
AGE x PREVALENCE	4	12.44	$p = 0.014$
SEX x AGE x PREVALENCE	4	3.05	$p = 0.55$

5.3.2 THE ROLE OF AGE, LENGTH OF ILLNESS AND SEX IN SEVERITY

In Part I it was noted that although age and length of illness were closely related, some variables remained significantly correlated with length of illness even when age had been partialled out. Thus, with regard to movement disorder, an attempt was made at this point to evaluate the effects of both these components of the passage of time.

Three arbitrary ranges of AIMS totals were defined to reflect the normal - mild/moderate - severe continuum. These were :

No abnormality

AIMS total $\leqslant 5$

AIMS total $\geqslant 6$

Two way ANOVA was used to assess differences in age and length of illness in each of these ranges in both sexes.

ANOVA with age as the dependent variable demonstrated significant main effects of both sex and AIMS total score ($F = 32.05$, $df = 1, 405$, $P < 0.0001$: $F = 5.78$, $df = 2, 405$, $P = 0.003$ respectively). Thus males were significantly younger than females in all categories and there was a significant (positive) relationship between higher AIMS totals and increasing age. The absence of an interaction between sex and AIMS totals in the ANOVA indicates the positive effects of age on these totals to be the same in both sexes.

ANOVA with length of illness as the dependent variable likewise showed significant main effects of sex and AIMS totals ($F = 14.46$, $df = 1,404$, $P<0.0002$: $F = 5.56$, $df = 2,404$, $P = 0.004$ respectively). Thus, males had significantly shorter lengths of illness than females,

and higher AIMS totals were associated with longer lengths of illness. Once again there was no sex/AIMS total interaction, demonstrating consistency of effect in both sexes. These results are summarised in TABLE 2:5:3.

Thus, significant effects of time were demonstrated, with differences emerging between the sexes, in that females were older and had longer lengths of illness. Such an analysis however, does not assess the relevance of that part of each component of time that is independent of the strong correlation between the two. In order to examine the effect of age independent of length of illness and vice versa, analysis of covariance (ANCOVA) was conducted for each time component with the effect of the other removed. The same groupings were used as for the ANOVA.

ANCOVA with age as the dependent variable and length of illness covaried again revealed the significant main effect of sex ($F = 17.26$, $df = 1, 405$, $P < 0.0001$). The corrected age values (i.e. the estimated age of the groups had they all the same lengths of illness) confirmed that the explanation of this lay in the males being significantly younger than the females in all groups (TABLE 2:5:4).

However, by removing length of illness from age by means of ANCOVA, the significant main effect of AIMS totals disappears ($F = 1.04$, $df = 2, 405$, N/S). There is once again no significant interaction term.

ANCOVA with length of illness as the dependent variable and age covaried revealed no significant main effects of either sex or AIMS totals ($F = 0.3$, $df = 1, 404$, N/S : $F = 0.83$, $df = 2, 404$,

TABLE 2:5:3

ANALYSIS OF VARIANCE: AGE AND LENGTH OF ILLNESS IN MALES AND FEMALES

AGE	NO ABNORMALITY	⩽ 5	⩾ 6
MALES	52.8	55.3	59.3
FEMALES	61.4	62.4	64.9

SEX $F = 32.05$ $df = 1,405$ $p < 0.0001$

AIMS $F = 5.78$ $df = 2,405$ $p = 0.003$

LENGTH OF ILLNESS	NO ABNORMALITY	⩽ 5	⩾ 6
MALES	27.2	29.3	32.2
FEMALES	32.6	32.4	35.4

SEX $F = 14.46$ $df = 1,404$ $p = 0.0002$

AIMS $F = 5.56$ $df = 2,404$ $p = 0.004$

TABLE 2:5:4

ANALYSIS OF COVARIANCE: AGE AND LENGTH OF ILLNESS IN MALES AND FEMALES

CORRECTED AGES	NO ABNORMALITY	⩽ 5	⩾ 6
MALES	56.6	57.2	58.6
FEMALES	60.3	61.5	61.3

SEX $F = 17.26$ $df = 1,405$ $p < 0.0001$

AIMS $F = 1.04$ $df = 2,405$ N/S

CORRECTED LENGTHS OF ILLNESS	NO ABNORMALITY	⩽ 5	⩾ 6
MALES	31	31.6	32
FEMALES	31.2	30.4	31.9

SEX $F = 0.3$ $df = 1,404$ N/S

AIMS $F = 0.83$ $df = 2,404$ N/S

N/S respectively) and no interaction. The corrected length of illness values (the estimated lengths of illness of the groups had they been of the same age) were comparable in all groups (TABLE 2:5:4).

Thus although time factors were of great importance with regard to AIMS total scores this study was unable to separate the interwoven effects of age and length of illness. Sex only appears to be of relevance in this sample insofar as females are older than males. Although females are older, both sexes have comparable lengths of illness, thus the women must have in general been admitted to long-term care at a later age than the men.

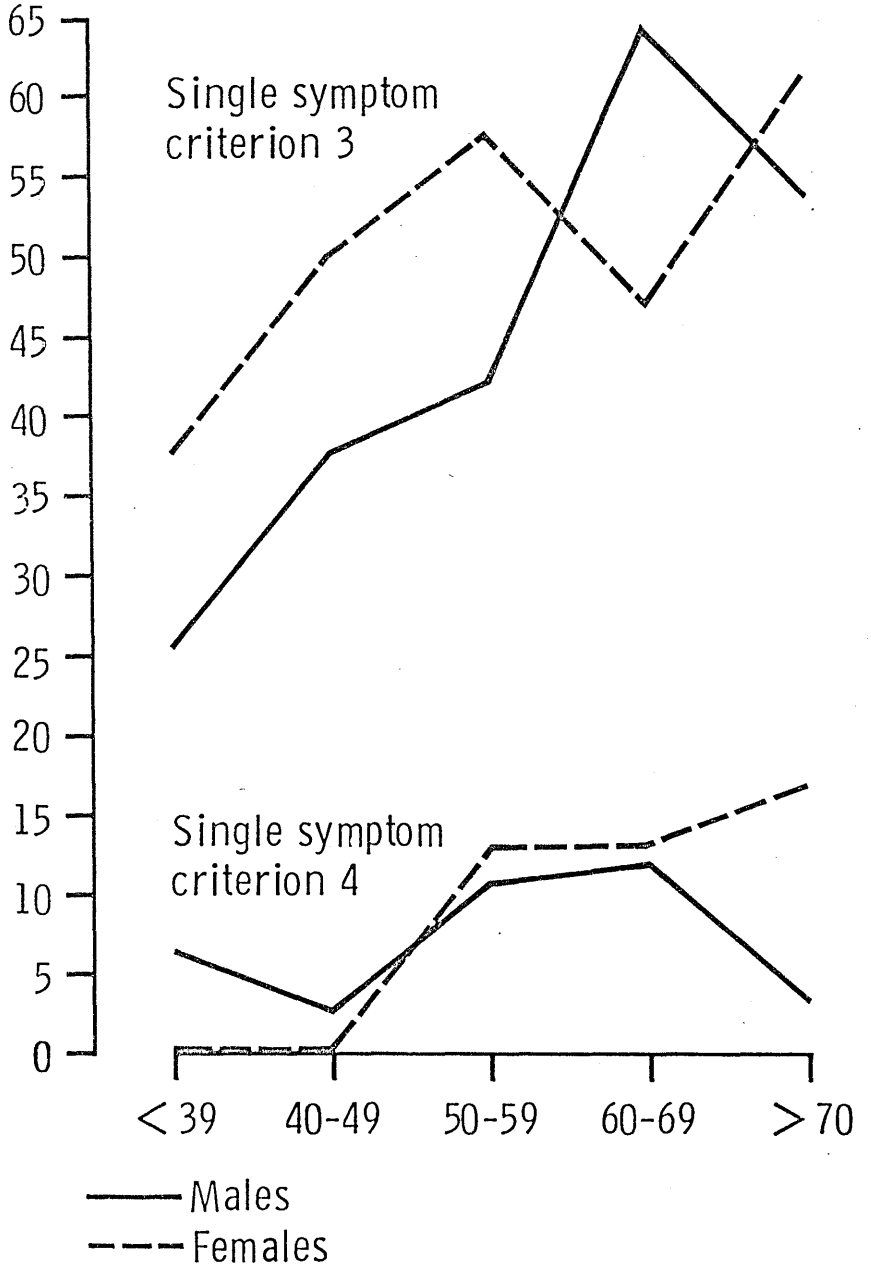
5.3.3 FURTHER EVALUATION OF THE ROLE OF SEX

These results assessing time and sex factors in relation to the presence of involuntary movement disorders have used AIMS total scores, arbitrarily divided, to determine correlations. However, it remains possible that subtle differences between the sexes may be masked by such a technique. It could be that with the passage of time the sexes may respond differentially in terms of the number and severity of the individual movements constituting the total AIMS scores.

Although it has been shown that in the present sample the cumulative effects of age/length of illness are inextricable, the question of potential but subtle differential sex effects was examined only in relation to age. This was to keep the analysis manageable, to maintain adequate numbers in comparison cells, and to make the present analysis comparable with the published literature. It is however accepted that this may present limitations in

FIG 2:5:8

AIMS: Prevalence by age at single symptom criterion of 4 and 3 in both sexes



interpreting the following data.

The prevalence of movement disorder using (a) a single symptom criterion of 4, and (b) one of 3, was compared for both sexes in five age bands. Fig 2:5:8 shows that females do have a significantly higher prevalence of at least a single rating of '4' compared to males ($X^2 = 9.98$, df = 4 , P = 0.04), but that this is due entirely to a higher prevalence in females over 70 years of age ($X^2 = 7.38$, df = 1 , P = 0.007). With a single symptom criterion of 3, there is again a highly significant overall difference between the sexes ($X^2 = 18.83$, df = 4 , $P < 0.001$). However, in this case the effect springs from an interaction between sex and prevalence in those over 60 years of age (Fig 2:5:8). This may represent a chance finding.

TABLE 2:5:5 shows the F:M ratio at increasing criteria of severity, and increasing age. The total sample and only those treated with neuroleptics are shown separately. The relatively small number of neuroleptic-free patients and their male predominance precluded a similar analysis in this group. As can be seen, there was a slight, but not significant nor exclusive female predominance throughout. Only at a single symptom criterion of 4 in the over 70s is this striking and this was found in both the total sample and those exposed to neuroleptics considered separately.

TABLES 2:5:6 and 2:5:7 show the results of the same analysis considering the AIMS facial items and limbs/trunk items separately. The difference in total scores persists on facial items, but there is no evidence of a similar excess of females scoring at least a single 4 in limbs/trunk regions. Indeed if anything, the opposite is

TABLE 2:5:5

F:M PREVALENCE RATIOS BY AGE AND INCREASING SINGLE SYMPTOM CRITERIA - ALL BODY AREAS

AGE	SEVERITY CRITERION	TOTAL SAMPLE MALES % RATING	TOTAL SAMPLE FEMALES % RATING	F:M	NEUROLEPTIC TREATED ONLY MALES % RATING	NEUROLEPTIC TREATED ONLY FEMALES % RATING	F:M
< 40	2	41.9	50	1.19	41.9	50	1.19
	3	25.8	37.5	1.45	25.8	37.5	1.45
	4	6.5	-	-	6.5	-	-
40-49	2	54.1	50	0.92	51.4	50	0.97
	3	40.5	50	1.23	38.9	50	1.29
	4	2.7	-	-	2.7	-	-
50-59	2	60.9	73.1	1.2	60.3	73.1	1.21
	3	42.2	57.7	1.37	42.2	57.7	1.37
	4	10.9	13.5	1.24	10.9	13.5	1.24
60-69	2	74.6	64.2	0.86	69.1	63.5	0.92
	3	64.2	47.2	0.73	57.9	47.2	0.82
	4	11.9	13.2	1.11	10.6	13.2	1.25
> 70	2	67.9	74.6	1.1	57.1	73.7	1.29
	3	53.6	61	1.14	43.5	60.3	1.39
	4	3.6	16.9	4.69	3.6	15.5	4.31

TABLE 2:5:6

F:M PREVALENCE RATIOS BY AGE AND INCREASING SINGLE SYMPTOM CRITERIA - FACE ONLY

AGE	SEVERITY CRITERION	TOTAL SAMPLE MALES % RATING	TOTAL SAMPLE FEMALES % RATING	F:M	NEUROLEPTIC TREATED ONLY MALES % RATING	NEUROLEPTIC TREATED ONLY FEMALES % RATING	F:M
< 40	2	32.3	37.5	1.16	32.3	37.5	1.16
	3	16.1	37.5	2.33	16.1	37.5	2.33
	4	3.2	-	-	3.2	-	-
40-49	2	48.6	41.7	0.86	45.7	41.7	0.91
	3	29.7	33.3	1.12	29.7	33.3	1.12
	4	2.7	-	-	2.7	-	-
50-59	2	59.4	55.8	0.94	58.7	55.8	0.95
	3	34.4	44.2	1.28	34.4	44.2	1.28
	4	6.3	11.5	1.83	6.3	11.5	1.83
60-69	2	68.7	60.4	0.88	57.1	59.6	1.04
	3	58.2	47.2	0.81	47.2	47.2	1
	4	9	9.4	1.04	7.6	9.4	1.24
> 70	2	67.9	66.1	0.97	67.9	65.5	0.96
	3	53.6	55.9	1.04	53.6	55.2	1.03
	4	3.6	15.3	4.25	3.6	13.8	3.83

TABLE 2:5:7

F:M PREVALENCE RATIOS BY AGE AND INCREASING SINGLE SYMPTOM CRITERIA - UPPER/LOWER LIMBS AND TRUNK

AGE	SEVERITY CRITERION	TOTAL SAMPLE MALE % RATING	TOTAL SAMPLE FEMALE % RATING	F:M	NEUROLEPTIC TREATED ONLY MALE % RATING	NEUROLEPTIC TREATED ONLY FEMALE % RATING	F:M
< 40	2	29	37.5	1.29	29	37.5	1.29
	3	19.4	-	-	19.4	-	-
	4	6.5	-	-	6.5	-	-
40-49	2	21.6	25	1.16	19.4	25	1.29
	3	18.9	25	1.32	16.7	25	1.5
	4	-	-	-	-	-	-
50-59	2	34.4	55.8	1.62	33.3	55.8	1.67
	3	26.6	42.3	1.59	26.6	42.3	1.59
	4	7.8	3.8	0.49	7.8	3.8	0.49
60-69	2	26.9	32.1	1.19	19.7	32.1	1.63
	3	22.4	24.5	1.09	16.1	24.5	1.52
	4	4.5	7.5	1.67	4.5	7.5	1.67
> 70	2	25	33.9	1.36	25	31.6	1.26
	3	17.9	27.1	1.51	17.9	25.9	1.45
	4	3.6	1.7	0.47	3.6	1.7	0.47

demonstrated.

It would seem reasonable to postulate that if females are more likely to rate at least one severe rating of 4 when over 70 years of age, some difference in mean scores, hidden in the earlier ANOVA/ANCOVA may be detectable on closer analysis. Fig 2:5:9 shows that this is not the case. The sexes do not significantly differ in their mean AIMS totals at any age band, a finding which applies to the total sample as well as to the neuroleptic-treated patients alone (Fig 2:5:10). While Fig 2:5:10 also shows the neuroleptic-free females to have lower means than their male counterparts, the small number of these women (7) makes this a doubtful finding.

It is still possible that the sexes may differ on the mean number of abnormal movements recorded with increasing age. However, Fig 2:5:11 shows that no such difference could be detected.

Thus, while females over 70 years of age show approximately 4 - 5 times the prevalence of severe abnormality than males when the single symptom criterion method is used, this is only found in ratings of facial movements, and is not reflected in this sample in corresponding differences between the sexes in AIMS mean scores or mean number of movements rated positively (2 or more).

FIG 2:5:9

AIMS mean totals as a function of age and sex:total:sample

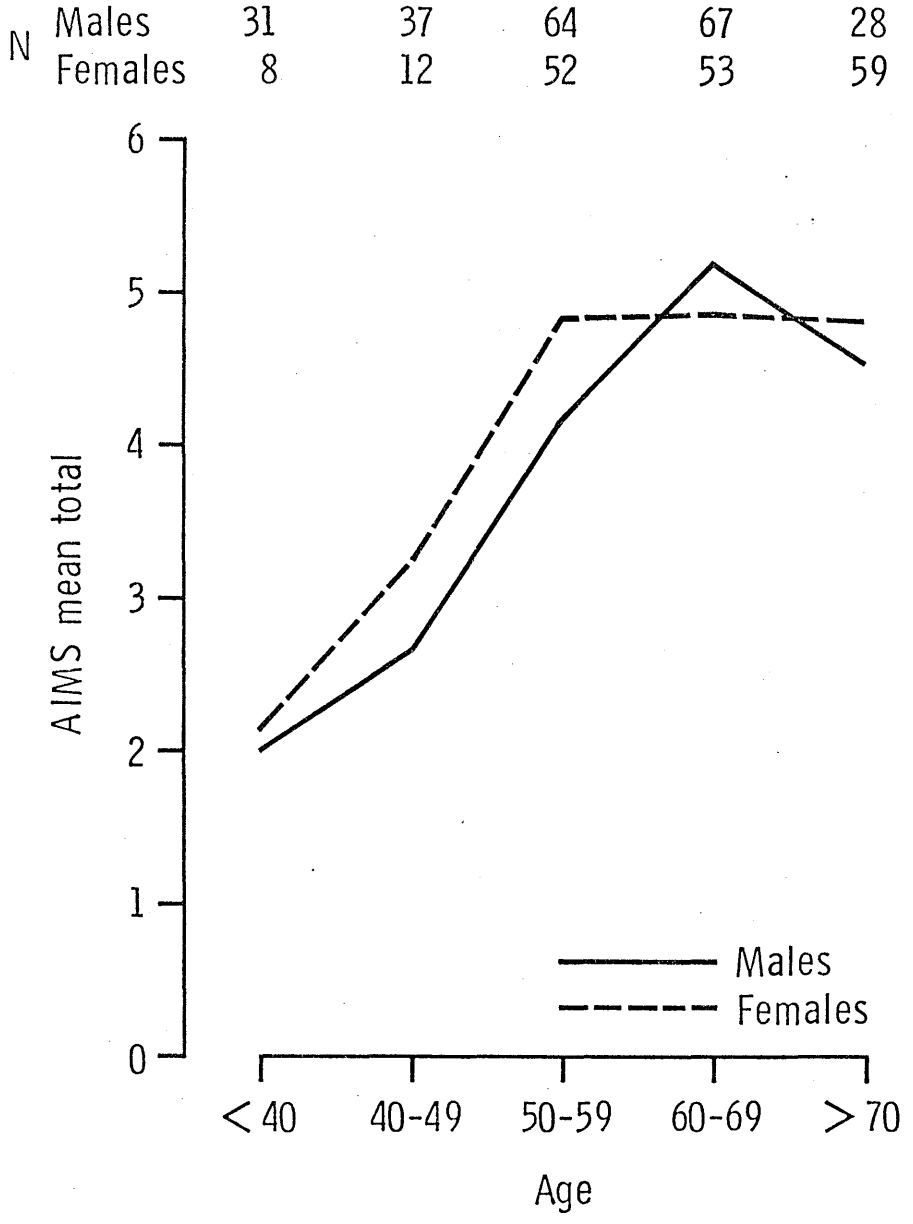


FIG 2:5:10

AIMS mean totals as a function of age and sex

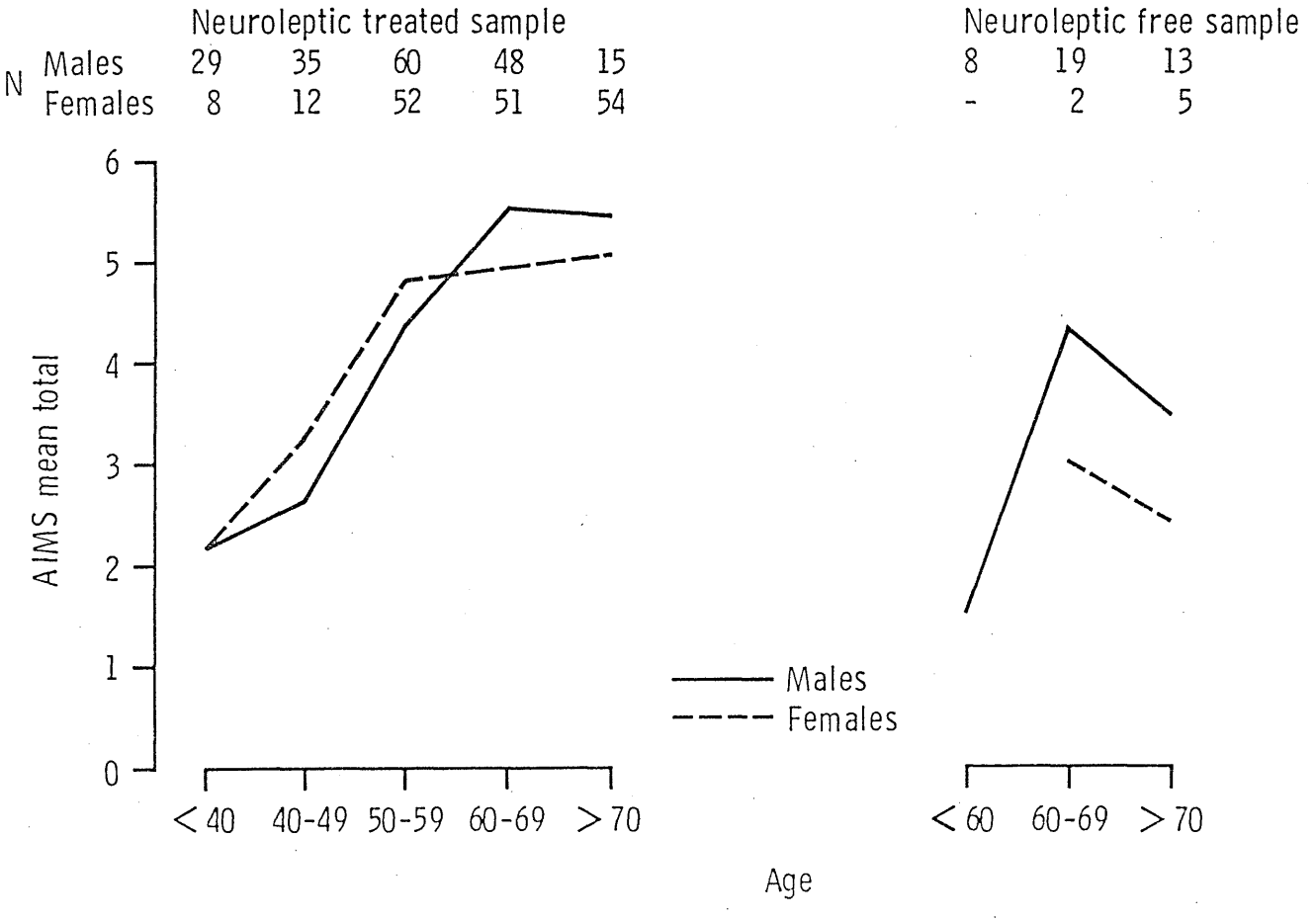
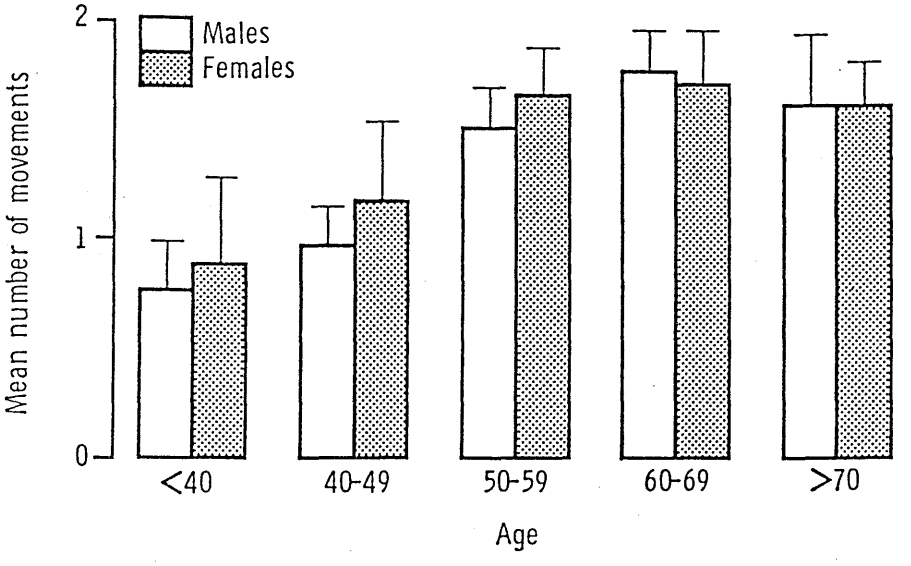


FIG 2:5:11

AIMS

Mean number of movements (± SEM) by age and sex - total sample



5.4 THE ROLE OF NEUROLEPTIC MEDICATION PAST AND PRESENT

By combining information gathered after the first and second examinations, six categories of neuroleptic status were devised. With reference to these categories, neuroleptic treatment "in the past" means 'at any time up to the second examination'.

The categories were :

1)	Never on neuroleptics at any time.	1,2,3:	Those not receiving neuroleptics when examined for the second time. i.e.'currently' OFF.
2)	'Some'* neuroleptic exposure in the past but not receiving them when examined for the second time.		
3)	'Much'* neuroleptic exposure in the past but not receiving them when examined for the second time.		
4)	Never on neuroleptics in the past but receiving them when examined for the second time.	4,5,6:	Those receiving neuroleptics when examined for the second time. i.e.'currently' ON
5)	'Some'* neuroleptics in the past and receiving them when examined for the second time.		
6)	'Much'* neuroleptic exposure in the past and receiving them when examined for the second time.		

* For definitions of 'some' and 'much' see TABLE 1:3:3 Part 1.

Categories 2 and 3 represent patients whose neuroleptics have been discontinued at some point. Owing to the quality of the information available in the drug records no mean duration of time that they had been off these drugs could be calculated. For some, drug withdrawal may have occurred at some point between examinations while for others, it could have taken place many years ago. Some may have had depot drugs stopped while others may only have been on oral preparations. Category 4 represents the small but important group who were commenced on neuroleptics for the first time between the two examinations. Again this may have been oral or depot in type.

Categories 5 and 6 are those with continuity of neuroleptic exposure. This does not mean however that account can be taken of minor changes in drug regime that may have been prescribed between the two examinations.

Such a division is not highly specific. It has been adopted in order to allow a general evaluation of the role of neuroleptic administration at the time of the examination and also of past neuroleptic exposure. In addition, the importance of the degree of past exposure to these preparations could be assessed.

The patients represented in these categories of neuroleptic status also differed in terms of mean ages and lengths of illness. The mean ages and lengths of illness are shown in TABLE 2:5:8. The differences between the groups are highly significant (AGE : $F = 20.98$, $df = 5, 405$, $P < 0.0001$; LENGTH OF ILLNESS: $F = 12.28$, $df = 5, 405$, $P < 0.0001$).

It was therefore necessary to account for these differences before assessing the relationships between neuroleptic status and

TABLE 2:5:8

MEAN AGE AND LENGTH OF ILLNESS OF SUBJECTS IN EACH CATEGORY OF NEUROLEPTIC STATUS

NEUROLEPTIC CATEGORY	MEAN AGE (± S.D.)	MEAN LENGTH OF ILLNESS (± S.D.) IN YRS
1	68.18 (11.82)	36.5 (10.3)
2	67.13 (11.54)	37.15 (9)
3	64.91 (12.4)	35.87 (9.85)
4	58.4 (19.57)	35.8 (16.33)
5	60.97 (10.66)	32.01 (9.39)
6	53.76 (12)	28.03 (10.1)

involuntary movement disorder. This was attempted by arbitrarily adopting an age range which was both narrow enough to militate against age effects on AIMS scores yet broad enough to include representatives of each neuroleptic status category. The age range thus adopted was 58 - 82 years. While considering only subjects within this constant age band dramatically reduced the very highly significant age differences in the different categories of neuroleptic status, unfortunately it did not dispel them completely ($F = 4.29$, $df = 5,405$, $P < 0.001$). In particular, those in category 6 remained younger than the rest. However, narrowing the age band further would have considerably reduced the numbers of subjects in each category and would have eliminated the small but important group in category 4. Since the relationship of age to movement disorder is a positive one, the major effect of the inequality of age in categories of neuroleptic status is likely to be that of somewhat diminishing the comparative abnormality of those in category 6, which will require to be considered in interpretation of the findings.

Thus, subsequent analyses were conducted in the knowledge that the significant relationships between age and neuroleptic status as delineated had been reduced greatly but not completely abolished. On the other hand, the significant overall differences between neuroleptic categories and lengths of illness disappeared when considering only the age band 58 - 82 years. With the above proviso therefore, those being studied within this age band will be referred to as the 'age - controlled' group.

Frequency distribution histograms were obtained of the total

scores achieved by patients in each of the categories of neuroleptic status. Using the basic 0 - 1 normality cut-off, the prevalence of movement disorder was compared across categories. The statistical technique employed was unified analysis of variance by ranks.

Fig 2:5:12 illustrates the findings with regard to the role of current and previous neuroleptic exposure in the prevalence of movement disorder in the age - controlled group of the total study sample. The top half of the diagram represents the prevalences in each of the six categories of neuroleptic status, while the bottom half shows the prevalence considering current (bottom left) and past (bottom right) neuroleptic exposure.

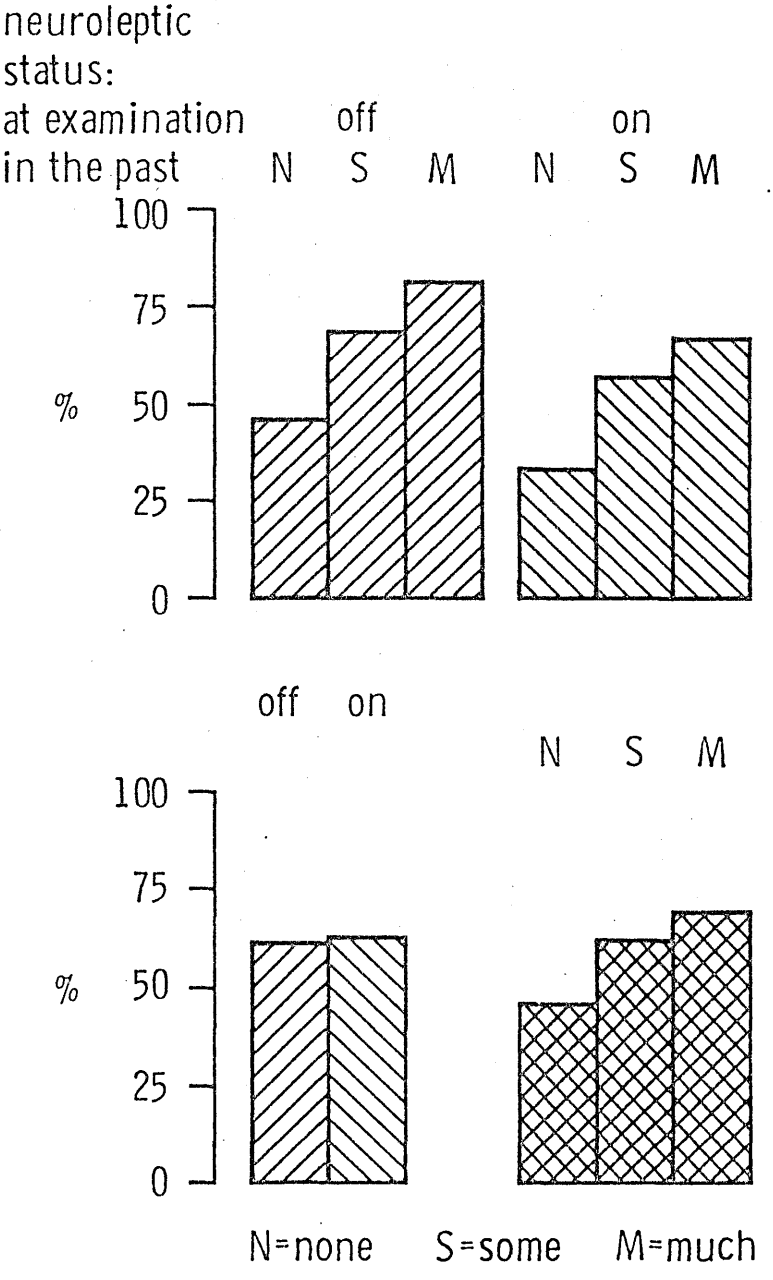
Overall, there was a non-significant relationship between AIMS abnormality and categories of neuroleptic status separately ($H = 9.56$, $df = 5$, $P = 0.088$). Likewise, there was no significant effect of receiving neuroleptics at the time of the AIMS assessment (Fig 2:5:12 bottom left) - i.e. of 'current' neuroleptic status (z - value $= 0.17$, N/S).

There was a highly significant relationship between the presence of abnormality on the AIMS and categories representing past neuroleptic exposure (Fig 2:5:12 bottom right). A progressive and significant increase was found in the prevalence of movement disorder with increasing past neuroleptic exposure ('none' v 'some' v 'much' : z - value $= 2.54$, $P = 0.011$).

The base-line of involuntary movement disorder was very high in this population. Of those never exposed to neuroleptics at any time 46.1 % achieved AIMS totals of 2 or more. Despite this, the effects of past neuroleptics were striking. Although there was a tendancy for

FIG 2:5:12

AIMS: prevalence of abnormality (total 2 or more) in relation to neuroleptic exposure



more of those heavily treated in the past (groups 3 and 6) to rate abnormality than the others combined (groups 1, 2, 4, 5) (z - value = 1.86 , $P = 0.06$), the major difference lay between those never exposed to neuroleptics in the past (categories 1 and 4) and those who had received these drugs regardless of degree (categories 2, 3, 5, 6). As Fig 2:5:12 demonstrates, while 45.2 % of those never exposed in the past had abnormality, the corresponding figure in categories representing past exposure was 66.1 % (z - value = 2.5 , $P = 0.012$).

There was no interaction between past neuroleptic exposure and 'current' neuroleptic administration.

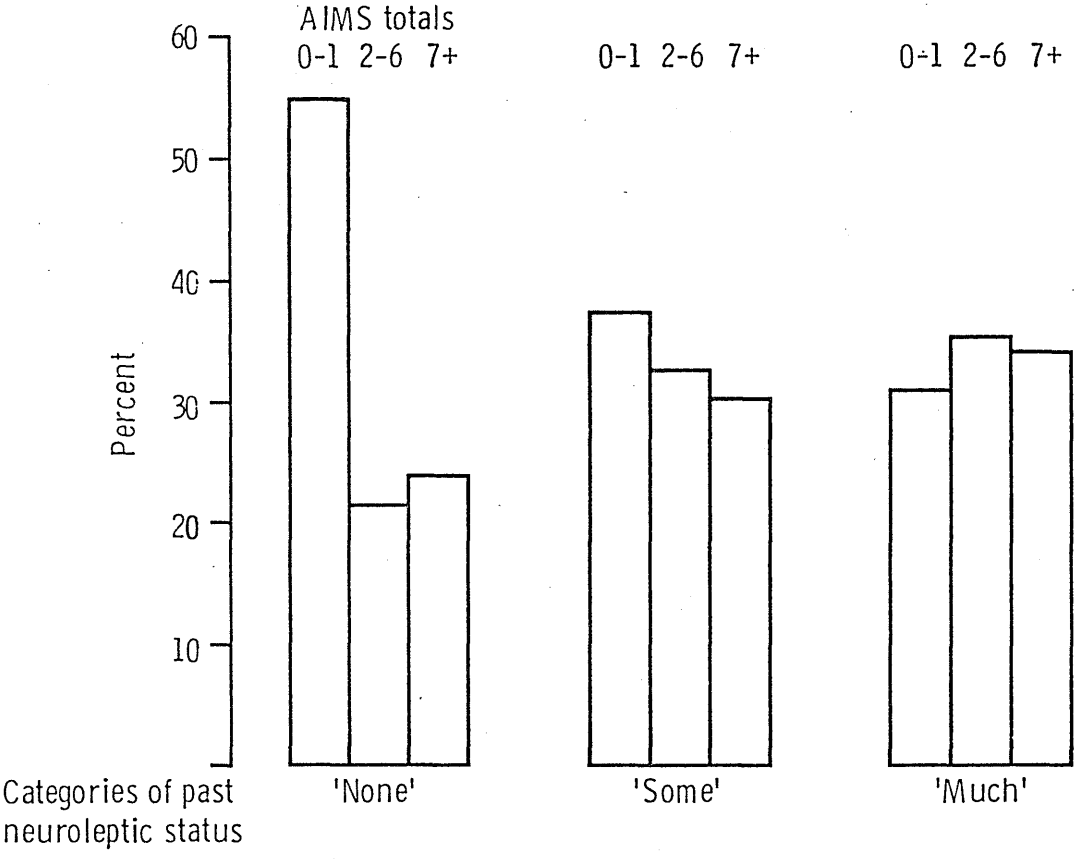
By arbitrarily dividing the AIMS totals into three bands, it was possible to assess the role of past exposure with regard to severity of movement disorder. AIMS totals were divided into the ranges 0 - 1, 2 - 6 and 7 +. The relationship between increasing AIMS totals and past neuroleptic exposure is shown in Fig 2:5:13.

Using these divisions, there was a positive relationship between neuroleptic exposure and severity of movement disorder (z - value = 2.20 , $P = 0.026$). There was a non-significant trend towards more severe movement disorders in those heavily treated in the past (categores 3 and 6) compared to the rest (z - value = 1.66 , $P = 0.094$), but the major contribution to this overall relationship came from significantly more severe movement disorder in those exposed to neuroleptics than was found in those never treated (z - value = 2.11 , $P = 0.032$).

This general classification, in addition, allowed consideration of what happened when neuroleptics were stopped in this population

FIG 2:5:13

Relationship between increasing AIMS totals (severity) and past neuroleptic exposure



and what was the effect of recently commencing them. The top half of Fig 2:5:12 shows the prevalence of abnormality in each category of neuroleptic status. By considering only the three left hand categories (i.e. 1 - 3) it is possible to get some impression of the effect of discontinuing neuroleptics, as categories 2 and 3 represent patients whose drugs had been stopped at some time.

There was a significant linear relationship between the prevalence of movement disorder and these first three categories of neuroleptic status (z - value = 2.65, P = 0.008). This was due largely to a significantly higher prevalence in those exposed to neuroleptics (categories 2 and 3) compared to those in category 1 who had never been exposed (z - value = 2.54 , P = 0.01). The prevalence in those heavily treated but then discontinued (category 3) was only slightly higher than that found in the 'never' and lightly treated subjects together (z - value = 1.77 , P = 0.072). There was, in addition, a significant relationship between severity and having had neuroleptics stopped. Those in categories 2 and 3 had more severe movement disorder than those in category 1 (z - value = 2.10 , P = 0.034).

Analysis of the effects of having had neuroleptics recently commenced - i.e. at some time in the 2 years between examinations - is less reliable than the above results because of the small number of patients to whom this applied (those in category 4). Nonetheless, it can be said that those recently commenced did not differ significantly in prevalence from those who had never been exposed at any time ($X^2 = 0.43$, df = 1 , N/S). Severity could not be evaluated. There was a tendancy to a greater prevalence of abnormality

of greater severity in those consistently treated (categories 5 and 6) than in the recently treated patients, but these associations did not achieve statistical significance, probably in view of the discrepant numbers in the comparison cells.

5.5 THE ROLE OF ANTICHOLINERGIC MEDICATION

In order to investigate the role of anticholinergic medication in involuntary movement disorder, two types of analysis were conducted. The first was evaluation by analysis of trends, (i.e. unified analysis of variance by ranks) of prevalence and severity based on categories of medication status similar to those produced previously for neuroleptics. The second was by a maximum likelihood/log linear analysis of prevalence.

It was not appropriate to divide the sample for the first of these analyses by current neuroleptic status as the small number of subjects on anticholinergics but not having neuroleptics would be receiving treatment in exceptional circumstances - e.g. coincidental Parkinson's Disease. Only categories of past neuroleptic exposure were maintained.

The sample was divided along the lines of 'none', 'some' and 'much' past neuroleptic exposure as before and each category then subdivided according to whether or not patients were receiving anticholinergics when examined. This subdivision made no reference to the amount or duration of anticholinergic exposure, only to its presence or absence at that point in time. There were therefore six trend/contrast groupings.

No patient with a history of never being exposed to neuroleptics

had received anticholinergics. As analysis of trends is inappropriate when one cell comprises entirely zeros, an arbitrary value of '1' was inserted into this cell for all comparisons. Prevalence analysis was conducted using a low (0 - 1) and a higher (0 - 2) normality cut-off, and severity using the three arbitrary divisions of AIMS total scores defined earlier (p 172).

No significant relationships could be established between anticholinergic medication and either the prevalence or the severity of involuntary movement disorder. This was true for all patients together, for males and females separately and for a low or a higher cut-off for normality with AIMS total scores.

The maximum likelihood/log linear analysis, which takes account of the effects of the individual components of the analysis (in this case age, sex, past neuroleptic exposure, anticholinergic treatment and movement disorder), gave a similar result. Movement disorder was significantly related to past neuroleptic exposure ($X^2 = 6.81$, df = 2 , P = 0.03) but not to treatment with anticholinergics ($X^2 = 0.02$, df = 1 , P = 0.9).

5.6 RELATIONSHIPS BETWEEN MOVEMENT DISORDER AND ITEMS OF RECORDED INFORMATION

Relationships were sought between the presence of spontaneous involuntary movement disorder and the major items of Recorded Information described in Part I. These items, and the groupings of patients on the basis of these items, are shown in TABLE 2:5:9.

Age and length of illness, previously considered separately, were shown to be of importance with regard to AIMS scores. Hence

TABLE 2:5:9

RECORDED INFORMATION AND MOVEMENT DISORDERS: ORGANISATION OF DATA FOR ANALYSIS

RECORDED INFORMATION	COMPARISON CATEGORIES		
FAMILY HISTORY OF SCHIZOPHRENIA	DEFINITELY ABSENT	DOUBTFUL	DEFINITELY PRESENT
HISTORY OF BIRTH TRAUMA/ HEAD INJURY	PRESENT		ABSENT
FITS	PRESENT		ABSENT
PAST ACADEMIC RECORD	ABOVE AVERAGE ('SUPERIOR')	AVERAGE	BELOW AVERAGE ('BACKWARD')
LEUCOTOMY	YES		NO
HISTORY OF EXPOSURE TO INSULIN COMA	'NONE'	'SOME'	'MUCH'
HISTORY OF EXPOSURE TO E.C.T.	'NONE'	'SOME'	'MUCH'

analyses were conducted only on subjects within the 'age-controlled' group. In accounting for the effects of neuroleptic drugs, 'current' status, shown to be irrelevant to AIMS totals, was disregarded, with only categories of past neuroleptic status being retained.

For purposes of this analysis, the data were arranged as follows. Within the 'age-controlled' sample, frequency distributions of AIMS totals were determined under each of the sub-headings of Recorded Information items - e.g. 'present'/'absent' : 'Yes'/'No' etc. These cells were then further divided according to past neuroleptic status - i.e. 'none', 'some', 'much'. Thus, for Recorded Information items broken down three ways (e.g. family history of schizophrenia) nine separate sub-divisions of the 'age-controlled' sample were generated. For those items broken down two ways, six sub-divisions for comparison were produced.

In the initial search for relationships between movement disorder and items of Recorded Information, the AIMS total cut-off for normality defined previously (0 - 1) was adopted. Statistical evaluation was by unified analysis of variance by ranks.

The relationships between these additional items of Recorded Information and involuntary movements using the 0 - 1 cut-off are shown in TABLE 2:5:10. With the highly significant effects of past neuroleptics accounted for, no independent relationships between these items and movement disorder could be established. A significant interaction term emerged between past neuroleptic and past insulin coma treatment, though this is an artifact of small numbers in those categories of patients who had received 'much'

TABLE 2:5:10

AIMS DATA: ANALYSIS OF RELATIONSHIPS BETWEEN MOVEMENT DISORDER AND ITEMS OF RECORDED INFORMATION AND ASSESSED ABNORMALITY (NORMALITY CUT-OFF 0-1)

	VARIABLES	NO. OF TREND/CONTRAST CATEGORIES (df = N-1)	UNIFIED ANALYSIS OF VARIANCE BY RANKS: OVERALL ANALYSIS H-VALUE	OVERALL ANALYSIS SIGNIFICANCE	RELATIONSHIP WITH AIMS ABNORMALITY Z-VALUE	RELATIONSHIP WITH AIMS ABNORMALITY SIGNIFICANCE	INTERACTION BETWEEN INDEPENDENT VARIABLES Z-VALUE	INTERACTION BETWEEN INDEPENDENT VARIABLES SIGNIFICANCE
RECORDED INFORMATION	FAMILY HISTORY	9	15.4	$p = 0.05$	0.56	N/S	1.25	$p = 0.2$
	BIRTH TRAUMA/HEAD INJURY	6	9.05	$p = 0.11$	0.33	N/S	0.7	N/S
	FITS	6	10.03	$p = 0.074$	0.95	N/S	1.82	$p = 0.066$
	PAST ACADEMIC RECORD	9	18.19	$p = 0.02$	1.22	$p = 0.22$	0.79	N/S
	LEUCOTOMY	6	18.47	$p < 0.003$	0.05	N/S	0.96	N/S
	INSULIN COMA	9	10.99	$p = 0.2$	0.29	N/S	2.21	$p = 0.026$
	ELECTROCONVULSIVE THERAPY	9	11.92	$p = 0.15$	0.65	N/S	1.39	$p = 0.16$
ASSESSED ABNORMALITIES	POSITIVE FEATURES OF THE MENTAL STATE	9	13.78	$p < 0.09$	0.38	N/S	0.36	N/S
	NEGATIVE FEATURES OF THE MENTAL STATE	9	22.81	$p = 0.004$	2.67	$p < 0.008$*	0.14	N/S
	COGNITIVE PERFORMANCE	9	13.58	$p = 0.093$	1.00	$p = 0.32$	0.16	N/S
		6	11.16	$p = 0.048$	2.09	$p < 0.04$+	1.4	$p = 0.16$
	BEHAVIOURAL PERFORMANCE	9	29.13	$p = 0.0005$	3.01	$p < 0.004$+	0.59	N/S

* POSITIVE RELATIONSHIP

\+ NEGATIVE RELATIONSHIP

N/S = $p > 0.5$

insulin. Of the nine such patients, only one had no movement disorder, and this subject was in the middle (i.e. 'some') category of past neuroleptic treatment. A non-significant trend towards an interaction between past neuroleptics and a history of fits is similarly artifactual.

5.7 RELATIONSHIPS BETWEEN MOVEMENT DISORDER AND OTHER ITEMS OF ASSESSED ABNORMALITY

Relationships were sought between the presence of involuntary movements and those other abnormalities assessed at examination - namely the 'positive' and 'negative' features of the mental state (Krawiecka Scale), cognitive performance (Withers and Hinton battery) and overall behavioural performance (Current Behavioural Schedule).

For each of the four items of assessed abnormality, the 'age - controlled' sample was arbitrarily divided into three groups on the basis of the distribution histograms shown in Part I. The divisions were chosen to allow for roughly equal numbers in each group. The ranges selected were :

'Positive' features of the Mental State (Krawiecka Scale)

0 - 1 ; 2 - 5 ; 6 - 15

'Negative' features of the Mental State (Krawiecka Scale)

0 - 1 ; 2 - 3 ; 4 - 8

Cognitive Performance (Withers and Hinton battery)

0 -20 ; 21 - 60 ; 61 - 107

Behavioural Ability (Current Behavioural Schedule)

0 -30 ; 31 - 40 ; 41 - 50

For each Assessed Abnormality variable, the subjects in these three arbitrary groups were then sub-divided on the basis of their history of past exposure to neuroleptic medication ('none', 'some', 'much'). There were thus nine sub-divisions for each variable. Frequency distributions of AIMS totals within these sub-divisions were determined for each Assessed Abnormality variable in turn. Statistical evaluation was by unified analysis of variance by ranks, comparing those with no abnormality (AIMS totals 0 - 1) with those having higher scores.

The results are illustrated in Figs 2:5:14 to 2:5:17. The lay-out of these is as for Fig 2:5:12. The top half of each diagram represents the prevalence in each category of past neuroleptic status for each range of scores adopted for the Assessed Abnormality variables. Bottom left is the past neuroleptic effect and bottom right the independent relationship between movement disorder and the variable under consideration. The statistical analysis is summarised in TABLE 2:5:10.

Accounting for the highly significant effect of past neuroleptics, there was no significant independent relationship of AIMS abnormality to 'positive' features of the mental state - either overall or with any comparisons between the different ranges of scores of 'positive' features defined above.

There was a highly significant association between the presence of abnormal movements and 'negative' features in the mental state. The major contribution to this relationship came from the much greater prevalence of movement disorder in those scoring 2 or greater for 'negative' features than in those with a 'negative'

FIG 2:5:14

AIMS: prevalence of abnormality (total 2 or more) in relation to positive mental state features

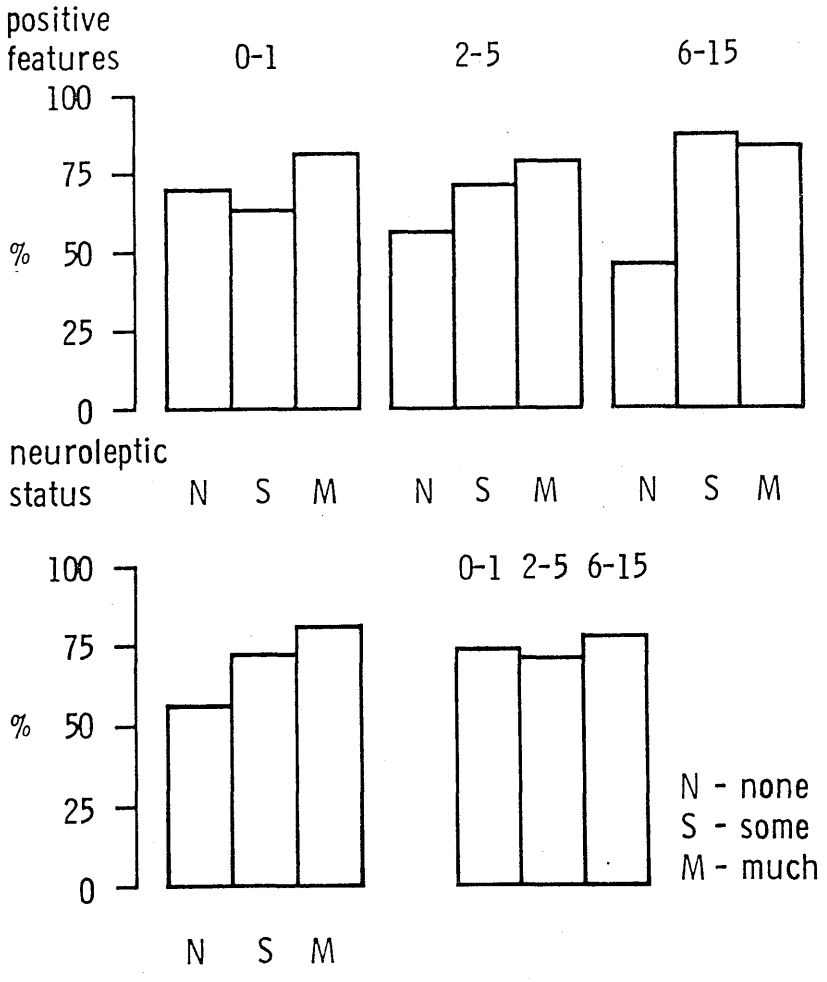


FIG 2:5:15

AIMS: prevalence of abnormality (total 2 or more) in relation to negative mental state features

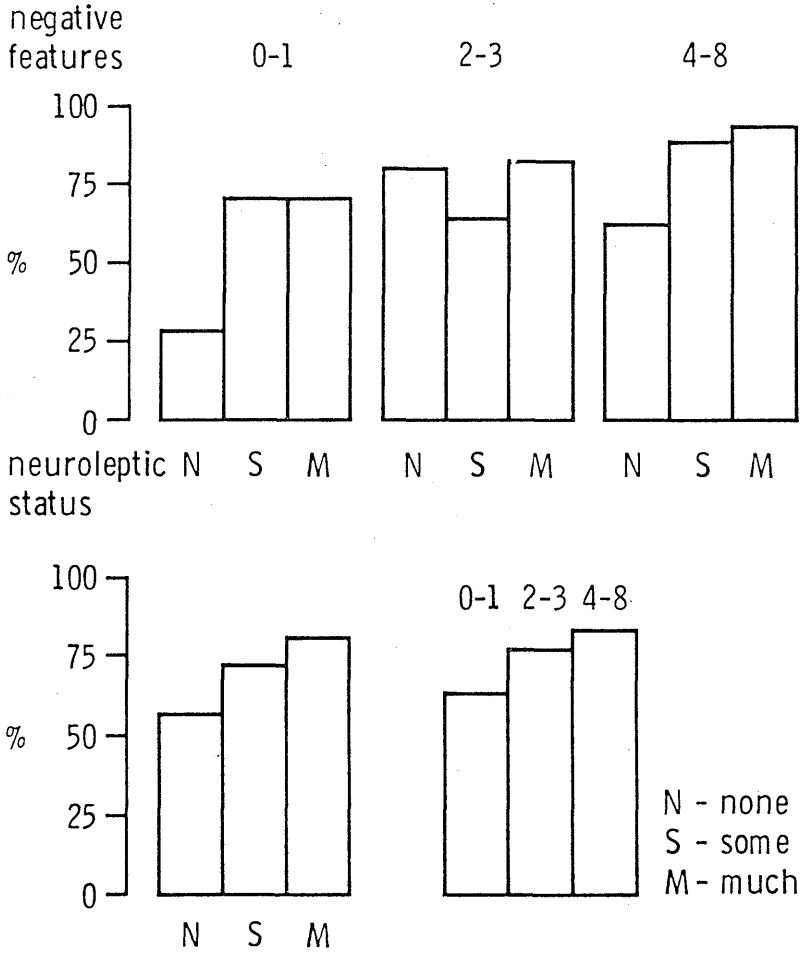


FIG 2:5:16

AIMS: prevalence of abnormality (total 2 or more) in relation to cognitive performance

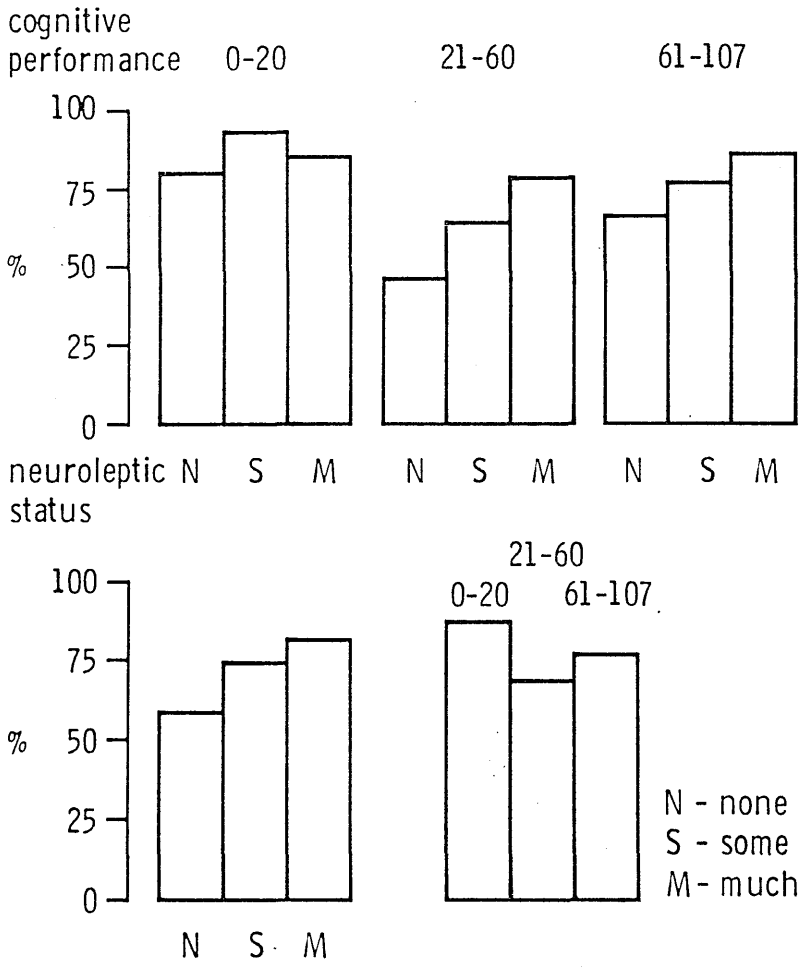
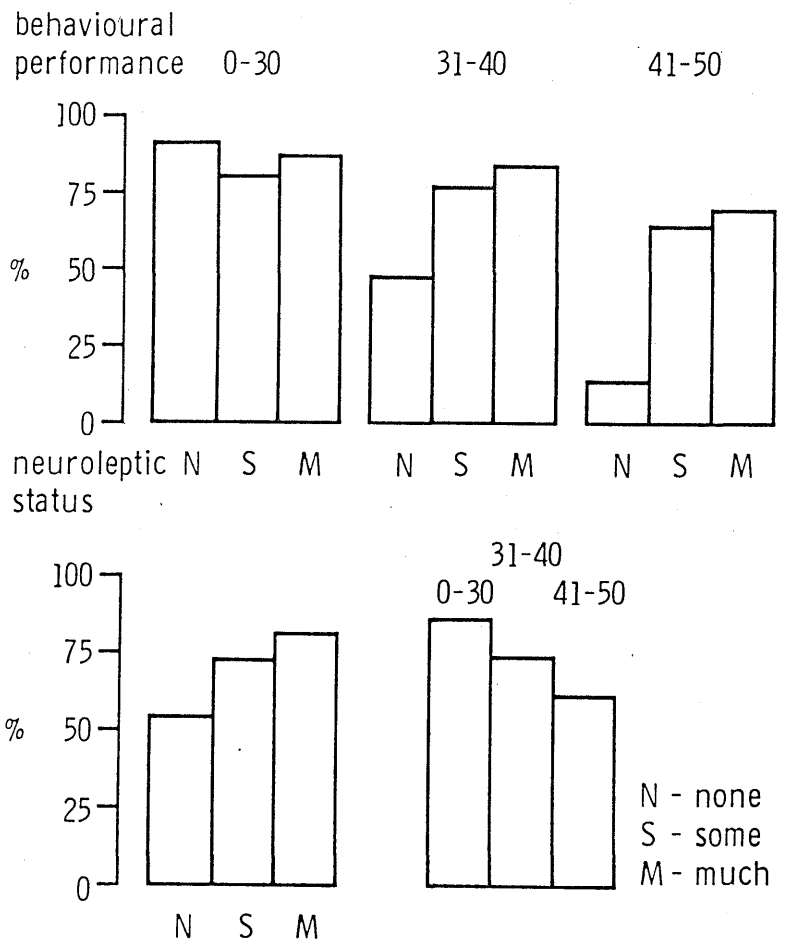


FIG 2:5:17

AIMS: prevalence of abnormality (total 2 or more) in relation to behavioural performance



feature total of 0 - 1 (z - value = 2.67 , P = 0.008), although those in the highest score range for negative mental state features (total 4 - 8) also had a significantly greater prevalence than the others (z - value = 2.07 , P = 0.036).

Maintaining the nine trend categories of cognitive performance separate, the relationship of this to movement disorder did not reach statistical significance. However, when the two highest Withers and Hinton ranges (21 - 60 and 61 - 107) were combined and compared with the lowest range (0 - 20) those in the latter category rated movement abnormality with significantly greater prevalence than the rest (z - value = 2.09 , P = 0.034).

Impaired behavioural performance was highly significantly correlated with the presence of movement disorder. This came equally from differences between the lowest behavioural grouping (0 - 30) compared to the rest (z - value = 2.39 , P = 0.016), and the highest (41 - 50) compared to the rest (z - value = 2.56, P = 0.01). There was therefore a gradual decrease in the presence of abnormal movements from the most behaviourally impaired group to the least.

Thus the presence of abnormal movements can be shown to be significantly more common in those with 'negative' features in the mental state, marked cognitive impairment and behavioural deterioration.

5.8 RAISING THE AIMS CUT-OFF FOR NORMALITY

As mentioned earlier the aforegoing analyses were conducted on a cut-off for normality on the AIMS of 0 - 1. However, as an

AIMS total of 0 - 1 may be considered too limited a criterion for normality, the analyses of Recorded Information and Assessed Abnormality variables were repeated raising the cut-off for normality to 0 - 2. The results are summarised in TABLE 2:5:11, and the relationships with Assessed Abnormalities illustrated in Figs 2:5:18 to 2:5:21.

As can be seen this did not alter the basic relationships established with the lower AIMS total cut-off. Once again, none of the relationships between the presence of movement disorder and items of Recorded Information approached statistical significance. The same applied to 'positive' mental state features. For the other Assessed Abnormality variables, the association with AIMS abnormality remained, and indeed for cognitive and behavioural performance, the negative relationships increased in significance.

Thus, allowing that the lower cut-off may be overinclusive, while the higher one may slightly underestimate abnormality, a balance of the two strongly indicates that the presence of spontaneous involuntary movements of the type recorded on the AIMS is associated with the presence of 'negative' features in the mental state, with cognitive impairment and with behavioural deterioration, and that these relationships are independent of time factors (age/length of illness) and exposure to neuroleptic drugs.

TABLE 2:5:11

AIMS DATA: ANALYSES OF RELATIONSHIPS BETWEEN MOVEMENT DISORDER AND ITEMS OF RECORDED INFORMATION AND ASSESSED ABNORMALITY: (NORMALITY CUT-OFF 0-2)

	VARIABLES	NO. OF TREND/CONTRAST CATEGORIES (df = N-1)	UNIFIED ANALYSIS OF VARIANCE BY RANKS: OVERALL ANALYSIS H-VALUE	SIGNIFICANCE	RELATIONSHIP WITH AIMS ABNORMALITY Z-VALUE	SIGNIFICANCE	INTERACTION BETWEEN INDEPENDENT VARIABLES Z-VALUE	SIGNIFICANCE
RECORDED INFORMATION	FAMILY HISTORY	9	8.28	p = 0.41	1.06	p = 0.28	1.09	0 = 0.28
	BIRTH TRAUMA/HEAD INJURY	6	5.17	p = 0.4	0.88	N/S	1.17	p = 0.24
	FITS	6	5.28	p = 0.38	1.29	p = 0.196	1.35	p = 0.17
	PAST ACADEMIC RECORD	9	10.67	p = 0.22	0.03	N/S	1.36	p = 0.17
	LEUCOTOMY	6	10.85	0 = 0.054	0.5	N/S	1.35	p = 0.17
	INSULIN COMA	9	9.71	p = 0.29	0.44	N/S	1.9	p = 0.054
	ELECTROCONVULSIVE THERAPY	9	12.00	p = 0.15	0.02	N/S	1.49	p = 0.13
ASSESSED ABNORMALITIES	POSITIVE FEATURES OF THE MENTAL STATE	9	11.88	p = 0.16	0.19	N/S	0.18	N/S
	NEGATIVE FEATURES OF THE MENTAL STATE	9	16.8	p = 0.032	2.11	p = 0.032*	1.18	p = 0.24
	COGNITIVE PERFORMANCE	9	8.18	p = 0.42	1.48	p = 0.134+	0.19	N/S
		6	7.27	p = 0.2	2.43	p = 0.014+	0.13	N/S
	BEHAVIOURAL PERFORMANCE	9	19.56	p = 0.012	3.00	p = 0.003+	0.99	N/S

* POSITIVE RELATIONSHIP

\+ NEGATIVE RELATIONSHIP

N/S = $p > 0.5$

FIG 2:5:18

AIMS: prevalence of abnormality (total 3 or more) in relation to positive mental state features

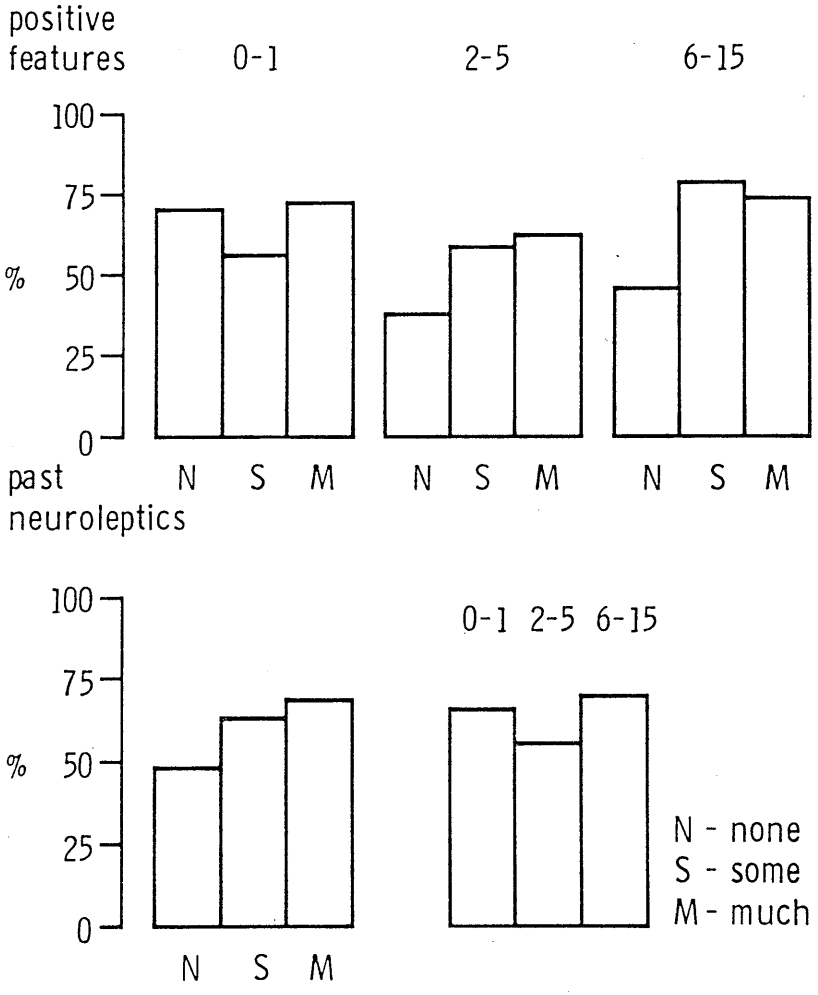


FIG 2:5:19

AIMS: prevalence of abnormality (total 3 or more) in relation to negative mental state features

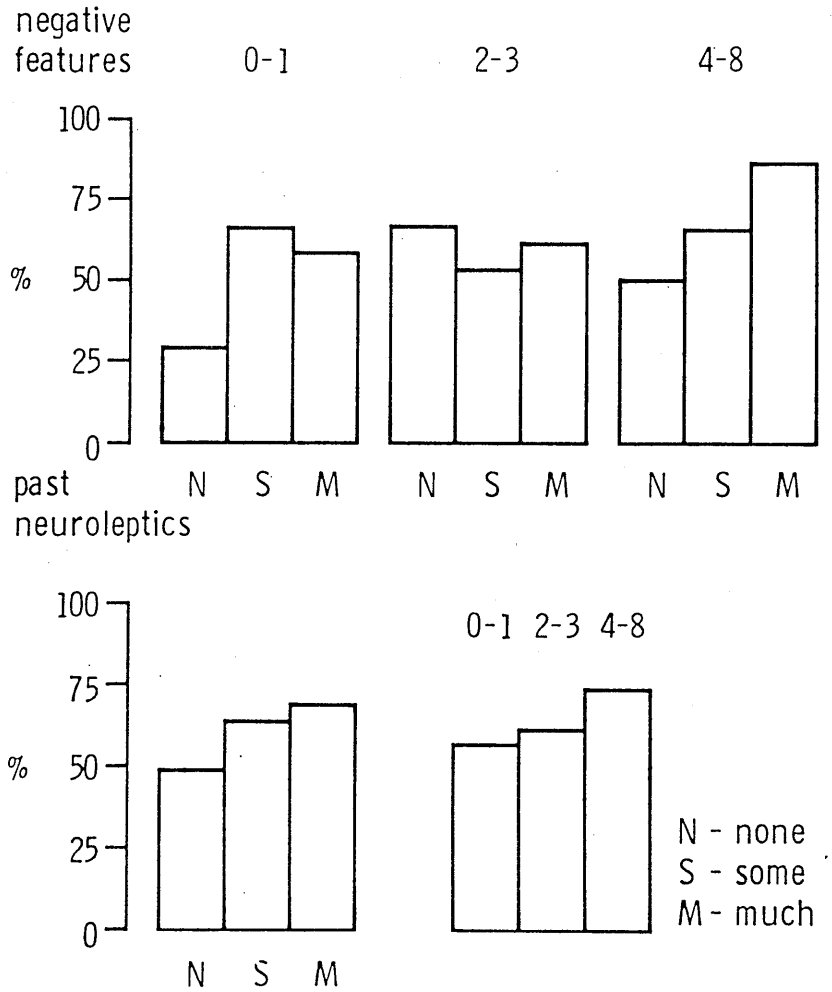


FIG 2:5:20

AIMS: prevalence of abnormality (total 3 or more) in relation to cognitive performance

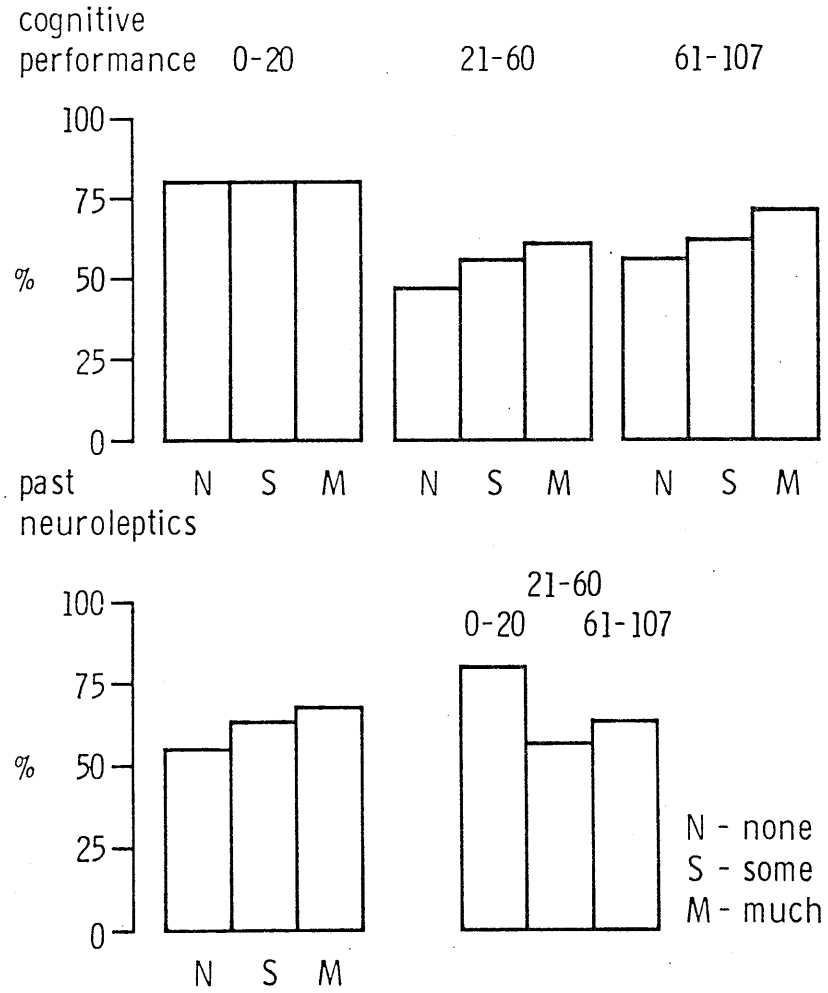
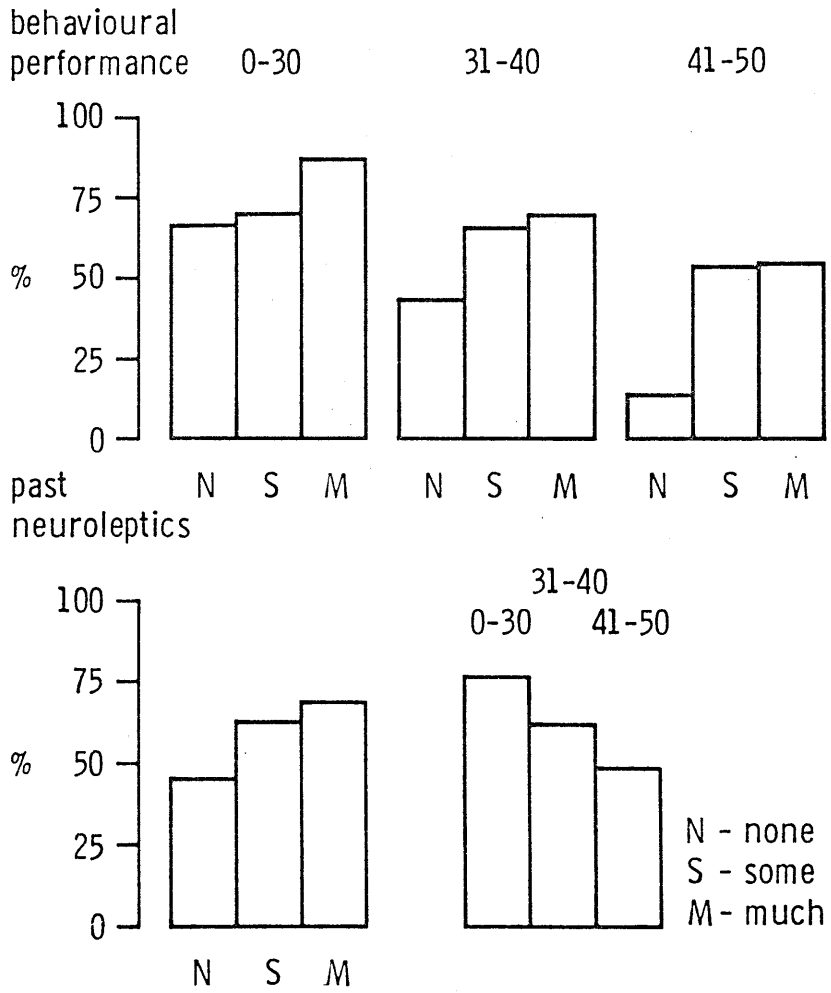


FIG 2:5:21

AIMS: prevalence of abnormality (total 3 or more) in relation to behavioural performance



5.9 SUMMARY OF ANALYSIS OF AIMS DATA

In this population of long-stay schizophrenics :

1) The prevalence of movement disorder depends on the criteria of severity, but overall is high.

2) Abnormal movements are predominantly orofacial in distribution, with tongue, lips and jaw being the commonest sites.

3) Spontaneous involuntary disorders of movement of the sort recorded on the AIMS are commonly found, and can be a feature of long standing schizophrenia which has not been modified by neuroleptic drugs. In this situation movements do not differ in form or distribution from those commonly attributed to neuroleptics.

4) The presence of a history of neuroleptic exposure is insufficient in itself to differentiate those who have been exposed from those who have not, with regard to their movement disorders.

5) Time factors are potent determinants of AIMS total abnormality. Increasing age is associated with increasing prevalence of movement disorder, though there appears to be some evidence of a plateau effect in middle age. Age and length of illness are inextricably interwoven with regard to their effects on severity of abnormality.

6) The role of sex is complicated and to some extent dependent on the technique of analysis used, but has not in general been shown to be of relevance. It is not important with regard to prevalence using total scores and is only a determinant with regard to severity insofar as females are older. Using single symptom criteria females over 70 years of age have a prevalence of abnormality four times that of males of the same age. This results from facial abnormality only. However, this difference is not reflected in mean scores or mean number of movements.

7) Time factors are potent determinants of neuroleptic treatment patterns. Those being consistently and heavily treated with these drugs are significantly younger than those in other treatment groups.

8) When attempts are made to account for these effects of age/length of illness on patterns of drug administration, significant positive relationships do exist between the presence of movement disorder and past neuroleptic exposure with some relationship demonstrable with the degree of past treatment. The differences lie especially between those

who have never been exposed in the past and those who have. Receiving neuroleptics or not at the time of assessment is not of relevance.

9) Past neuroleptic exposure is, in addition, related to the severity of movement disorder.

10) Those on neuroleptics in the past but whose drugs have been stopped at some point, have not returned to the base-line of abnormality shown by comparable patients never exposed. The degree of past exposure is only marginally relevant in this regard.

11) Those recently commenced on neuroleptics for the first time do not significantly differ in prevalence of movement disorder from those never exposed at any time.

12) Anticholinergic status at examination is not of relevance with regard to either the prevalence or severity of abnormal movements.

13) Present movement disorder is not related to historical items of Recorded Information apart from time factors.

14) Spontaneous abnormal movements are related to the presence of 'negative' features in the mental state, cognitive impairment, and behavioural deterioration. These relationships are independent of time factors and past exposure to neuroleptic drugs.

15) Findings 12, 13, and 14 remain valid regardless of whether a low or a higher cut-off for normality is adopted.

Chapter 6 - Results - The Rockland Scale Data

Similar analyses were performed on data recorded on the Rockland Scale (RS), as were carried out on AIMS data. As was mentioned, this scale is used here to record dyskinesias in the sense of 'any abnormal kinesis'. The results to be presented concentrate on abnormality recorded in any body part, but in particular contexts where more detailed information can be extracted, regional subscores will be examined separately.

The lay-out of the presentation is the same as was used for AIMS data, and the detail behind this will not be repeated.

6.1 THE TOTAL SAMPLE

6.1.1 PREVALENCE AND SEVERITY

The distribution of RS total scores in the sample of 411 is shown in Fig 2:6:1. The prevalence of abnormality (RS total 2 or more) is extremely high - namely 82.97 %. The distribution of scores is more closely exponential than with the AIMS and there is no middle - range score which occurs especially frequently. This probably reflects the fact that with four grades of severity, there is less chance of the central tendency effect operating. The mean score for the total sample was 8.63 $\pm$ SD 8.29, which, as with the AIMS data, reflects the distribution.

Fig 2:6:2 shows the prevalence of dyskinesia at increasing criteria of severity in all body regions together and each separately using single symptom criteria. The prevalence rates of abnormality

FIG 2:6:1

Distribution of pathological (>2) Rockland scale total scores (n = 341)

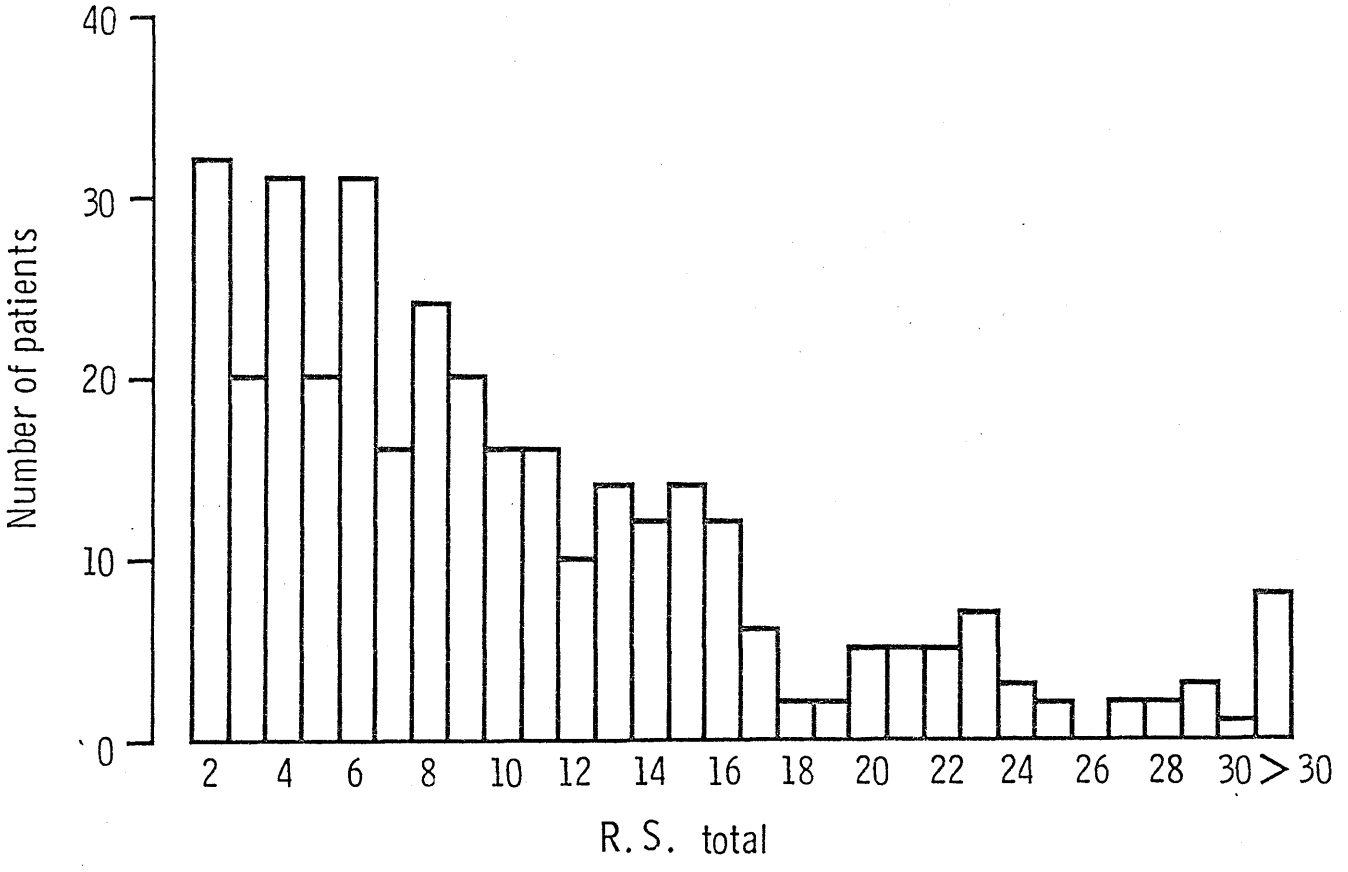
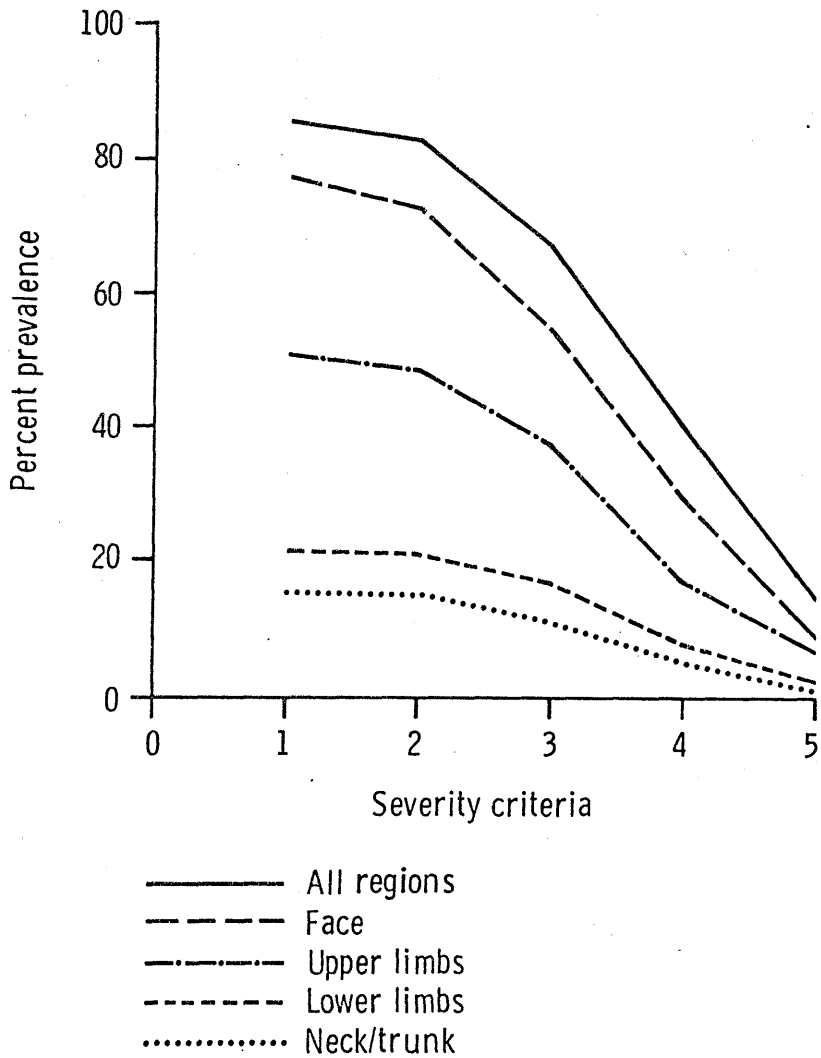


FIG 2:6:2

Regional prevalences at different severity criteria on Rockland



were even higher with this recording instrument than with the AIMS. Using criterion 3 (moderate), 67.6 % of subjects had demonstrable abnormal movements, which again came mainly from ratings of facial items.

6.1.2 THE DISTRIBUTION OF MOVEMENT PATTERN

The percentage of the total sample who achieved a pathological rating (at least one rating of '2') is shown for each RS item in TABLE 2:6:1. For comparative purposes, the comparable figures with the AIMS that were illustrated previously in TABLE 2:5:1 have been incorporated. This allows some impression of the individual movements constituting the AIMS items. Those RS movements that would not be appropriately recorded on the AIMS are listed on the right-hand side of the table.

Two points must be noted however. Firstly, RS items can only be approximated to those of the AIMS. Thus, the RS items are those which involve predominantly but not exclusively, the AIMS area against which they are listed.

Secondly, discrepancies arise between AIMS and RS percentages because certain movements rated in the grosser regional classifications of the former are not covered by any of the 34 specified items of the RS and are therefore recorded as one of the nine items reserved for movements not otherwise specified. The conventions adopted in this study for the use of these non-specific RS items are shown in Appendix VII.

Tongue movements were the commonest group of abnormalities in this sample. Choreoathetosis (including lingual myokymia) affected

TABLE 2:6:1

DISTRIBUTION OF INVOLUNTARY MOVEMENTS ON AIMS AND ROCKLAND SCALE AT SEVERITY CRITERION OF 2 OR MORE

(TOTAL SAMPLE N = 411)

AIMS		ROCKLAND			
AREA	% PREVALENCE	MAJOR COMPONENT MOVEMENTS OF AIMS AREAS	% PREVALENCE	ADDITIONAL MOVEMENTS	% PREVALENC
TONGUE	35.4	CHOREOATHETOID MOVEMENTS OF TONGUE	21		
		BON-BON	12.7		
		TONGUE PROTRUSION	8.8		
				TONGUE TREMOR	17.8
				*'RABBIT SYNDROME'	2
LIPS	28.1	PUCKERING OF LIPS	12		
		SUCKING	7.8		
		SMACKING	7.6		
		POUTING	5.9		
				ITEM 16 ('OTHER PERIORAL MOVEMENTS')	20.5
JAWS	23.7	CHEWING	17.3		
FACIAL EXPRESSION	18.3	GRIMACING	7.3		
		EYE BLINKING	6.4		
		*FACIAL TICS	0.7		
				EYE LID TREMOR	9.8
				ITEM 15 ('OTHER PERIORBITAL MOVEMENTS')	7.6
EXTREMITIES - UPPER	14.4	*BALLISTIC MOVEMENTS	2.4		
		CHOREOATHETOID MOVEMENTS-FINGERS	11.7		
		*CHOREOATHETOID MOVEMENTS-WRISTS	3.7		
				PILL-ROLLING MOVEMENTS	10.7
				*CARRESSING OR RUBBING FACE AND HAIR	3.9
				*RUBBING OF THIGHS	3.9
				ITEM 31 ('OTHER' MOVEMENTS - REGULAR FAST TREMOR)	19.8
				ITEM 32 ('OTHER' MOVEMENTS - NOT SPECIFIED ELSEWHERE)	14.4
EXTREMITIES - LOWER	15.6	ROTATION AND/OR FLEXION OF ANKLES	5.4		
		*TOE MOVEMENTS	1.5		
		*STAMPING MOVEMENTS-STANDING	1.5		
		STAMPING MOVEMENTS-SITTING	5.4		
		RESTLESS LEGS	3.4		
		*CROSSING/UNCROSSING LEGS-SITTING	1.5		
				ITEM 39 ('OTHER' MOVEMENTS REGULAR FAST TREMOR)	5.1
				ITEM 40 ('OTHER' LEG MOVEMENTS NOT SPECIFIED ELSEWHERE ,	5.6
NECK, SHOULDER, HIPS	13.7	HEAD NODDING	4.4		
		*RETROCOLLIS	0.7		
		*SPASMODIC TORTICOLLIS	1.5		
		*TORSION MOVEMENTS (TRUNK)	2.7		
		*AXIAL HYPERKINESIA	2.2		
		ROCKING MOVEMENT	4.4		
				*ITEM 23 ('OTHER' MOVEMENTS UPPER LIMB GIRDLE)	2.4
				*ITEM 24 ('OTHER' MOVEMENTS - TRUNK)	1.7
				*HOLOKINETIC MOVEMENTS	0.5
				*AKATHISIA	1.2
				*ITEM 43	0.7

* NUMBERS TOO SMALL FOR STATISTICAL ANALYSIS

21 %, while tremor of the tongue was found in 17.8 %. Although uncommon, dystonic type abnormalities were found, and tremor of the 'pill-rolling' variety was present in over 10 % of subjects.

6.2 COMPARISONS OF NEUROLEPTIC TREATED and NEUROLEPTIC-FREE SUBGROUPS

6.2.1 PREVALENCE AND SEVERITY

Fig 2:6:3 shows the prevalence of abnormality at increasing criteria of severity using RS scores in the 364 patients with a history of neuroleptic exposure and the 47 who had remained neuroleptic-free. All regions together and each separately are shown.

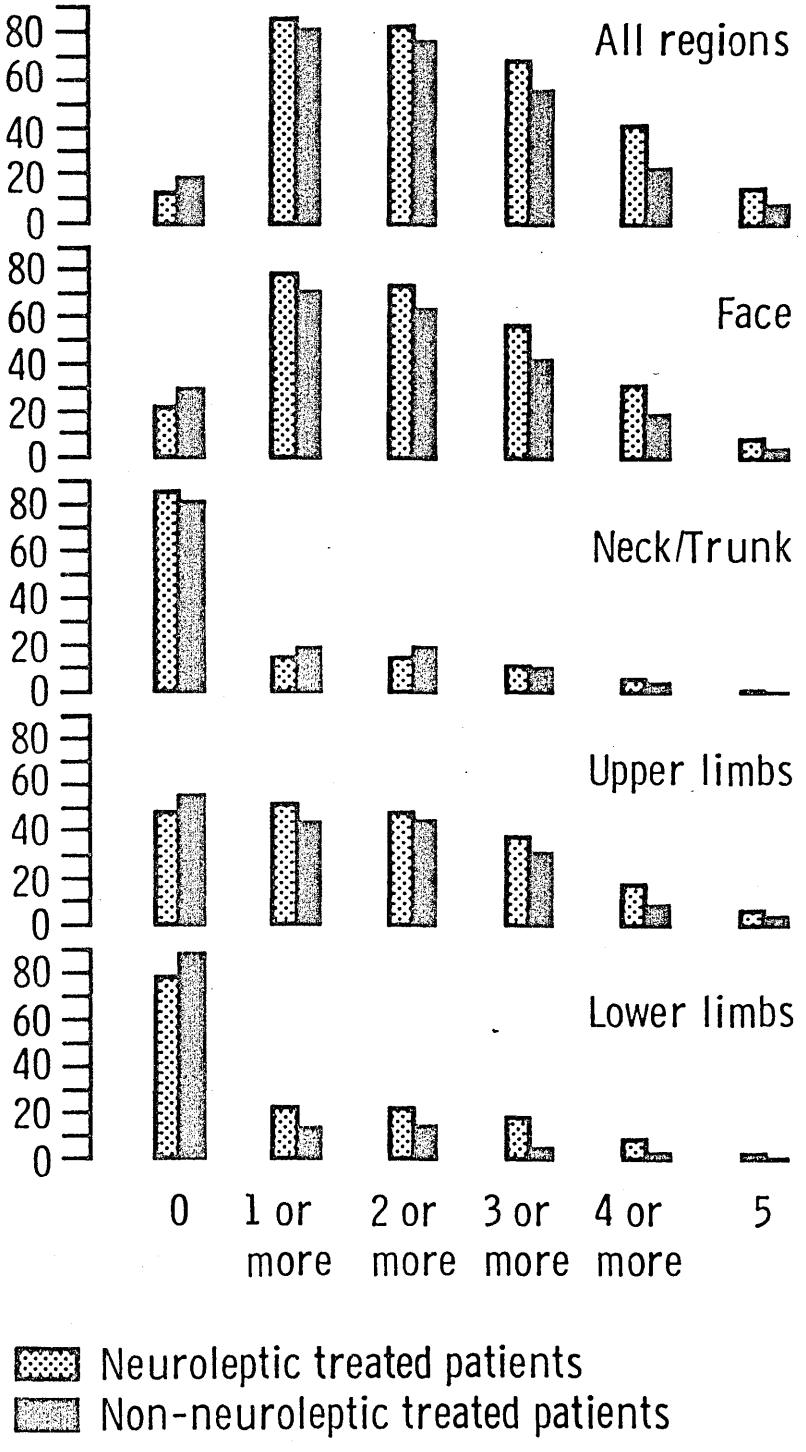
X^2 analysis revealed no significant differences between the groups on any comparison. The prevalence of abnormality was very high using the RS recording technique, even in those never exposed to neuroleptics, 76. 6 % of whom scored at least a single rating of 2.

6.2.2 MEAN SCORES

The mean total and regional scores for neuroleptic-treated and neuroleptic-free groups are shown in Fig 2:6:4. None of the differences between the groups reached significance at the 5 % level.

FIG 2:6:3

Prevalence (as percentage) of abnormality for increasing criteria of severity on Rockland scale



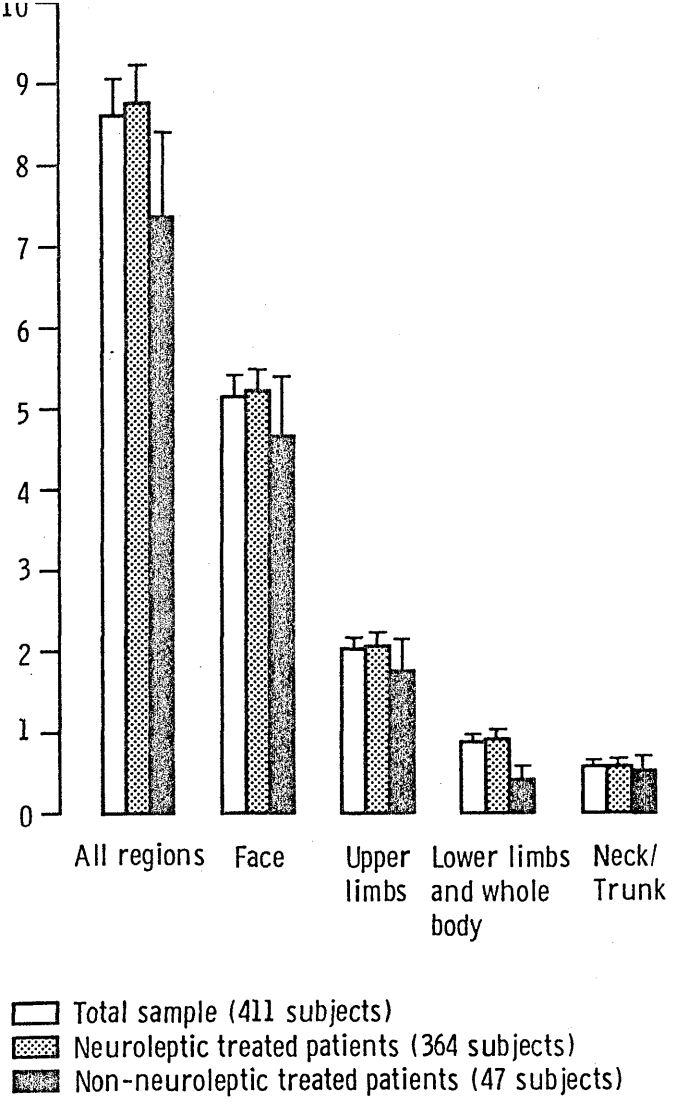
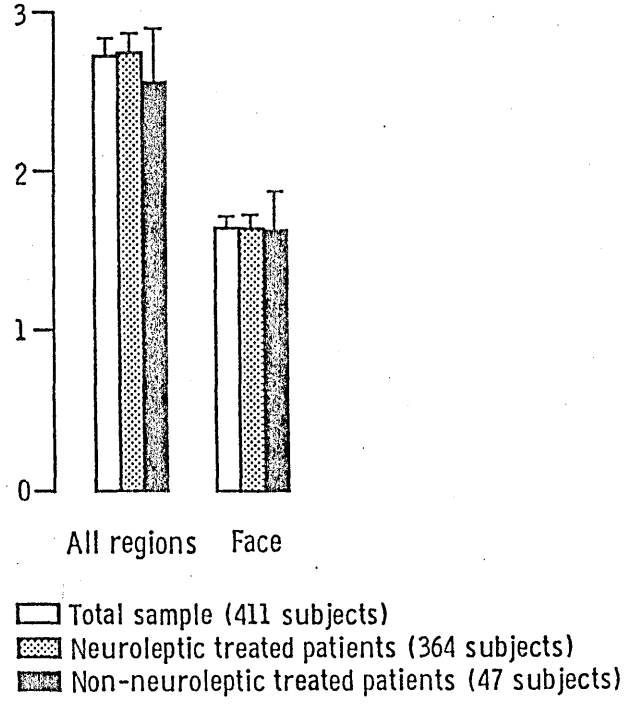


FIG 2:6:5

Mean number of movements rated 2 or more on Rockland (with standard errors)



6.2.3 MEAN NUMBER OF MOVEMENTS

These are illustrated for both groups in Fig 2:6:5: (all regions together plus face alone). There were once again no significant differences.

6.2.4 DISTRIBUTION OF MOVEMENT PATTERNS

As with AIMS data, X^2 analysis was conducted on 2 x 2 contingency tables, comparing the prevalence of a pathological rating on each item in neuroleptic-treated and free groups. This was carried out for the 25 RS items rated 2 or more sufficiently often in the total sample to allow of reliable statistical analysis. Those items which occurred insufficiently frequently for this analysis are indicated in TABLE 2:6:1.

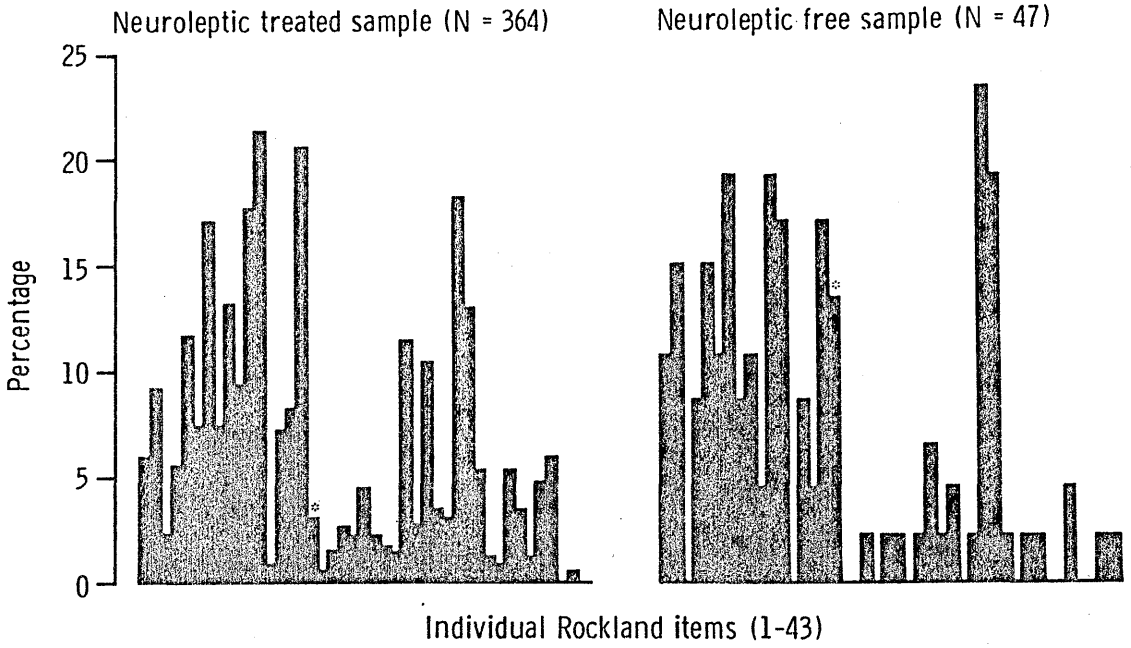
The profile of abnormality for neuroleptic-treated and non-treated groupsin terms of the RS items is shown in Fig 2:6:6. Only one statistically significant difference emerged between the groups. Head nodding (RS item 17) occurred more frequently in the neuroleptic-free group than in the neuroleptic-treated sample ($X^2 = 9.03$, $df = 1$, $P < 0.005$).

A similar analysis taking severity into account showed more severe choreoathetosis of the tongue ($P < 0.05$) and grimacing ($P < 0.025$) in the neuroleptic-treated group, but more severe head nodding in the neuroleptic-free patients ($P < 0.005$).

As in the AIMS analysis, those patients rating 2 or more on any one or more items were defined from the point of view of movement disorder as the 'morbid' group (341 subjects). The

FIG 2:6:6

Distribtuion of pathological (2 or more) ratings on Rockland scale within total sample (N = 411)



* $p < 0.005$

distribution of abnormality within this morbid sample again showed a significantly greater preponderance of 'head nodding', and in addition more 'eyelid tremor', in those never exposed to neuroleptics.

In summary, analysis of RS data, like that from the AIMS, did not identify any striking differences of note between patients with and without a history of treatment with neuroleptic drugs, when only this historical treatment variable is considered. Such differences as did emerge were few and must be seen in the light of the large number of comparisons conducted.

6.3 THE ROLE OF TIME AND SEX

The following analyses are identical to those conducted on AIMS data (Chapter 5.3).

6.3.1 THE ROLE OF AGE AND SEX IN PREVALENCE

The relationship between an RS grand total of 2 or more and increasing age in the whole sample and in females and males separately is illustrated in Fig 2:6:7. Analyses are laid out in TABLE 2:6:2.

As with the AIMS, age is highly important with regard to prevalence while sex, independent of age is not. The corrected F : M ratios for RS totals are as shown and illustrate the lack of a role for female sex in relation to prevalence.

FIG 2:6:7

Relationship of prevalence (R.S. total 2 or more) to age

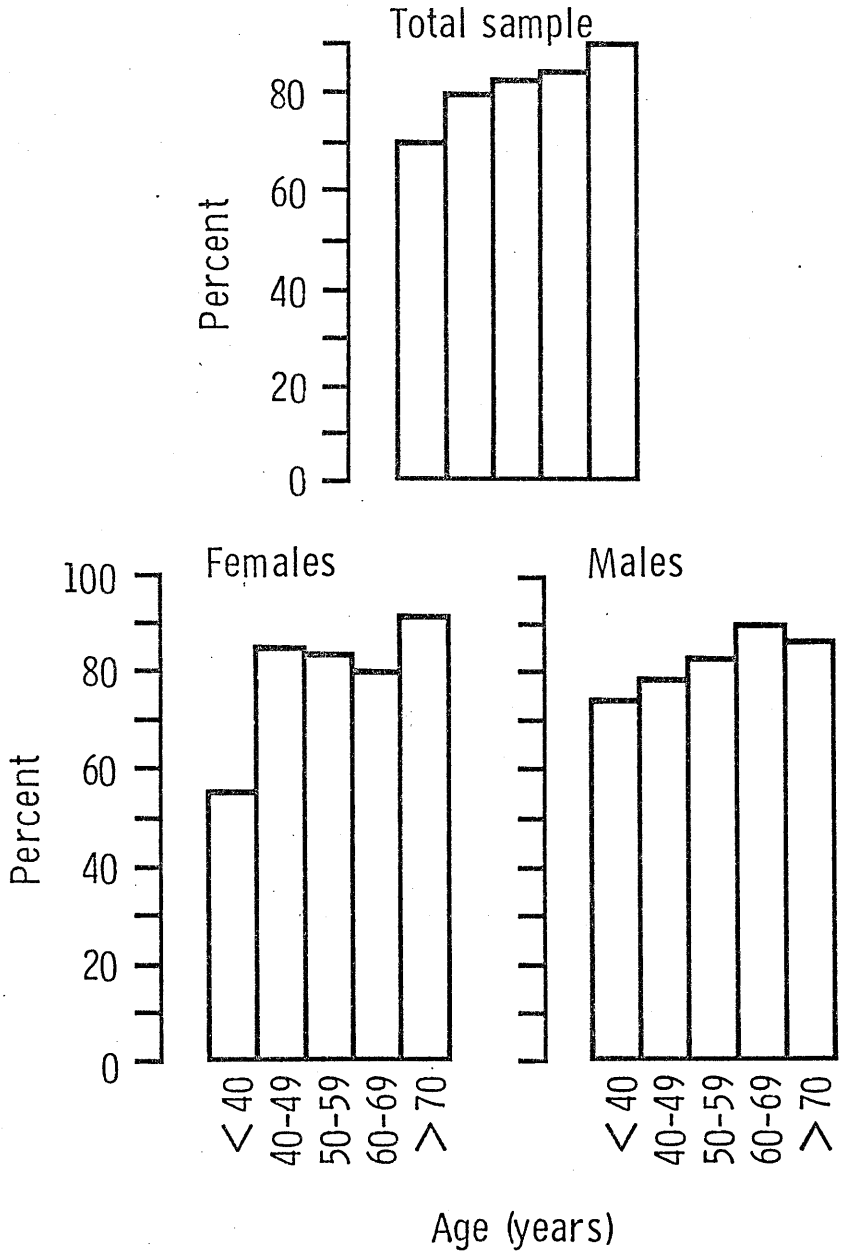


TABLE 2:6:2

ANALYSIS (MAX. LIKELIHOOD/LOG LINEAR) OF THE RELATIONSHIP BETWEEN THE PREVALENCE OF MOVEMENT DISORDER, AGE AND SEX

EFFECT	D.F.	CHI-SQUARE	PROBABILITY
SEX	1	1.29	$p = 0.26$
AGE	4	77.65	$p < 0.0001$
PREVALENCE	1	209.93	$p < 0.0001$
SEX x AGE	4	42.22	$p < 0.0001$
SEX x PREVALENCE	1	0.82	$p = 0.36$
AGE x PREVALENCE	4	9.83	$p = 0.04$
SEX x AGE x PREVALENCE	4	4.49	$p = 0.34$

40	1.18
40-49	1.08
50-59	1.01
60-69	0.89
70	1.06

With this wide concept of 'dyskinesia', the plateauing effect noted with AIMS scores appears to occur even earlier in the females.

6.3.2 THE ROLE OF AGE, LENGTH OF ILLNESS AND SEX IN SEVERITY

The arbitrary cut-offs adopted for RS total scores were taken to represent the normal/minimal - mild/moderate - severe ranges on the severity continuum while allowing a roughly equitable distribution of numbers for analysis.
The ranges defined with each sex were:

RS total	0 - 3
RS total	4 - 9
RS total	10 or more

ANOVA with age as dependent variable (TABLE 2:6:3) demonstrated significant main effects of both sex and RS totals ($F = 34$, $df = 1, 405$, $P < 0.0001$; $F = 5.83$, $df = 2, 405$, $P = 0.003$ respectively). The main effect of age on sex was that males were significantly younger than females in all ranges, while age was significantly

TABLE 2:6:3

ROCKLAND SCALE DATA

ANALYSIS OF VARIANCE: AGE AND LENGTH OF ILLNESS IN MALES AND FEMALES

AGE	⩽ 3	4-9	⩾ 10
MALES	53.3	54.3	58.9
FEMALES	60.2	63.3	65

SEX F = 34.00 df = 1,405 p < 0.0001

ROCKLAND F = 5.83 df = 2,405 p = 0.003

LENGTH OF ILLNESS	⩽ 3	4-9	⩾ 10
MALES	27.5	28.1	32.3
FEMALES	33	32.5	35

SEX F = 16.45 df = 1,404 p = 0.0001

ROCKLAND F = 5.12 df = 1,404 p = 0.006

TABLE 2:6:4

ROCKLAND SCALE TOTALS

ANALYSIS OF COVARIANCE: AGE AND LENGTH OF ILLNESS IN MALES AND FEMALES

CORRECTED AGES	⩽ 3	4-9	⩾ 10
MALES	56.8	57.2	58
FEMALES	58.7	62.2	61.6

SEX F = 16.98 df = 1,405 p < 0.0001

ROCKLAND F = 2.43 df = 2,405 p = 0.089

CORRECTED LENGTHS OF ILLNESS	⩽ 3	4-9	⩾ 10
MALES	31	31	32.4
FEMALES	32.2	29.9	31.4

SEX F = 0.16 df = 1,404 p = N/S

ROCKLAND F = 1.73 df = 2,404 p = N/S

positively associated with RS totals. There was no significant interaction.

ANOVA with length of illness as the dependent variable (TABLE 2:6:3) also showed significant main effects of sex and RS totals ($F = 16.45$, $df = 1$, $P = 0.0001$; $F = 5.12$, $df = 2$, 404 , $P = 0.006$ respectively). Thus, males have significantly shorter lengths of illness than females and higher RS totals were associated with longer lengths of illness. Again no significant interaction emerged.

Thus, significant effects attributable to the passage of time could be demonstrated as could the fact that females were older and had longer lengths of illness than males. As with AIMS results, analysis of covariance was carried out in an attempt to separate the effects of the two time components.

ANCOVA with age as the dependent variable and length of illness covaried revealed once again a persistently significant main effect of sex (TABLE 2:6:4), but in addition a persistent, though only marginally significant effect of RS totals. The corrected age values shown in TABLE 2:6:4 confirm that when length of illness is accounted for, males are significantly younger than females. Unlike findings with AIMS data, however, a marginally significant effect of age on RS totals persists, even after the strongly correlated variable of length of illness is removed. The interaction term was again non-significant.

ANCOVA with length of illness as the dependent variable and age covaried gave no significant main effect of sex or RS totals (TABLE 2:6:4) and there was no significant interaction term. The

corrected length of illness values shown in TABLE 2:6:4 were comparable in all ranges.

Thus, although once again time factors of age and length of illness are closely related, there is some evidence from these analyses that age may provide the dominant contribution with regard to RS total scores. As in the previous (AIMS) analysis, sex is only important with regard to severity of movement disorder insofar as females are older than males, though the comparable lengths of illness in both sexes again indicate that females must have been admitted to long-term care at a later age.

6.3.3 FURTHER EVALUATION OF THE ROLE OF SEX

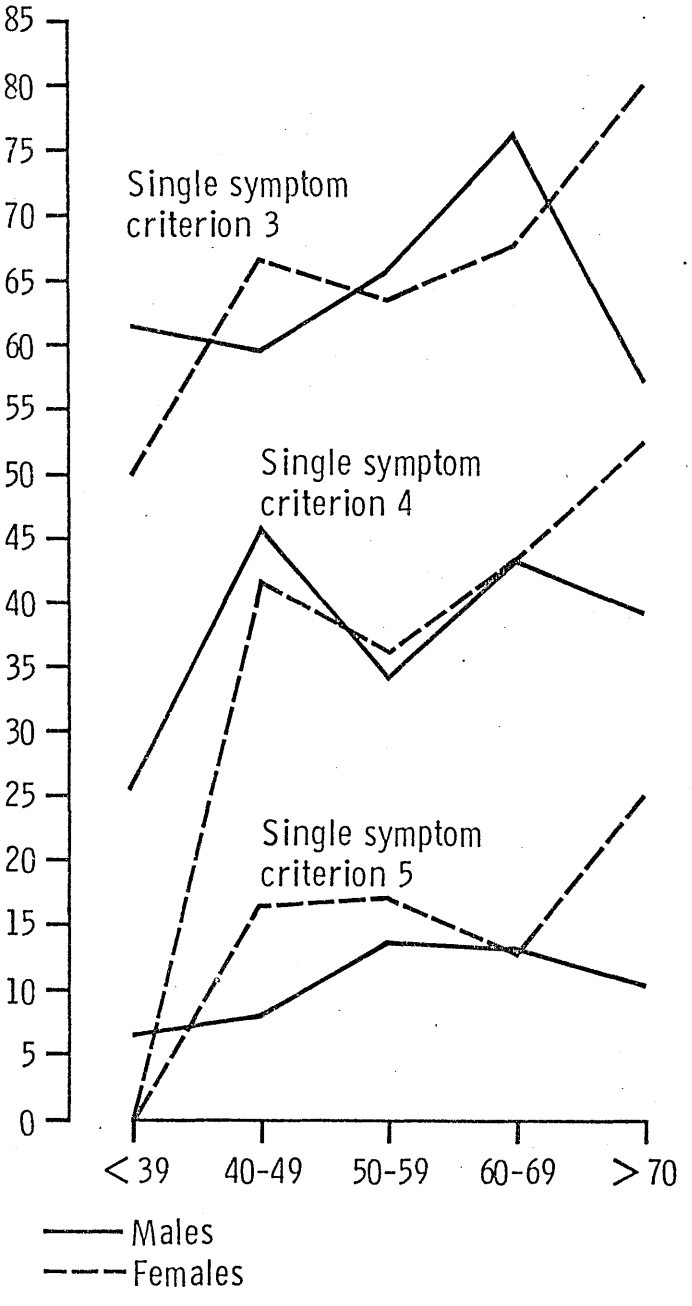
A comparison was conducted of the prevalence of abnormality in males and females with advancing age using the technique of single symptom criteria.

Comparison of the prevalence of abnormality with a decreasing single symptom criterion (5, 4 and 3) by sex and age is shown in Fig 2:6:8. In general terms the pattern is comparable to the AIMS findings but the overall difference between the sexes is more striking, at least statistically. This is especially true for those over 70 years of age.

At a single symptom criterion of 5, the females differed in prevalence overall from the males ($X^2 = 9.76$, df = 4, P = 0.045). This was largely, but not exclusively, accounted for by the significantly higher prevalence recorded in females over 70 years ($X^2 = 7.89$, df = 1 , P = 0.005).

FIG 2:6:8

R.S: Prevalence by age at single symptom criterion of 5, 4, and 3 in both sexes



At the two lower single symptom criteria, the position is complicated by the effects of age on prevalence. At criterion 4 the age effect is comparatively much greater in females while at criterion 3, that for females is roughly linear but that for males, curvilinear. Nonetheless, at both these criteria levels, the females over 70 showed a strikingly greater prevalence than the males (Criterion 4 : X^2 = 15.92 , df = 1 , $P < 0.0001$: Criterion 3 : X^2 = 25.85 , df = 1 , $P < 0.00001$).

The F : M ratios at increasing single symptom criteria with advancing age are shown for all body areas together and for face and limbs/trunk separately in TABLES 2:6:5, 2:6:6 and 2:6:7 respectively. The total sample and only those exposed to neuroleptics are shown separately.

In general, comparing those in the total sample, this does not reveal the striking sex differences in the over 70's noted above. Only at criterion 5, is the female prevalence, at 2 - $2\frac{1}{2}$ times in excess of that for males, strikingly greater. It is likely that with very high rates of abnormality differences revealed using absolute numbers are diluted in the calculations of percentages, thus tending to abolish the differences described above (which may represent a valid criticism of the data presented in each of these three tables). As was found using the AIMS data, this difference in the total sample is due entirely to a greatly increased female prevalence on facial ratings only.

When just those exposed to neuroleptics are considered, the overall increase in female prevalence in the elderly using severe criteria is striking, being 6 - 7 times that in males. However, as

TABLE 2:6:5

F:M PREVALENCE RATIOS BY AGE AND INCREASING SINGLE SYMPTOM CRITERIA: ALL BODY AREAS

AGE	SEVERITY CRITERION	TOTAL SAMPLE MALES % RATING	TOTAL SAMPLE FEMALES % RATING	F:M	NEUROLEPTIC TREATED ONLY MALES % RATING	NEUROLEPTIC TREATED ONLY FEMALES % RATING	F:M
< 40	2	74.2	62.5	0.84	73.3	62.5	0.85
	3	58.1	50	0.86	56.7	50	0.88
	4	25.8	-	-	25.8	-	-
	5	6.5	-	-	6.5	-	-
40-49	2	78.4	83.3	1.06	77.1	83.3	1.08
	3	59.5	66.7	1.12	57.1	66.7	1.17
	4	45.9	41.7	0.91	45.9	41.7	0.91
	5	8.1	16.7	2.06	8.1	16.7	2.06
50-59	2	82.8	82.7	1	82.3	82.7	1
	3	65.6	63.5	0.97	65.1	63.5	0.98
	4	34.4	36.5	1.06	33.3	36.5	1.1
	5	14.1	17.3	1.23	14.1	17.3	1.23
60-69	2	89.6	79.2	0.88	86	78.8	0.92
	3	77.6	67.9	0.88	72.2	67.3	0.93
	4	43.3	43.4	1	38.7	43.4	1.12
	5	13.4	13.2	0.99	12.1	13.2	1.09
> 70	2	82.1	89.8	1.09	72.2	89.3	1.24
	3	57.1	78	1.37	45.5	77.2	1.7
	4	39.3	52.5	1.34	29.2	51.7	1.77
	5	10.7	25.4	2.37	3.8	24.1	6.34

TABLE 2:6:6

F:M PREVALENCE RATIOS BY AGE AND INCREASING SINGLE SYMPTOM CRITERIA: FACE ONLY

AGE	SEVERITY CRITERION	TOTAL SAMPLE MALES % RATING	TOTAL SAMPLE FEMALES % RATING	F:M	NEUROLEPTIC TREATED ONLY MALES % RATING	NEUROLEPTIC TREATED ONLY FEMALES % RATING	F:M
< 40	2	61.3	50	0.82	60	50	0.83
	3	41.9	37.5	0.89	40	37.5	0.94
	4	12.9	-	-	12.9	-	-
	5	-	-	-	-	-	-
40-49	2	75.7	66.7	0.88	74.3	66.7	0.9
	3	45.9	41.7	0.91	45.9	41.7	0.91
	4	37.8	25	0.66	37.8	25	0.66
	5	8.1	-	-	8.1	-	-
50-59	2	78.1	61.5	0.79	77.4	61.5	0.79
	3	50	50	1	50	50	1
	4	21.9	26.9	1.23	21.9	26.9	1.23
	5	7.8	13.5	1.73	7.8	13.5	1.73
60-69	2	83.6	67.9	0.81	78.4	67.3	0.86
	3	71.6	52.8	0.74	65.5	51.9	0.79
	4	35.8	30.2	0.84	30.6	30.2	0.99
	5	7.5	9.4	1.25	6.1	9.4	1.54
> 70	2	75	81.4	1.09	66.7	81	1.21
	3	53.6	66.1	1.23	43.5	65.5	1.51
	4	35.7	37.3	1.04	28	36.2	1.29
	5	3.6	15.3	4.25	3.6	13.8	3.83

TABLE 2:6:7

F:M PREVALENCE RATIOS BY AGE AND INCREASING SINGLE SYMPTOM CRITERIA: LIMBS AND TRUNK

AGE	SEVERITY CRITERIA	TOTAL SAMPLE MALES % RATING	TOTAL SAMPLE FEMALES % RATING	F:M	NEUROLEPTIC TREATED ONLY MALES % RATING	NEUROLEPTIC TREATED ONLY FEMALES % RATING	F:M
< 40	2	54.8	50	0.91	53.3	50	0.94
	3	41.9	25	0.6	40	25	0.63
	4	19.4	-	-	19.4	-	-
	5	6.5	-	-	6.5	-	-
40-49	2	40.5	50	1.23	37.1	50	1.35
	3	35.1	33.3	0.95	31.4	33.3	1.06
	4	21.6	25	1.16	21.6	25	1.16
	5	2.7	16.7	6.19	2.7	16.7	6.19
50-59	2	57.8	71.2	1.23	57.1	71.2	1.25
	3	45.3	57.7	1.27	44.4	57.7	1.3
	4	17.2	28.8	1.67	15.9	28.8	1.81
	5	9.4	7.7	0.82	9.4	7.7	0.82
60-69	2	67.2	60.4	0.9	60.7	59.6	0.98
	3	52.2	47.2	0.9	47.5	46.2	0.97
	4	23.9	22.6	0.95	22.7	22.6	1
	5	7.5	7.5	1	7.5	7.5	1
> 70	2	50	61	1.22	36.4	58.9	1.62
	3	32.1	52.5	1.64	17.4	50.9	2.93
	4	14.3	30.5	2.13	4	29.3	7.33
	5	10.7	11.9	1.11	3.8	11.9	3.13

TABLES 2:6:6 and 2:6:7 show, in this situation the difference is fairly evenly accounted for by increases in both facial and limb/trunk abnormality.

The mean RS scores for males and females in each of the five age-bands is illustrated in Fig 2:6:9. None of these differences reach conventional (5 %) significance levels. In Fig 2:6:10, the neuroleptic-treated and non-treated patients have been separated. As will be seen, the form of the curves does not alter, though the impression is that differences between the sexes over 60 heighten when only neuroleptic-treated patients are considered - in the direction of higher mean scores in males. However, none of the differences between the sexes in any age band achieve conventional levels of significance. While male values in the 60 - 69 years age band are 35 % higher again than the females, the variance is also very large. With both the AIMS and RS, the pattern in the neuroleptic-free subjects is the same - namely a stabilisation, or even a slight but not significant fall, in the mean scores after the age of 60. As the figure shows, with RS scores, the pattern in neuroleptic-free males almost exactly mirrors that for neuroleptic-treated males, but at a slightly (but not significantly) lower level.

The mean number of RS movements rated 2 or more was not significantly different between the sexes considering the total sample (Fig 2:6:11).

Thus, as with the AIMS, a much greater prevalence of severe abnormality is noted with the RS in females over 70 using the single symptom criterion method, especially in those treated with neuroleptics. In the case of the RS however, differences in the drug-exposed group

FIG 2:6:9

Rockland scale mean totals as a function of age and sex

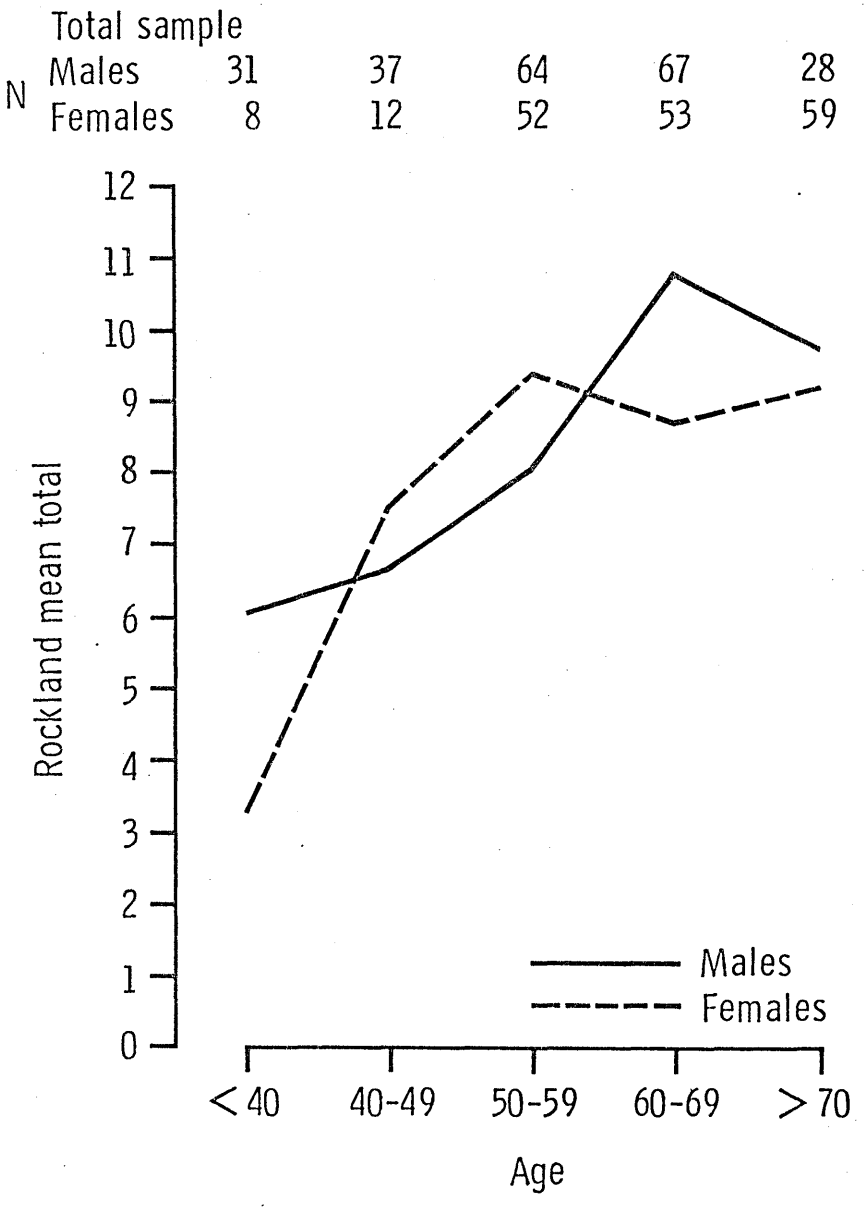


FIG 2:6:10

Rockland scale mean totals as a function of age and sex

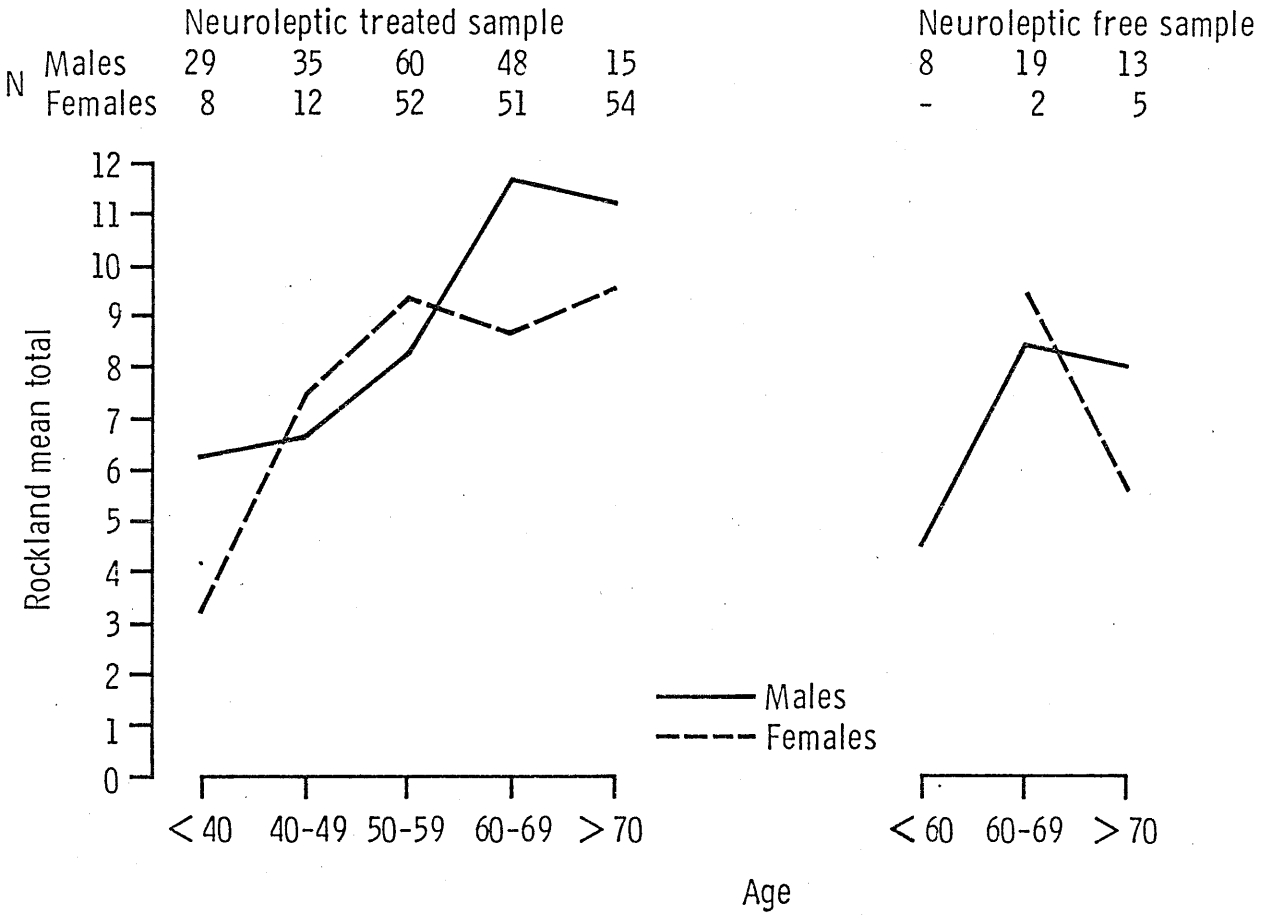
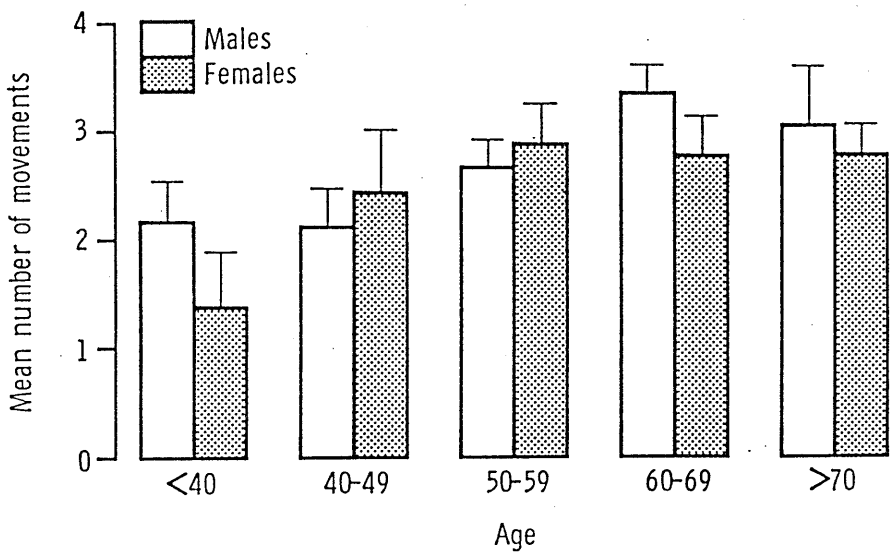


FIG 2:6:11

Rockland scale

Mean number of movements (± SEM) by age and sex - total sample



are not restricted to a greater frequency of severe facial ratings. These sex differences are not reflected in differences in mean scores with age, or in the mean number of movements rated positively.

6.4 ADDITIONAL INFORMATION FROM ROCKLAND DATA - THE ROLE OF AGE AND SEX ON INDIVIDUAL ITEMS

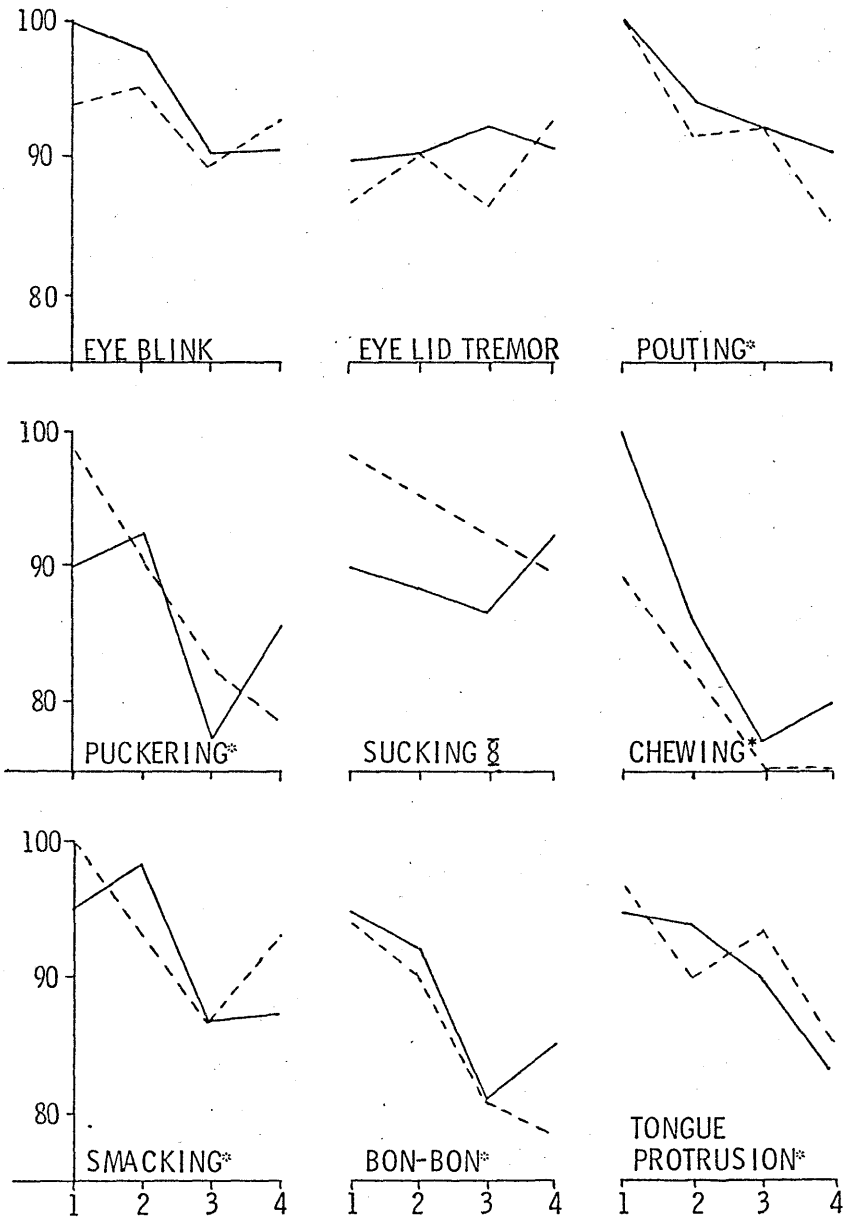
Additional information was extracted from the Rockland data by analysing those individual items rated often enough, in order to assess those to which age and sex made major contributions. Fig 2:6:12 illustrates the prevalence of abnormality (2 or more) in four arbitrarily defined age bands (20 - 50: 51 - 60: 61 - 70: 71 +) for males and females separately. The slope of the lines represents graphically the effect of age on each item, while the separation represents that of sex. Significance of these differences was gauged by X^2 analysis.

Of the twenty five items rated positively with sufficient frequency to allow examination (TABLE 2:6:1) only the orofacial components of pouting (item 4), puckering (item 5), chewing (item 7), smacking (item 8), bon bon (item 9), and tongue protrusion (item 10) showed significant positive age effects (Fig 2:6:12). The significance with rocking (item 22) which was somewhat inconsistent and negative, was probably a chance phenomenon resulting from small numbers. Only tongue tremor (item 11), sucking (item 6), and pill-rolling (item 28) showed significant sex effects, the first of these being commoner in males while both the others were more common in females.

This analysis took no account of the possible effects of past neuroleptic status considered subsequently or length of illness, as

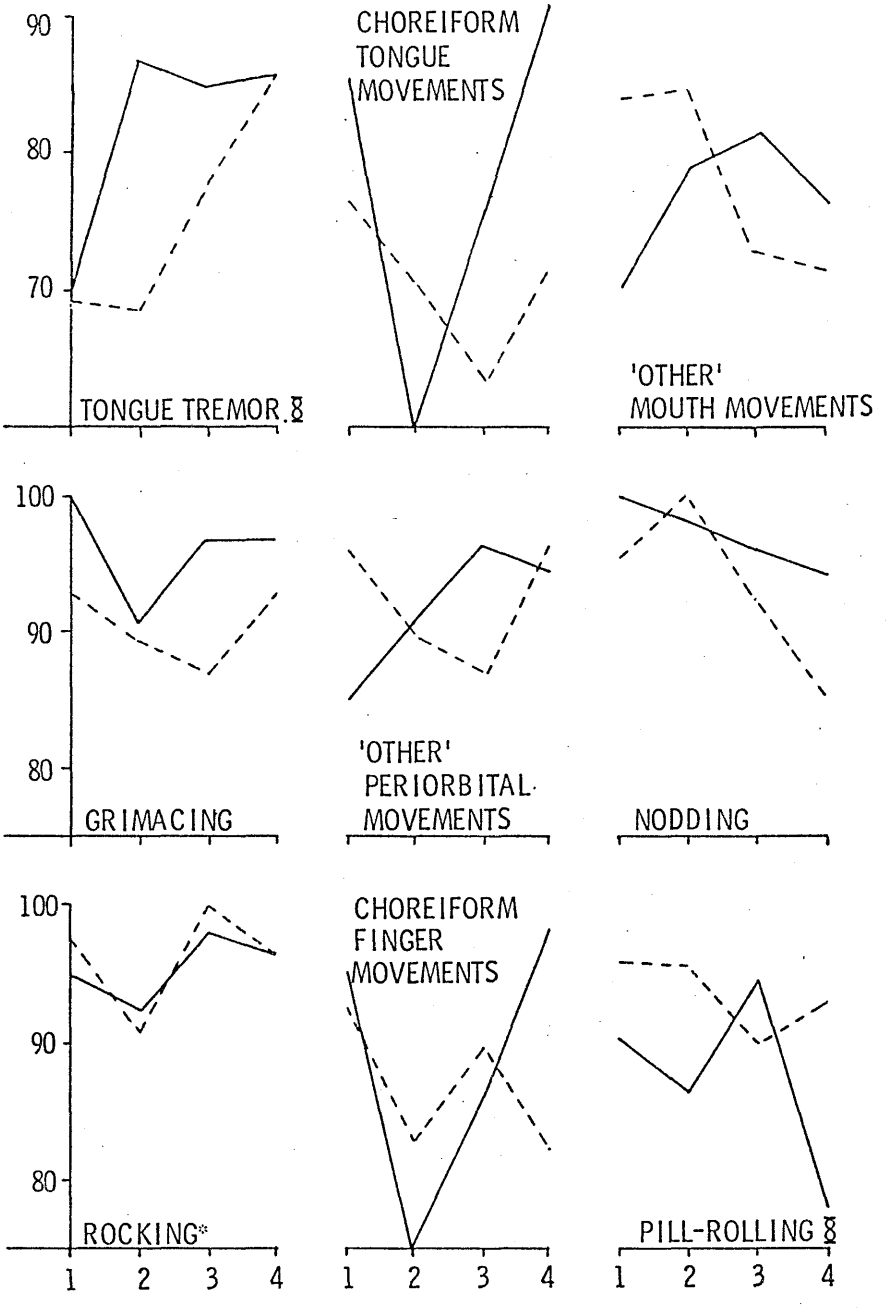
FIGURE 2:6:12

PERCENTAGE OF TOTAL SAMPLE WITH NO ABNORMALITY ON MAJOR R.S. ITEMS BY AGE AND SEX



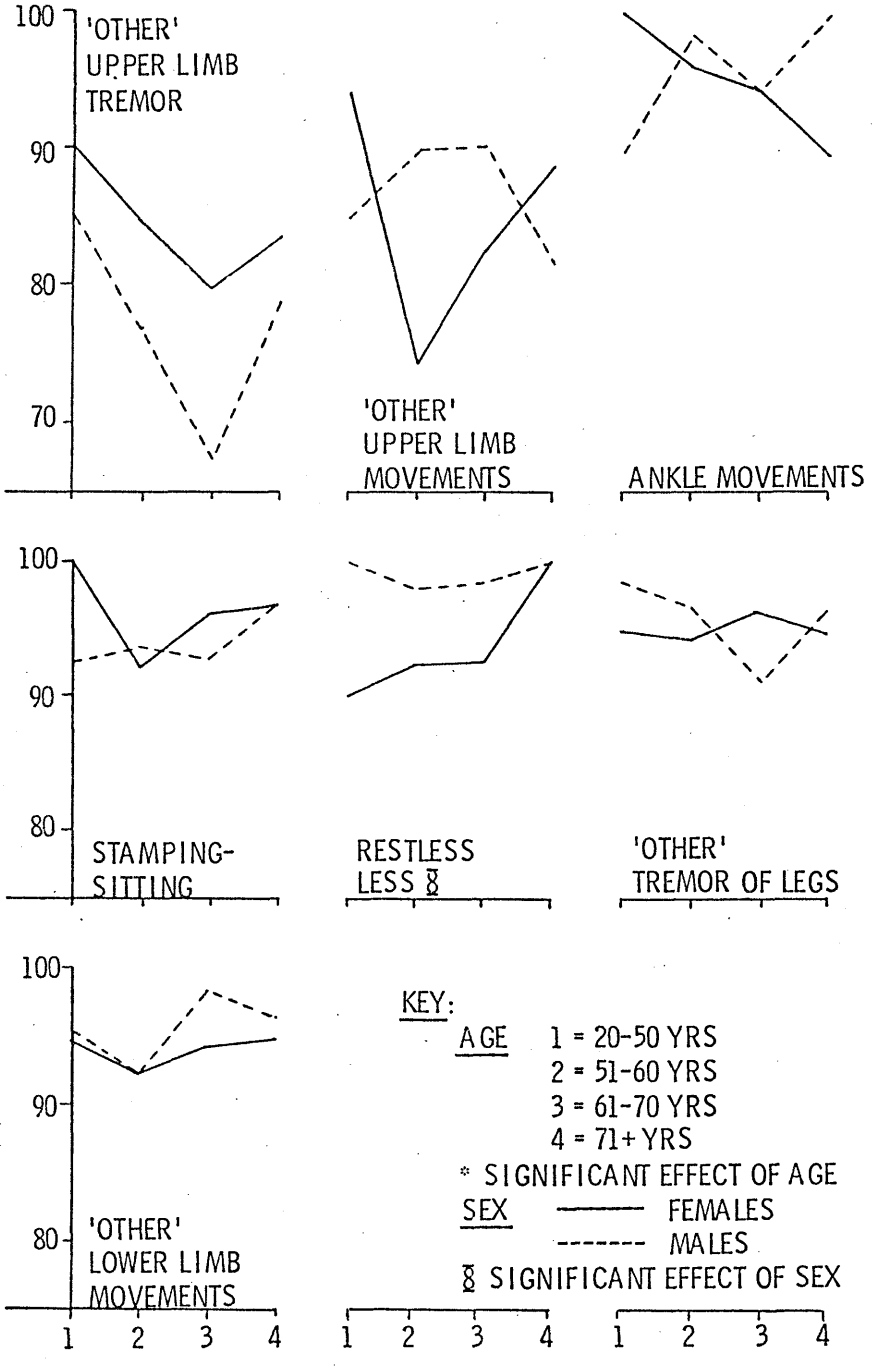
FOR KEY, SEE OVER

FIGURE 2:6:12 (CONTD)



FOR KEY, SEE OVER

FIGURE 2:6:12 (CONTD)



to have done so would have reduced the numbers beyond those suitable for statistical analysis. This must be borne in mind when interpreting this finding. However, subdividing the total sample into those scoring only on individual items can be expected to dilute considerably the age effects found in the group as a whole. Thus for individual items to show age effects suggests that these effects are powerful. It is thus of some interest that the buccomasticatory lingual (BML) features of involuntary movement disorder stand out so strikingly in this regard, even allowing for the necessary limitations of the analysis.

6.5 THE ROLE OF NEUROLEPTIC MEDICATION PAST AND PRESENT

As the Rockland Scale provides more detail of involuntary movements of a wider range than the AIMS, the analyses in this section were performed not only on RS total scores but also on each of the regional subscores separately, where sufficient positive ratings made this possible. The subscores examined were those for Face (items 1 - 16), Neck/Trunk (items 17 - 24), Upper Limbs (items 25 - 32) and Lower Limbs (items 33 - 40). Whole body movements (items 41 - 43) were rated too infrequently to be analysed separately.

The same neuroleptic status categories were employed as in analysis of AIMS data presented previously (Categories 1 - 6, Chapter 5.5), and the same 'age - controlled' group (with the previously stated proviso) selected to obviate the effects of age and length of illness.

The analyses were conducted with the basic RS normality cut-off used to date - i.e. 0 - 1. In light of the comments made

earlier regarding this (Chapter 3.2.2) and the importance of the questions being evaluated here, they were repeated using the higher cut-offs for total scores and regional subscores noted previously (Chapter 3.2.2). The statistical technique was unified analysis of variance by ranks.

6.5.1 THE ROCKLAND SCALE TOTAL SCORES

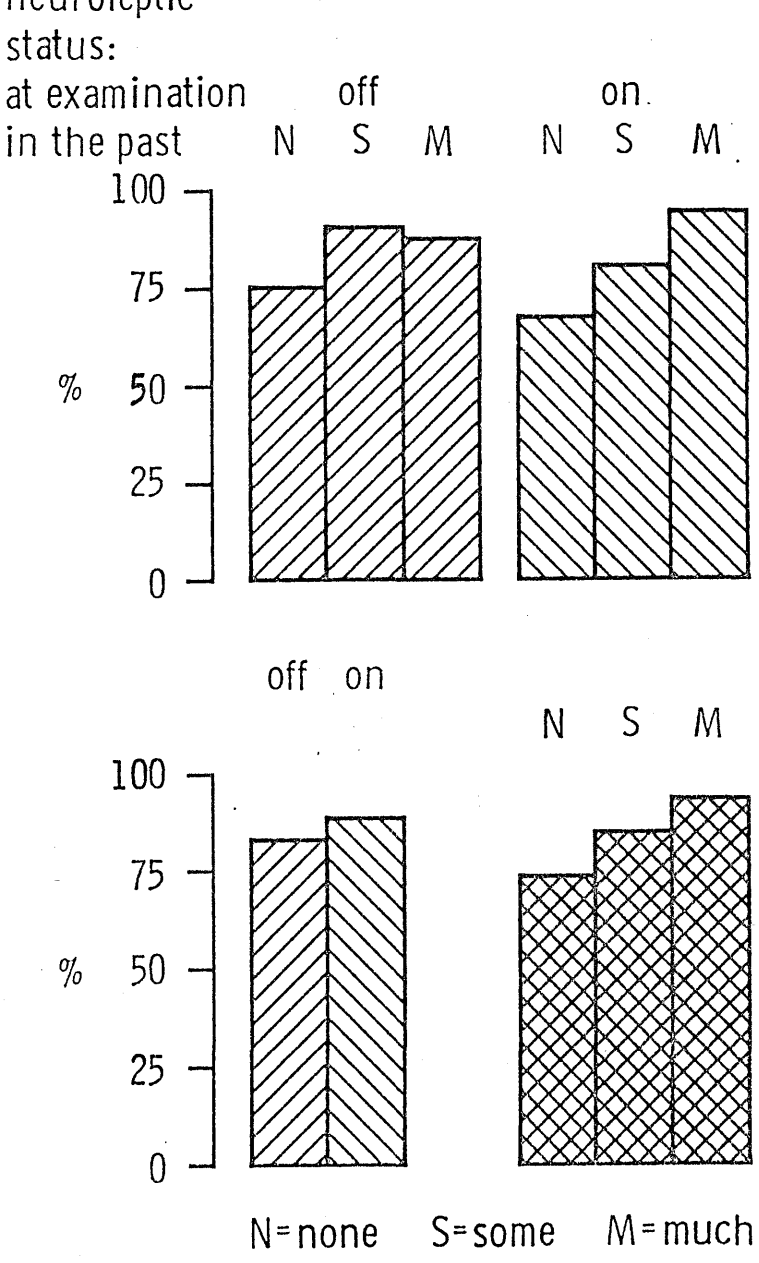
The relationships between RS total scores and the six categories of neuroleptic status are illustrated in Fig 2:6:13. The organisation of this diagram is identical to that for the presentation of AIMS data (Fig 2:5:12) and the explanation will not be repeated.

Overall, there was a relationship between RS total scores and categories of neuroleptic status ($H = 12.06$, $df = 5$, $P = 0.034$). There was no effect of being on neuroleptics at the time of examination (z - value $= 1.27$, $P = 0.2$), but increasing exposure to neuroleptics in the past (Fig 2:6:13 : bottom right) was significantly associated with an increasing prevalence of movement disorder (z - value $= 3.1$, $P = 0.002$). This was due to approximately equal differences between the groups. Thus, when those never exposed to neuroleptics were compared with those treated (73.8 % v 89.7 % abnormality), the difference remained highly significant (z - value $= 2.7$, $P = 0.006$) and comparable to that between the heavily treated sample and the rest (93.5 % v 81.6 % abnormality) (z - value $= 2.54$, $P = 0.01$). There was no significant interaction between past and present neuroleptic therapy (z - value $= 0.56$, N/S).

By arbitrarily dividing RS totals into three ranges relationships

FIG 2:6:13

Rockland: prevalence of abnormality (total 2 or more) in relation to neuroleptic exposure



were sought between severity of movement disorder and current/past neuroleptic exposure. The RS ranges were 0 - 2, 3 - 10, and 11 +.

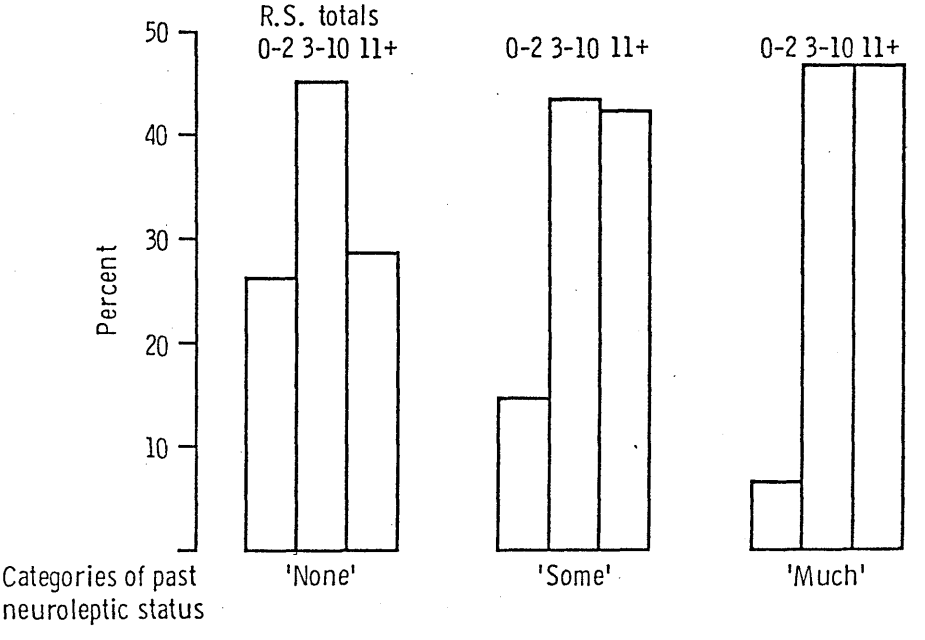
There was a non-significant trend towards severe movement disorder being found more often in those receiving neuroleptics at the time of examination (z - value = 1.78 , P = 0.07). Of those 'currently' on these preparations, 46.3 % had totals in the severe range compared to 35.4 % of those 'off' neuroleptics when examined.

Much more striking relationships, however, were found between severity and past neuroleptic exposure (Fig 2:6:14) (z - value = 2.69 , P = 0.007). This was largely, though not exclusively, due to the fact that severe abnormality was more common in those with a history of exposure regardless of degree, compared to those with no past history (z - value = 2.55 , P = 0.01), though severe movement disorder was also significantly more frequent in the heavily treated patients than in the rest combined (z - value = 2.05 , P = 0.038).

As with the AIMS results, consideration was given to the effect of having had neuroleptics stopped at some point in time. The data being analysed here are represented in the top, left-hand side of Fig 2:6:13. In general, the relationship between the prevalence of movement disorder and the first three categories of past neuroleptic status represented only a trend (z - value = 1.58 , P = 0.1). This was due entirely to the fact that movement abnormality was more frequently to be found in those whose neuroleptics had been stopped at some time, compared to those never exposed (z - value = 1.94 , P = 0.05). Those in the former categories had a non-significant trend towards more severe disorder when compared with those in the latter

FIG 2:6:14

Relationship between increasing Rockland totals (severity) and past neuroleptic exposure



category (z - value = 1.80 , P = 0.068).

No difference was found in prevalence of abnormality in those recently commenced on neuroleptics compared to those never exposed (X^2 = 0.29 , df = 1 , N/S). The question of differing severity in these two groups could not be explored owing to the small numbers in the former group (Category 4). There was a significant linear relationship between increasing prevalence in terms of RS totals and categories 4 - 6 of neuroleptic status (z - value = 2.63 , P = 0.008), though differences due to increasing severity did not reach significance.

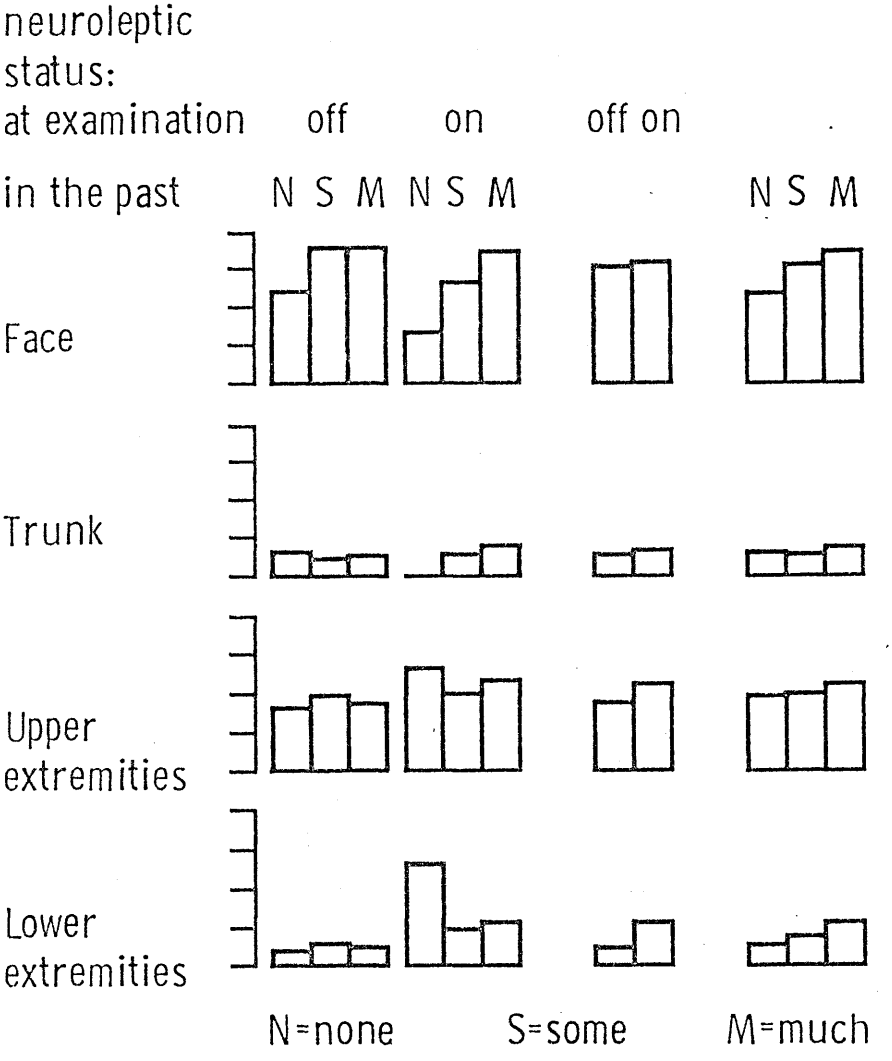
6.5.2 ROCKLAND SCALE FACE SUBSCORES (Items 1 - 16)

The subtotal of the 16 RS items devoted to facial movements was analysed in the same way as the grand totals for the whole scale. Fig 2:6:15 illustrates the findings from all four subscores analysed. The lay-out is as for grand total scores (Fig 2:6:13).

Considering these facial scores alone, there was overall, a highly significant relationship between the prevalence of movement disorder and categories of neuroleptic status (H = 19.87 , df = 5 , P = 0.002). There was no effect of being on neuroleptics when examined (z - value = 0.34 , N/S) but a very striking relationship with categories of past neuroleptic exposure was found (z - value = 3.56 , P = 0.0006). Fifty-eight percent of those never exposed in the past showed some facial abnormality compared with 82 % of those given neuroleptics (z - value = 3.35 , P = 0.0012). While comparisons of the difference in prevalence in the heavily treated category with that in the other two categories combined (86.3 % v 70.6 %

FIG 2:6:15

Rockland: regional prevalences of abnormality (total 2 or more) in relation to neuroleptic exposure



abnormality) continued to show significance, this was of a lesser order (z - value = 2.75 , $P = 0.006$). Thus the major difference within the facial subscores appears to lie in fewer of those never exposed to neuroleptics showing abnormality than the rest. There was no interaction between past and present neuroleptic status.

Severity of facial disorder was not related to 'current' neuroleptics (z - value = 0.4 , N/S) but was associated with past status (z - value = 2.31 , $P = 0.02$). This effect was contributed to roughly equally by the difference between those never exposed in the past compared to those treated regardless of degree (z - value = 2.00 , $P = 0.044$) as it was by the difference between the heavily exposed subjects and the others combined (z - value = 1.92 , $P = 0.05$).

As for the effect on facial scores of having had neuroleptics stopped at some time, there was a highly significant linear relationship between facial subscores and the first three categories of neuroleptic status (z - value = 2.75 , $P = 0.006$). This was due entirely to the higher prevalence in patients whose drugs had been stopped than in those never on them (z - value = 3.14 , $P = 0.002$). There was a trend towards a greater amount of severe abnormality in patients whose drugs had been discontinued but this narrowly missed significance (z - value = 1.88 , $P = 0.058$).

Facial prevalences did not differ in patients only recently started on neuroleptics from those never treated ($X^2 = 0.9$, df = 1 , N/S). A striking linear relationship existed between facial prevalences and categories 4 - 6 of neuroleptic status (z - value = 3.06 , $P = 0.0026$). A similar linear relationship was established

for severity (z - value = 1.95 , P = 0.048).

6.5.3 ROCKLAND SCALE NECK AND TRUNK SUBSCORES (Items 17 - 24)

No significant differences emerged between categories of current or past neuroleptic status and RS neck and trunk subscores. None of the analyses looking at prevalence, severity, or the effect of discontinuation or commencement of medication revealed any differences of note. The numbers rating pathological abnormality on these items were, however, small (TABLE 2:6:1).

6.5.4 ROCKLAND SCALE UPPER LIMB SUBSCORES (Items 25 - 32)

Overall, there was no significant relationship between categories of neuroleptic status and the prevalence of upper limb abnormality as recorded on the RS (H = 3.72 , df = 5 , N/S). There was however a marginal effect of actually receiving neuroleptics when examined, with 55.4 % of those on neuroleptics rating abnormality compared with 44.8 % of those not having them at the time (z - value = 1.54 , P = 0.1).

In the upper limbs, there was no significant relationship between past neuroleptic treatment and local movement disorder, though a trend in the anticipated direction could be detected (z - value = 1.38 , P = 0.16). Thus, the prevalence of movement disorder in each category of past neuroleptic status was 42.9 %, 49.4 % and 55.4 % ('none' - 'some' - 'much' respectively). No interaction emerged between past and present neuroleptic administration.

As with prevalence, there was a trend towards more severe abnormality in those taking neuroleptics when seen (z - value = 1.70 , P = 0.086), though severity significantly related to past neuroleptic exposure (z - value = 2.00 , P = 0.04). This resulted from small, but roughly equal differences between the categories in the direction established for other areas.

There was no difference in prevalence or severity of abnormal upper limb movements in those whose neuroleptics had been stopped at some time compared to those never exposed. Likewise, analysis of the effects of recently commencing neuroleptics revealed no findings of note.

6.5.5. ROCKLAND SCALE LOWER LIMB SUBSCORES (Items 33 - 40)

There was an overall relationship between RS lower limb subscores and categories of neuroleptic medication (H = 11.25 , df = 5 , P = 0.045). In the lower limbs, however, the components of this general association were different from what had been established in other body regions.

Although past neuroleptic treatment was related to lower limb movements, this amounted to only a trend (z - value = 1.65 , P = 0.09). The increase in prevalence was progressive from those never exposed, to the heavily treated group. However, there was a highly significant effect of actually receiving neuroleptics when the lower limb examinations were performed. While 27.9 % of those 'currently' on these drugs had abnormal movements, the comparable prevalence in those not receiving them was 12.4 % (z - value = 2.79 , P = 0.005).

This basic reversal of prevalence findings noted in other body regions also applied to severity. Thus although there was a weak relationship between severity of movement disorder and categories of past neuroleptic exposure in the previously reported direction (z - value = 1.87 , $P = 0.058$), more severe abnormality was strikingly commoner in those receiving neuroleptics when assessed (z - value = 2.79 , $P = 0.006$).

No differences were found in the lower limb movements of those whose neuroleptics had been stopped at some time compared to those never prescribed them.

As Fig 2:6:15 shows, these lower limb findings - strikingly divergent from those reported for other body regions - can be accounted for by the much greater prevalence (and severity) of movement disorder occurring in this region in those whose neuroleptic treatment was only recently commenced (i.e. category 4). This group demonstrated significantly more lower limb abnormality than patients never exposed ($X^2 = 2.73$, $df = 1$, $P = 0.003$), though, despite the appearances shown in Fig 2:6:15, not significantly more than patients consistently exposed. There were no differences in severity.

6.5.6. THE EFFECT OF RAISING R.S. CUT-OFF FOR NORMALITY

Comparison of the significance levels achieved for relationships between the prevalence of movement disorder reflected in the RS grand totals and regional subscores, and categories of neuroleptic status using the low and the higher cut-off for normality, is shown in TABLE 2:6:8. In general, it will be seen

TABLE 2:6:8

RELATIONSHIPS BETWEEN ROCKLAND SCALE SUBSCORES AND TOTALS AND CATEGORIES OF NEUROLEPTIC MEDICATION STATUS WITH A LOW AND A HIGHER CUT-OFF FOR NORMALITY

	FACE		NECK/TRUNK		UPPER LIMBS		LOWER LIMBS		TOTALS	
	CUT-OFF		CUT-OFF		CUT-OFF		CUT-OFF		CUT-OFF	
	0-1	0-3	0-1	0-3	0-1	0-3	0-1	0-3	0-1	0-4
CURRENT NEUROLEPTIC MEDICATION	p>0.5	p>0.5	p>0.5	p>0.5	p=0.11	p=0.1	p=0.0054	p=0.066	p=0.2	p=0.24
PAST NEUROLEPTIC MEDICATION	p=0.0006	p=0.078	p>0.5	p=0.19	p=0.16	p=0.018	p=0.096	p=0.0088	p=0.0024	p=0.018
INTERACTION OF CURRENT & PAST NEUROLEPTIC MEDICATION	p>0.5	p>0.5	p=0.14	p>0.5	p>0.5	p>0.5	p>0.5	p=0.14	p>0.5	p>0.5
NEUROLEPTIC STATUS CATEGORIES 1 & 4 v THE REST	p=0.0012	p=0.034	p>0.5	p>0.5	p=0.26	p=0.024	p=0.2	p=0.08	p=0.0068	p=0.042
NEUROLEPTIC STATUS CATEGORIES 3 & 6 v THE REST	p=0.006	p>0.5	p>0.5	p=0.17	p=0.22	p=0.036	p=0.13	p=0.009	p=0.011	p=0.048

that raising the cut-off did not fundamentally alter the pattern of relationships in the comparisons conducted. For the RS face subscore, the relationship with past neuroleptic status is reduced to borderline significance, while that comparing patients heavily treated in the past with the other categories combined fails to achieve signficance with the higher cut-off. Otherwise, those associations attaining conventional levels of statistical significance at a cut-off of 0 - 1, remained significant when the cut-off for normality was raised. Indeed, particularly with upper and lower limb subscores, a number of the relationships strengthen considerably.

With regard to the question of having had neuroleptics stopped (neuroleptic status categories 1 and 2/3), raising the cut-off in general reduced the strength of the significant values. With total scores, the difference between the persisting prevalence in those whose drugs had been discontinued and those never treated was reduced to a trend, while in the face it remained significant, but with a slightly diminished P - value ($P = 0.016$). The trend towards a relationship between severity and the first three categories of neuroleptic status with grand total and facial subscores disappeared at the higher cut-off. There continued to be no relationship with either prevalence or severity on the limb subscores.

In view of the small sample size of category 4, it was felt unjustified to reanalyse the data on the effects of recently commencing neuroleptics with a higher cut-off.

6.6 THE ROLE OF ANTICHOLINERGIC MEDICATION

This was analysed in the same way as was described with AIMS data. Only Rockland grand totals were used and the maximum likelihood/log linear analysis was conducted using only the low (0 - 1) normality cut-off. The higher cut-off, which was in addition used in the analysis of trends, was again 0 - 4.

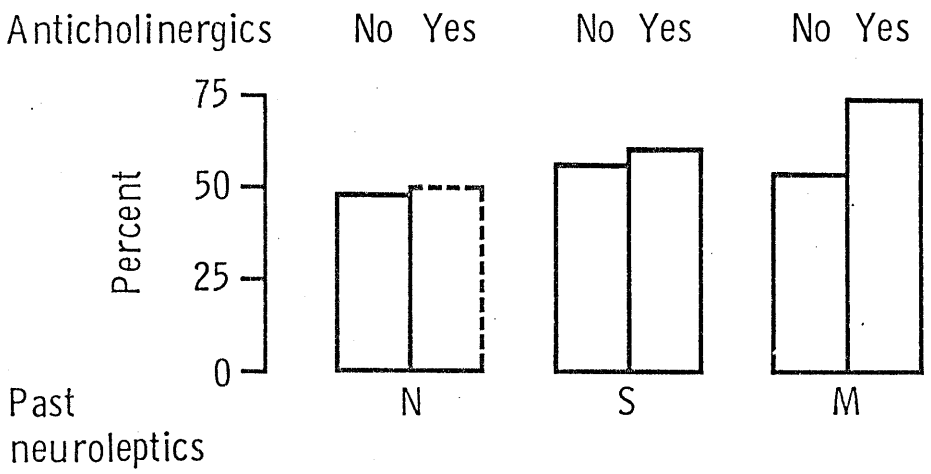
Analysis of trends showed no difference in prevalence of involuntary movements in those on anticholinergics as compared to those not receiving them, using the low normality cut-off for RS total scores (z - value = 1.54 , P = 0.12). However, movements present were more severe in the former group (z - value = 2.14 , P = 0.03). With the higher cut-off, both the prevalence (z - value = 2.25 , P = 0.024) and the severity (z - value = 2.06 , P = 0.038) were significantly greater in those on anticholinergics (Fig 2:6:16 and 2:6:17).

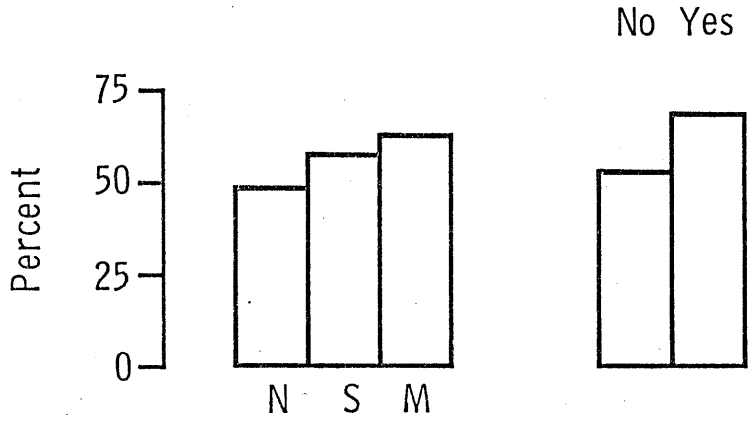
Analysis of males and females separately, revealed little difference with regard to prevalence. Both had a tendency (slightly more marked in the males) to show a higher prevalence when on anticholinergics using the higher cut-off for normality. However only the females showed more severe abnormality on anticholinergics, which emerged especially at the high cut-off (LOW : P = 0.024 . HIGH : P = 0.012). In this situation, 14.7 % of women not on anticholinergics had severe movement disorder while the comparable figure for those receiving anticholinergics was 37. 8 %.

Maximum likelihood/log linear analysis confirmed the role of past neuroleptics in relation to the presence of movement disorder on the RS (X^2 = 8.0 , df = 2 , P = 0.018), and also the lack of a

FIG 2:6:16

Rockland prevalence of abnormality (total 5 or more) in relation to anticholinergic medication

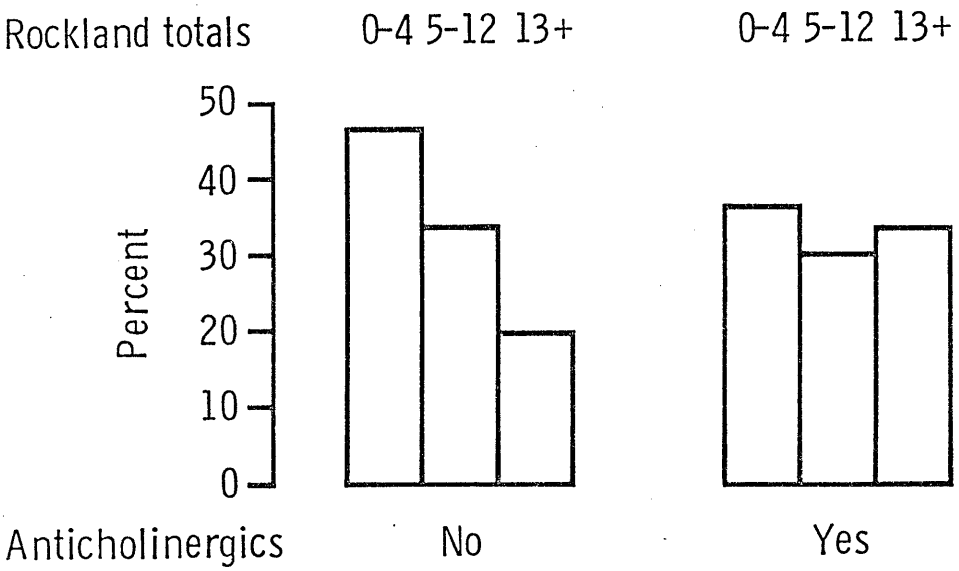




N = None
S = Some
M = Much

FIG 2:6:17

Relationship between increasing Rockland totals (severity) and anticholinergic medication



role for anticholinergics in prevalence ($X^2 = 0.22$, df = 1 , P = 0.64).

Thus, the prevalence of abnormal movements cannot be related to anticholinergic status at examination by two different analyses when a low cut-off point is used to define normality. However, when a more liberal definition of what is normal is applied by raising the total score cut-off, movement disorder of the kind appropriately recorded on the RS is found to be more common in those receiving anticholinergic drugs. In addition, more severe abnormality is noticeable in those on anticholinergic medication, though examination of the sexes separately shows this effect to be confined to the females.

6.7 RELATIONSHIPS BETWEEN MOVEMENT DISORDER AND ITEMS OF RECORDED INFORMATION.

This analysis is identical to that described with AIMS data (Chapter 5.6). The Recorded Information variables are as shown in TABLE 2:5:8. Only RS grand totals were used. Hence, this presentation concerns the relationships between the overall prevalence of movement disorder and historical information. The initial cut-off for normality adopted was 0 - 1.

The relationships are shown in TABLE 2:6:9. With the effects of past neuroleptic exposure accounted for, no unequivocal, independent associations emerged between the prevalence of involuntary movements and any of the Recorded Information variables. There was a marginally significant correlation between both a positive family history of schizophrenia and a history of birth trauma/head injury

TABLE 2:6:9

R.S. DATA: ANALYSES OF RELATIONSHIPS BETWEEN MOVEMENT DISORDER AND ITEMS OF RECORDED INFORMATION AND ASSESSED ABNORMALITY (NORMALITY CUT-OFF 0-1)

	VARIABLES	NO. OF TREND/CONTRAST CATEGORIES (df = N-1)	UNIFIED ANALYSIS OF VARIANCE BY RANKS: OVERALL ANALYSIS H-VALUE	OVERALL ANALYSIS SIGNIFICANCE	RELATIONSHIP WITH R.S. ABNORMALITY Z-VALUE	RELATIONSHIP WITH R.S. ABNORMALITY SIGNIFICANCE	INTERACTION BETWEEN INDEPENDENT VARIABLES Z-VALUE	INTERACTION BETWEEN INDEPENDENT VARIABLES SIGNIFICANCE
RECORDED INFORMATION	FAMILY HISTORY	9	12.11	p = 0.15	1.86	p = 0.06	1.16	p = 0.24
	BIRTH TRAUMA/HEAD INJURY	6	6.52	p = 0.26	1.66	p = 0.092	0.76	N/S
	FITS	6	5.24	p = 0.39	0.43	N/S	1.58	p = 0.11
	PAST ACADEMIC RECORD	9	12.88	p = 0.12	1.35	p = 0.17	0.91	N/S
	LEUCOTOMY	6	11.04	p = 0.05	0.97	N/S	2.17	p = 0.028
	INSULIN COMA	9	12.83	p = 0.12	0.08	N/S	2.7	p = 0.007
	ELECTROCONVULSIVE THERAPY	9	10.72	p = 0.22	0.69	N/S	1.4	p = 0.16
ASSESSED ABNORMALITIES	POSITIVE FEATURES OF THE MENTAL STATE	9	11.66	p = 0.17	0.17	N/S	0.88	N/S
	NEGATIVE FEATURES OF THE MENTAL STATE	9	19.77	p = 0.01	0.47	N/S	0.37	N/S
	COGNITIVE PERFORMANCE	9	9.35	p = 0.31	1.23	p = 0.22	0.51	N/S
	BEHAVIOURAL PERFORMANCE	9	23.97	p = 0.0027	1.14	p = 0.26	1.45	p = 0.14

N/S = $p > 0.5$

such that patients with each of these tended to demonstrate abnormal movements less frequently than those without such histories. This statistical association is likely to be artifactual.

Both leucotomy and past insulin coma produced highly significant interaction terms. For past insulin, the probable explanation is the same as that suggested in the AIMS analysis (Chapter 5.6). With leucotomy, it was striking that of those in the 'age-controlled' band with a history of this procedure (19 subjects), only one did not show movement disorder. The significant interaction term arose from this one subject falling into the intermediate ('some') category of past neuroleptic exposure. It is possible that this one case served to blurr an underlying relationship between the operation and present movement disorder rated on the RS, though in this regard it is noteworthy that the main effect term of leucotomy on RS totals did not even approach significance (z - value = 0.97 , $P > 0.5$).

6.8 RELATIONSHIPS BETWEEN MOVEMENT DISORDER AND OTHER ITEMS OF ASSESSED ABNORMALITY

The items of Assessed Abnormality considered, the arbitrary divisions of scores adopted for each, and the statistical technique for gauging significance were the same as those used for comparable analysis of AIMS data (Chapter 5.7). The cut-off for normality was initially an RS grand total of 0 - 1.

The results are shown in TABLE 2:6:9. Figs 2:6:18 to 2:6:21, which illustrate the findings, are laid out as was described previously (Chapter 5.7). No significant independent relationships

FIG 2:6:18

ROCKLAND: prevalence of abnormality (total 2 or more) in relation to positive mental state features

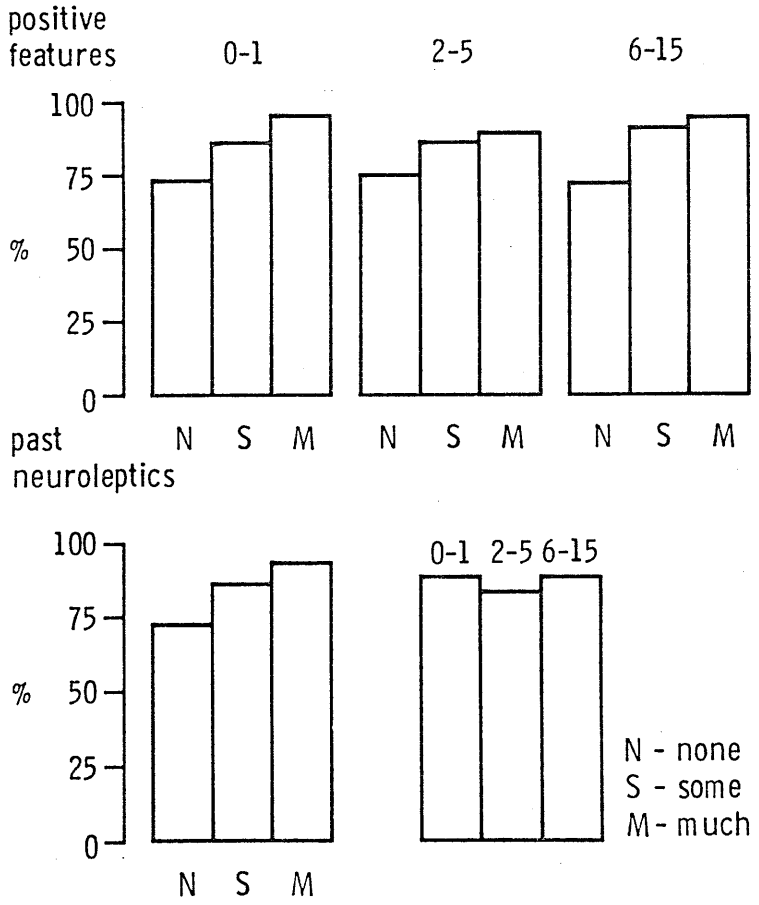


FIG 2:6:19

ROCKLAND: prevalence of abnormality (total 2 or more) in relation to negative mental state features

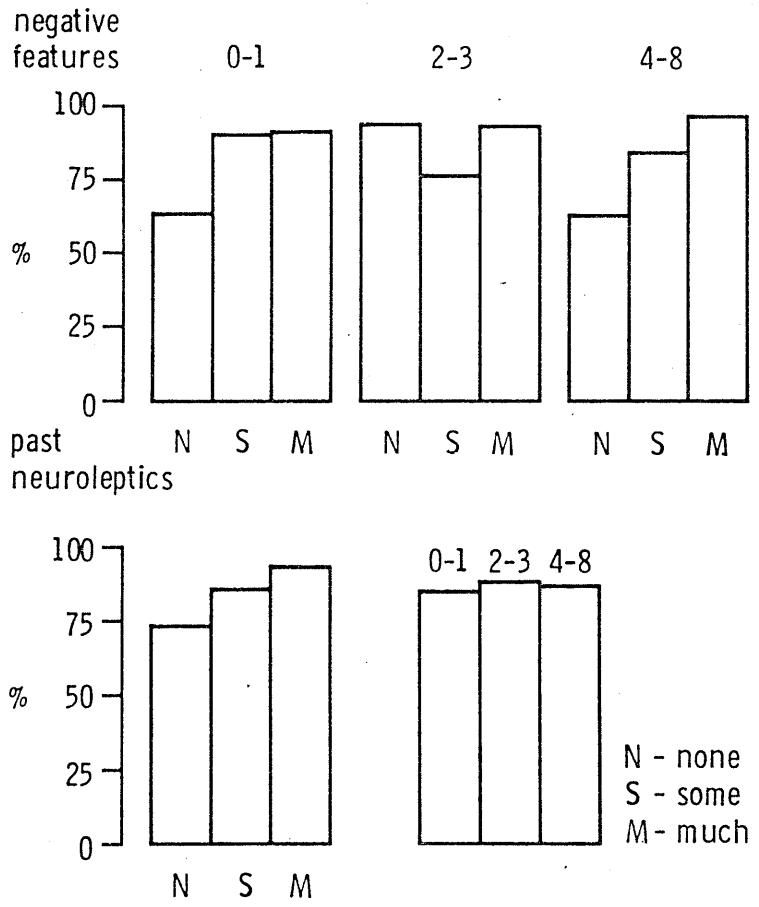


FIG 2:6:20

ROCKLAND: prevalence of abnormality (total 2 or more) in relation to cognitive performance

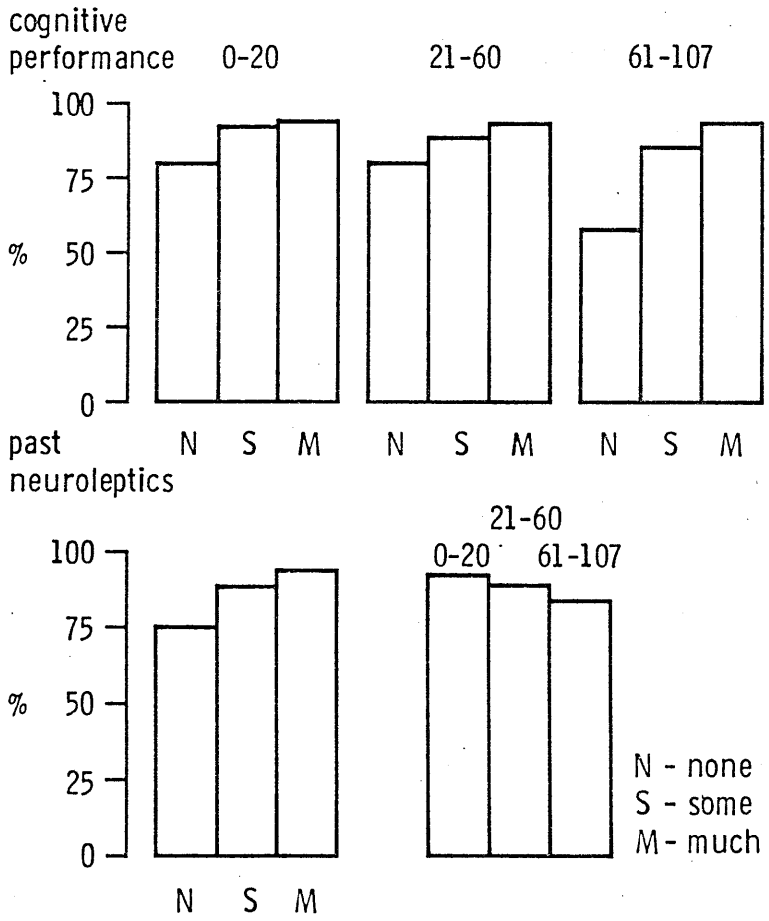
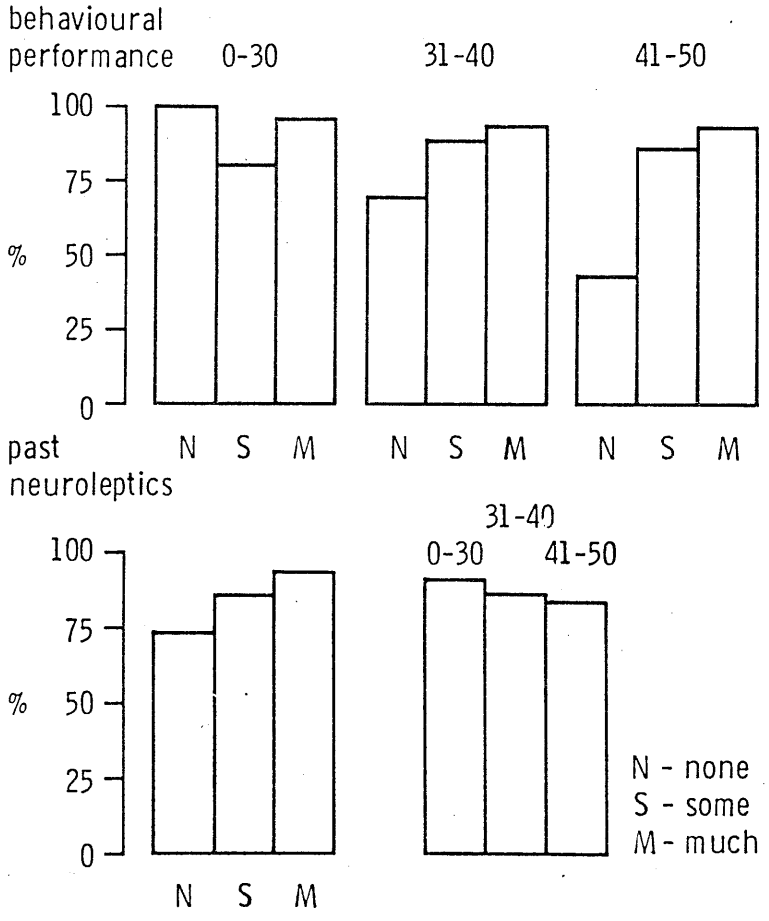


FIG 2:6:21

ROCKLAND: prevalence of abnormality (total 2 or more) in relation to behavioural performance



emerged between the presence of movement disorder using an RS cut-off of 0 - 1 and any of the other items of Assessed Abnormality, and there were no interactions.

6.9 RAISING THE R.S. CUT-OFF FOR NORMALITY

The above analyses investigating relationships between the prevalence of abnormal movements and Recorded Information and Assessed Abnormality variables were repeated adopting a higher cut-off of normality on RS grand total scores (Chapter 3.2.2.b).

The effect on the findings of raising the cut-off is shown in TABLE 2:6:10. Figs 2:6:22 to 2:6:25 illustrate the consequences with regard to Assessed Abnormality variables.

The effect of raising the cut-off was that a marginally significant independent relationship emerged between RS totals and 'negative' mental features, while relationships with cognitive impairment and behavioural deterioration attained significance. These are the same Assessed Abnormality variables which bore a significant relationship to the prevalence of involuntary movements using the AIMS data (TABLE 2:5:10 and 2:5:11).

Choosing a cut-off for normality on the RS is difficult, but as the present work shows, the choice is crucial with regard to the correlates which can consequently be established. In general, a balanced evaluation of the findings regarding the correlates of dyskinesias widely defined, would indicate that relationships can be established between the presence of these and 'negative' features in the mental state, cognitive impairment and behavioural deterioration and that these are independent of time factors and exposure to neuroleptic drugs.

TABLE 2:6:10

R.S. DATA: ANALYSES OF RELATIONSHIPS BETWEEN MOVEMENT DISORDER AND ITEMS OF RECORDED INFORMATION AND ASSESSED ABNORMALITY (NORMALITY CUT-OFF 0-4)

	VARIABLES	NO. OF TREND/CONTRAST CATEGORIES (df = N-1)	UNIFIED ANALYSIS OF VARIANCE BY RANKS: OVERALL ANALYSIS H-VALUE	OVERALL ANALYSIS SIGNIFICANCE	RELATIONSHIP WITH R.S. ABNORMALITY Z-VALUE	RELATIONSHIP WITH R.S. ABNORMALITY SIGNIFICANCE	INTERACTION BETWEEN INDEPENDENT VARIABLES Z-VALUE	INTERACTION BETWEEN INDEPENDENT VARIABLES SIGNIFICANCE
RECORDED INFORMATION	FAMILY HISTORY	9	5.04	N/S	0.37	N/S	0.63	N/S
	BIRTH TRAUMA/HEAD INJURY	6	8.02	p = 0.15	1.58	p = 0.11	0.41	N/S
	FITS	6	3.99	N/S	0.83	N/S	0.35	N/S
	PAST ACADEMIC RECORD	9	9.09	p = 0.33	0.81	N/S	0.78	N/S
	LEUCOTOMY	6	7.48	p = 0.19	0.95	N/S	0.99	N/S
	INSULIN COMA	9	12.1	p = 0.15	1.21	p = 0.22	1.48	p = 0.13
	ELECTROCONVULSIVE THERAPY	9	6.29	N/S	1.1	p = 0.28	0.57	N/S
ASSESSED ABNORMALITIES	POSITIVE FEATURES OF THE MENTAL STATE	9	9.48	p = 0.3	0.97	N/S	1.78	p = 0.072
	NEGATIVE FEATURES OF THE MENTAL STATE	9	26.29	p = 0.0012	1.61	p = 0.1*	0.89	N/S
	COGNITIVE PERFORMANCE	9	8.41	p = 0.39	2.1	p = 0.034+	0.79	N/S
	BEHAVIOURAL PERFORMANCE	9	15.89	p = 0.044	2.39	p = 0.016+	0.15	N/S

* POSITIVE RELATIONSHIP

\+ NEGATIVE RELATIONSHIP

N/S = p > 0.5

FIG 2:6:22

ROCKLAND: prevalence of abnormality (total 5 or more) in relation to positive mental state features

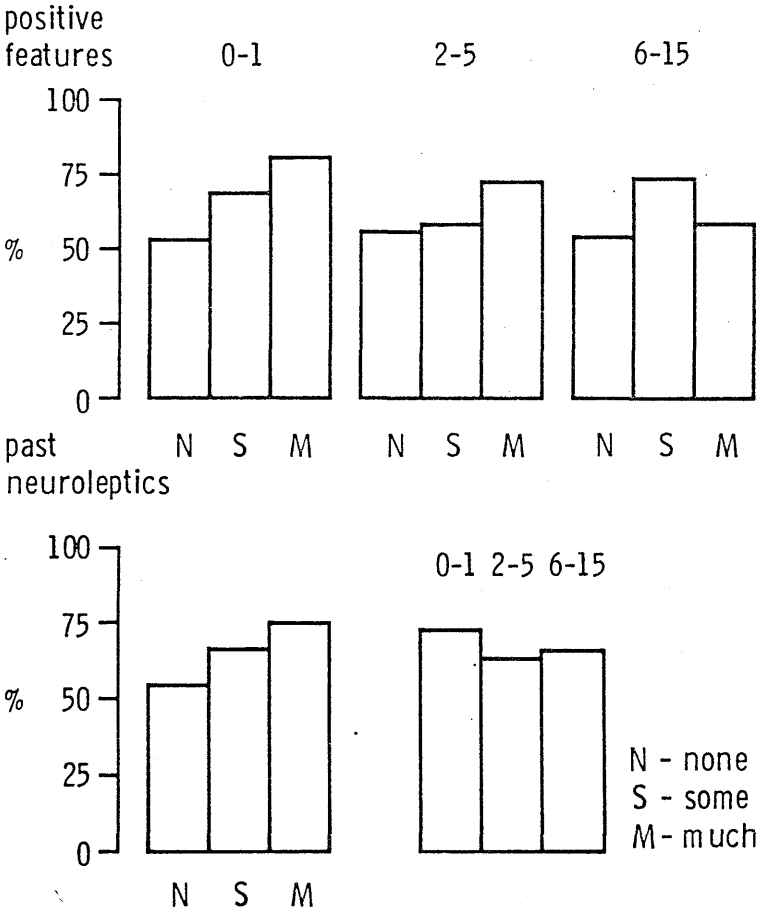


FIG 2:6:23

ROCKLAND: prevalence of abnormality (total 5 or more) in relation to negative mental state features

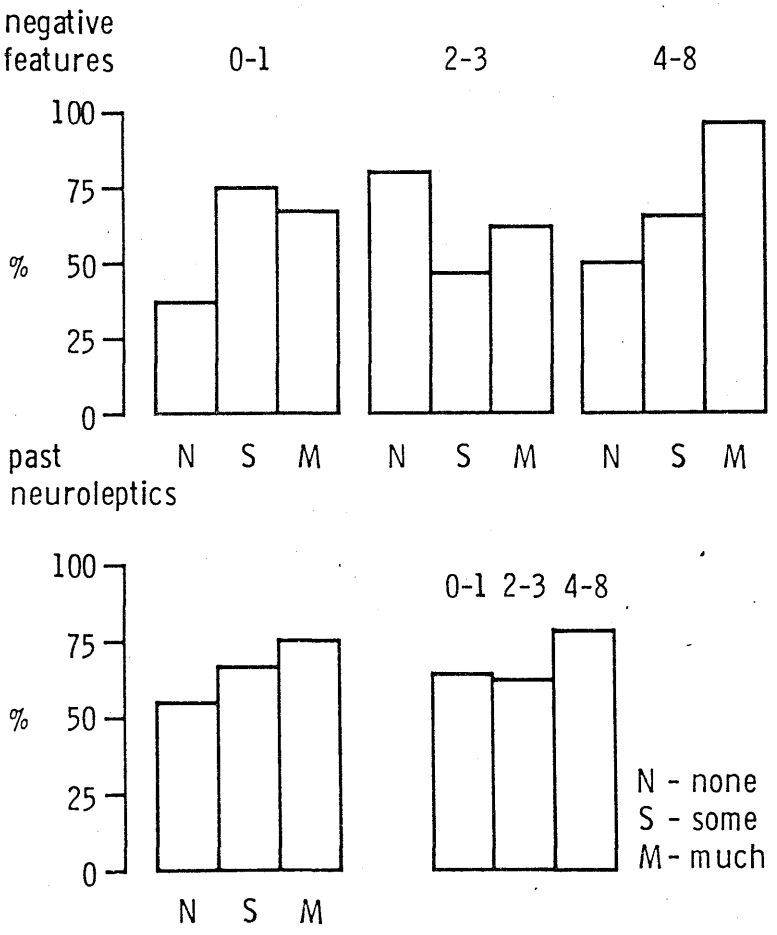


FIG 2:6:24

ROCKLAND: prevalence of abnormality (total 5 or more) in relation to cognitive performance

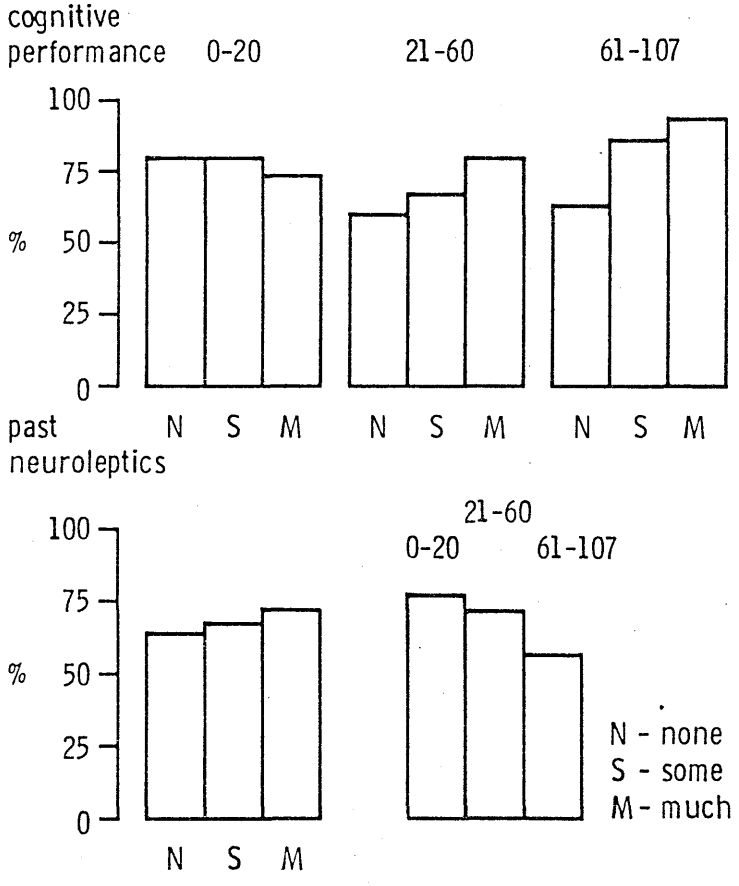
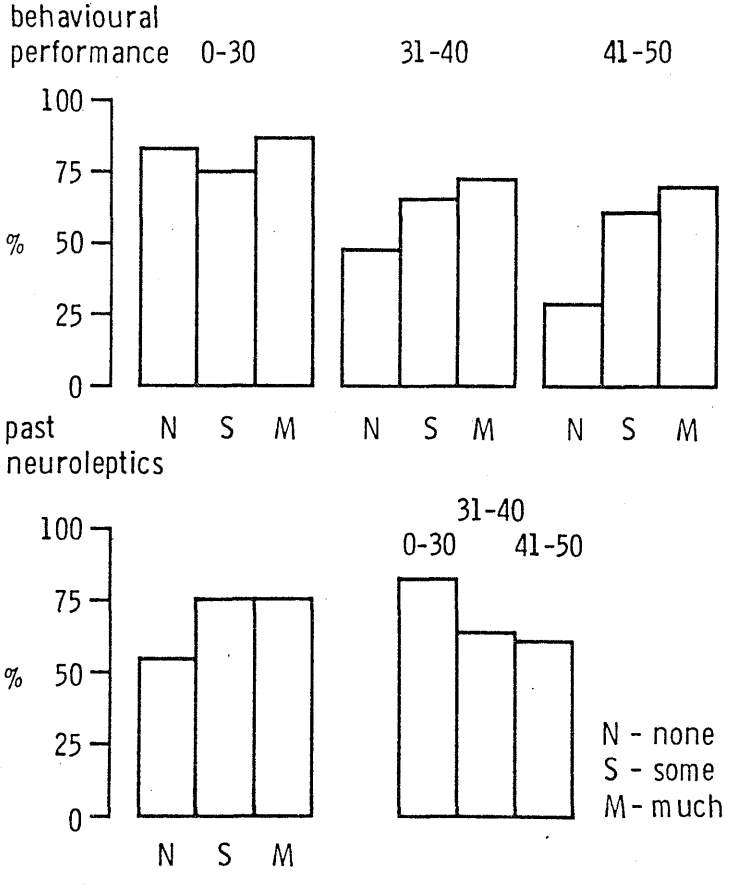


FIG 2:6:25

ROCKLAND: prevalence of abnormality (total 5 or more) in relation to behavioural performance



6.10 SUMMARY OF ANALYSIS OF ROCKLAND SCALE DATA

In this population of long-stay schizophrenics:

1) The prevalence of movement disorder depends on the severity criteria adopted, but is in general very high.

2) Movements are predominantly orofacial, choreoathetoid abnormality of the tongue being the commonest single positive rating. Tremor items were frequently recorded in all body parts.

3) Spontaneous involuntary motor activity of the type recorded on the RS is common, and can be a feature of established schizophrenia whose course has not been modified by the administration of neuroleptic drugs. Such differences in severity and distribution as can be attributed to drugs and nothing else are slight and of little clinical importance.

4) A history of neuroleptic exposure does not of itself allow neuroleptic-treated subjects to be distinguished from neuroleptic-free subjects with regard to their involuntary movements.

5) Time factors strongly correlate with RS total abnormality. The prevalence of involuntary movement disorder is positively correlated with age. There is some evidence that age may make a greater contribution to severity than length of illness.

6) An independent role for sex is difficult to establish. No relationship between prevalence or severity and sex per se can be established except when the single symptom criterion method is used to calculate prevalence. In this situation elderly females have a strikingly higher frequency of abnormality which, when only neuroleptic-treated patients are considered, results from increased ratings in all body parts. However this difference is not reflected in mean scores or number of movements.

7) Significant relationships exist between past neuroleptic exposure and the presence of abnormal movements using RS total scores, an increasing degree of treatment in the past being associated with an increasing prevalence of movement disorder. This overall association reflects heavily the increased prevalence of facial abnormality.

8) Although overall no effect can be demonstrated of actually receiving neuroleptics when examined, this does tend to increase the prevalence of movement disorder found in the upper limbs, and to strikingly increase lower limb abnormality.

9) More severe movement disorder is found in those with a history of past neuroleptic therapy, especially in facial and upper limb regions, though also to a lesser extent in lower limbs. More severe leg abnormality is found in those receiving these drugs when examined.

10) Movement disorder remains more common in patients who have been on neuroleptics but have had them stopped at some time, than in those never exposed, and the previously treated also have a tendency to exhibit more severe abnormality. This overall finding reflects the situation in the facial region.

11) Extending the cut-off for normality did not fundamentally alter these findings with regard to prevalence and severity when the summated scores method is used.

12) Those whose neuroleptic treatment is of relatively short duration do not differ in their prevalence of abnormal movements from those never exposed, in all regions taken together and for all separately, except for the lower limbs, where they have much more disorder. Recent exposure is associated with less spontaneous motor activity than moderate or heavy past exposure held consistently till the time of examination, except for the lower limbs. Facial movements are increasingly severe in those treated for longer periods compared to those recently commenced.

13) The presence of abnormal movements is not related to anticholinergic status at examination using a low total score cut-off to define normality. A greater prevalence is found in those receiving anticholinergics when a high cut-off is used. More severe movement disorder is associated with anticholinergic prescription at both cut-offs, due entirely to the female patients.

14) Movement disorder is not related to historical items of Recorded Information, apart from time factors. This applies whether a low or a higher cut-off for normality is used.

15) With a low cut-off for normality, RS totals are not related to items of Assessed Abnormality. However, using a higher cut-off, the presence of abnormal movements tends to be associated with 'negative' features of the mental state, and is definitely related to cognitive impairment and behavioural deterioration.

Chapter 7 - Discussion

This section of the project was concerned with evaluating a clinical neurological parameter in relation to both the schizophrenic illness and its treatment. Examinations were performed to a predetermined format that was maintained as far as possible with subjects of this type, and findings were recorded in standardised fashion. The examiner remained blind to the patients' personal and treatment histories.

No a priori judgements were made regarding the aetiology of such neurological abnormality as the patients may have demonstrated. To commence from this starting point was possible as approximately 1 in 9 of the sample had no history of neuroleptic exposure. Thus those neurological features related to the treatment of schizophrenia could be separated from those associated with the illness per se.

7.1 DIAGNOSTIC ISSUES

The question of the validity of the drug histories has already been discussed, but it is also relevant at this juncture to assess the validity of the diagnoses attributed to those comprising the study sample. The population was as stated diagnostically homogeneous by psychiatric criteria (Feighner and P.S.E. - cf Part 1). However, such criteria are fundamentally mental state based, and although a definite history of features compatible with organic brain disease effectively excludes a subject, psychotic symptoms can be prodromal manifestations of slowly evolving brain disease, the organic nature of which may be overlooked once a patient is admitted to long-term care.

It is therefore possible that the study population was contaminated by an assortment of neurological disorders manifesting as involuntary movements and psychosis.

Such a view seems untenable. Applying the inclusion criteria excluded one-fifth of the in-patient population given a case-note diagnosis of schizophrenia. Thus by predominantly mental state criteria alone, the sample was tightly defined. Omitting the features of parkinsonism and global cognitive impairment, which in a high proportion of subjects are likely to be illness and/or treatment related phenomena, gross localising neurological abnormality was not common (cf Part 1). In Part 1, the gross neurological features found in the total sample at first examination were noted (TABLE 1:3:7)。 In view of its relevance to the present point, these data are presented again in TABLE 2:7:1. As none of the patients omitted from the second examination had gross ('other neurology') signs, the numbers are the same as those in the earlier TABLE, but the findings are divided on the basis of the patients' history of exposure to neuroleptic drugs. Abnormality can be seen for the most part to be minor and peripheral.

In two cases only, could an alternative neurological diagnosis be entertained, though both were asymptomatic with regard to their motor systems. The first was a lady with gross horizontal nystagmus and bilateral pes cavus. The second lady had hyperreflexia of the lower limbs with sustained clonus and unilateral pes cavus. The significance of this latter feature was difficult to assess as she had suffered a gun-shot wound in adolescence resulting in an arterio-venous fistula in the lower third of the same leg. Nonetheless, her

TABLE 2:7:1 GROSS NEUROLOGIC ABNORMALITIES (EXCLUSIVE OF PARKINSONIAN FEATURES) IN 411 SUBJECTS OF SECOND EXAMINATIONS

CATEGORY	LONG TRACT (LT) SIGNS, NO.	SHORT TRACT (ST) SIGNS, NO.	PTOSIS, NO.	NYSTAGMUS, NO.	MISCELLANEOUS, NO.
Neuroleptic treated	Congenital Hemiparesis, 1 Diplegia, 1 Cerebrovascular accident, 1 Cervical spondylitis, 1 Isolated partial VII nerve (including 2 leuk*), 6+	Masseter atrophy (R), 1 Partial ulnar palsy (old elbow fracture), 1 Partial ulnar/median palsy (self-inflicted), 1 Dorsal interosseous atrophy, 1 R upper limb (indeterminate cause), 2 L upper limb (leuk*), 1	Unilateral, 1 Bilateral (including 1 leuk*), 4	Slight (including 1 leuk*), 5 Moderate, 1 Gross, 1+	Optic atrophy (tobacco amblyopia), 1 Hyperreflexia with lower-limb clonus, 1+ Catalepsy with flexiblitas cerea, 2 Pes cavus, 12+
Neuroleptic free	...	Bell's palsy, 1 R lower limb (indeterminate cause), 1	...	...	Fixed dilated pupil, 1 Pupillary inequality, 1 Pes cavus (doubtful), 1

* Leuk indicates patients who have had leukotomies.

+ Three patients with two abnormalities each.

father had died of "spinal degeneration" at a young age. The question is clearly raised that both these patients, especially the second, may have been carriers of, or have suffered a forme fruste of, some type of spino-cerebellar degeneration in which psychotic features predominated.

It remains possible that underlying brain pathology inappropriate in either degree or situation for the production of gross localising signs but sufficient to contribute to the production of involuntary movements, may be relevant. While unsuspected intra-cerebral lesions were detected on CT scan, the prevalence of these would be insufficient to account for the findings of the present section (this aspect will be discussed in Part 111).

Pertinent to the question of alternative neurological diagnoses is the fact that a number of the sample were old enough to have potentially been exposed to encephalitis lethargica. Approximately 75 % were over 50 years of age when examined and virtually all those in the neuroleptic-free group were in the older age range. Encephalitis was often manifest in vague, flu-like symptoms whose significance could have been overlooked in early life (Wilson 1940). It was however, a condition which caused great concern not only to the medical profession but to the lay public also, and it is a reasonable assumption that there was a high index of suspicion among admitting psychiatrists of the time. No evidence could be elicited that this diagnosis was entertained in any of the subjects of the study, all of whom conformed to two sets of criteria for what is now called schizophrenia. On admission, the next of kin, usually the parents, were required to complete the detailed Enquiry

Form which included information on past physical illnesses and infectious diseases the patient had contracted. It could not be established from this source either that encephalitis may have been a contaminating factor in these patients.

Thus it is concluded that the study population was diagnostically homogeneous and suffered from schizophrenia as this concept is currently understood in both the United Kingdom and among the more conservative authorities in the United States. As the findings presented in Part 1 show, the sample does, however represent schizophrenia in a severe form.

7.2 THE PREVALENCE

Comparison of results from the first examination, where only the presence or absence of movement disorder was considered, and the second using standardised recordings of severity, confirms that when severity of abnormality is recorded on an ordinal scale, prevalence rates increase due to the inclusion of milder degrees of abnormality. In other words the more closely the patient has to be examined, the more abnormality is found. This emphasises the role of ordinal ratings in inflating prevalence. These findings also suggest that, notwithstanding any short-term fluctuations, involuntary movements in chronic schizophrenics of the type described in this study, seem to exhibit considerable stability in gross distribution and severity (at least above a certain threshold)over an 18 month - 2 year period.

The findings presented here illustrate how the reported prevalence of involuntary movement disorder is dependent on two major

factors unrelated to the clinical condition itself :

1). The criterion of severity applied

2) The recording schedule used - implicit in which is the concept of dyskinesia being adopted

Figs 2:5:2 and 2:6:2 show the dramatic effects of different severity criterion. With 'mild' criteria the majority of this population showed abnormality with both scales, while using 'severe' criteria the prevalence shrank to a small minority. The difference in prevalence at 'moderate' severity criteria on both scales amounted to approximately 17 %. Such differences in breadth of concept and degree of spontaneous movement necessary to qualify as abnormal undoubtedly underly much of the discrepancy in prevalence reported over the years and illustrate the weakness of using pooled data to validate the idea of 'neuroleptic-caused' dyskinesia.

Allowing for this, the present investigation revealed a high prevalence of involuntary movement disorder in the study sample. Half the patients exhibited at least moderate abnormality using the AIMS scoring procedure and two-thirds using the more comprehensive Rockland ratings. Items of fast, regular tremor were the most frequently recorded ones in this population and although more sustained dystonic-type truncal and limb movements were recorded, albeit infrequently, abnormality was overwhelmingly of a dynamic kind.

It is only in recent years that standardised rating scales have been applied to record abnormality, of which the most frequently used is the AIMS. Of the published studies that of Smith et al (Smith et al 1979b) is the only one to provide information comparable to the present work, as the others have used either heterogeneous

diagnostic groups or outpatient samples. Using the AIMS, Smith et al assessed the prevalence of "tardive dyskinesia" in long stay patients (average length of hospitalisation 22.7 years) with "either a primary or secondary diagnosis of schizophrenia sometime during their hospitalisation". Their prevalence rates at criteria 2 (mild) or more and 4 (severe) on any AIMS item are similar to those reported here, but they found a much lower prevalence (30 %) using a moderate (3 or more) criterion than the 50.6 % presented earlier.

Consideration of individual items shows a highly significant difference between the present findings and those of Smith et al in all items except upper and lower limbs using the moderate criterion (TABLE 2:7:2). When the distribution of abnormalities among patients with dyskinetic activity is considered, significant differences persist on facial expression, lips/perioral and jaw items (TABLE 2:7:2). Thus, not only were more facial abnormalities found in the present study population as a whole, but also a significantly greater contribution to the total abnormality came from expressive, perioral and masticatory involvements.

Age differences cannot account for these discrepancies as both populations had comparable mean ages. However two other explanations are possible. Smith et al have shown elsewhere the relevance of rater bias in accounting for differences in prevalence rates (Smith et al 1979b). This is an obvious source of descrepancy in studies using standardised schedules which has been widely commented upon, and which is difficult to militate against with any permanency. This does however appear to be a fairly consistent phenomenon across items and although bias may contribute to the

TABLE 2:7:2

DISTRIBUTION OF ABNORMALITY WITHIN TOTAL AND DYSKINETIC* SAMPLES IN TWO STUDIES USING ABNORMAL INVOLUNTARY MOVEMENT SCALE (AIMS)

AIMS Area	Smith et al+			Present Study+		
	No. "Dyskinetic"	% of "Dyskinetic" Sample (N = 88)	% of Total Sample (N = 293)	No. "Dyskinetic"	% of "Dyskinetic" Sample (N = 209)	% of Total Sample (N = 411)
Muscles of facial expression	4	4.55	1.37	56	26.79	13.66
Lips and perioral area	23	26.14	7.85	88	42.10	21.47
Jaw	16	18.18	5.46	77	36.84	18.78
Tongue	42	47.73	14.33	101	48.33	24.64
Upper extremities	24	27.27	8.19	42	20.10	10.24
Lower extremities	25	28.41	8.53	51	24.40	12.44
Neck, shoulder, hips	11	12.50	3.75	41	19.60	10.00

* Smith's criterion of 3 or more on any one or more items.

+ Differences between two studies have following levels of significance. For category "% of 'Dyskinetic' Sample": muscles of facial expression, $P < .001$; lips and perioral area, $P < .01$; jaw, $P < .025$. For category "% of Total Sample": muscles of facial expression, lips and perioral area, jaw, and tongue, $P < .0001$; for neck, shoulders, and hips, $P < .025$.

differences between the two studies, it is hard to see how raters achieving agreement on some items could differ by a factor of ten on others by the operation of this alone. In Smith et al's work, the magnitude of the descrepancy attributable to this was between 25 % and 50 % of a scale point - i.e. of a much lesser order than that found between the two studies.

A more likely explanation lies in differences in the study populations. Subjects of the present investigation conformed to more rigorous inclusion criteria than those of Smith et al, who used a case-note diagnosis of schizophrenia applied at any time over the patients' admission period. With a mean hospitalisation of almost 23 years it is likely that many such American patients would not fulfill operational criteria currently used. It is therefore probable that the clinical deficits of the present sample were more severe. As was shown in the results above, and as will be discussed subsequently, neurological abnormality of this type correlates with certain other indices of severity in long-standing schizophrenia, and it is likely that samples showing greater deficits in other, predominantly mental state areas, exhibit more and severer movement disorder.

7.3 SCHIZOPHRENIA AND INVOLUNTARY MOVEMENTS

The first basic question posed concerned whether or not established schizophrenia, unmodified by neuroleptic drugs, could be associated with involuntary movement disorder. As 36.2 % of the 47 neuroleptic-free patients had abnormality of 'moderate' severity on the AIMS (single symptom criterion method), with a comparable RS figure

of 55.3 %, the answer is affirmative. The movements represented in these prevalences are indistinguishable in type and distribution from those found in samples who have been treated with neuroleptics. The point for consideration then becomes whether or not these prevalences are higher than those found in (a) non-psychiatric, elderly subjects and (b) non-schizophrenic, psychiatric patients.

It is not possible at this stage to make satisfactory consideration of these two questions separately from the evidence published in the literature. As a rule, studies have not addressed the potential role of psychiatric diagnoses in general and schizophrenia in particular as specific contributing variables.

Involuntary movements with an essentially orofacial distribution have been described in the non-neuroleptic treated, non-psychiatric elderly, with the designation of senile chorea (Brain & Walton 1969, Weiner & Klawans, 1973), and "mouthing" (Appenzeller & Biehl 1968), a presumed cerebellar sign, and attention has been drawn to the syndrome of blepharospasm - oromandibular dystonia or Meige's syndrome (Marsden 1976, Tolosa & Klawans 1979). No figures are available for the frequency of these diagnoses but they are likely to be uncommon.

Only one systematic study of normal elderly patients provides data that can be compared with the present work. Kane et al (1982a) examined 127 people (mean age 72.5 years) attending community-based activity programmes for senior citizens. None had psychiatric or neurological histories. Ratings were made on the Simpson (R.S.) Scale though abnormality was calculated on the basis of a single global impression. They found a 4 % prevalence of disorder all of which was

of mild severity. Of the 12 positive ratings made in 5 patients only 1 was not facial. These authors concluded that while involuntary movements can be found in the healthy elderly, " the aging process itself is not likely to produce abnormal involuntary movements without some additional factors coming into play".

Global impressions were not used in the present work, so comparisons cannot be exact. However, using the single symptom criterion technique, the present study provided strikingly different findings. Of the neuroleptic-free schizophrenics, 76.6 % scored at least a single 2 on the RS, the prevalences at increasing criteria of 3, 4 and 5 being respectively 55.3 %, 23.4 % and 8.5 %. Only 5 patients with some positive rating had no abnormality on facial items.

In actual fact the differences between two studies are unlikely to be quite as dramatic as would at first seem. Biases operating in deducing a global impression rating would favour less import being given to, say, upper limb tremor than choreoathetosis of the tongue, when both items were rated at the same point on the severity continuum. Hence if a number of subjects have only fine tremor or other movements not considered by the examiner to represent much in the way of overall disorder, the prevalence of abnormality using global impression will be lower than that found using a single symptom criterion, which avoids such subjective judgements. Nonetheless, even with the more restrictive AIMS, 53.2 % of neuroleptic-free subjects scored at least a single '2'. It should also be noted that the elderly subjects of Kane et al were approximately 6 years older than the neuroleptic-free schizophrenics described here.

The most widely available figures for movement disorder in neuroleptic-free elderly people are derived from pooled data which, as was previously mentioned, give a prevalence of 5 - 6 % (Jeste & Wyatt 1981, Kane & Smith 1982). This is strikingly similar to the figure reported by Kane et al discussed above. It is however not usually possible in this literature to divide samples on the basis of psychiatric status or otherwise from the data presented and hence the question of diagnosis cannot be reliably evaluated retrospectively. Only at the most severe criteria are the present findings in any way comparable with the pooled data or the figure of Kane et al. The prevalence in this study for all areas in the neuroleptic-free schizophrenics at criterion 4 on the AIMS was 4.25 % and at criterion 5 on the Rockland Scale was 8.5 %.

It does not seem tenable that the prevalence differences under discussion are attributable simply to the adoption of differing levels of severity. Most of the authors who have reported on neuroleptic-free samples are recognised authorities in the field of involuntary movements and it is very unlikely that they would note only the most severe disorder. Indeed, this cannot be so as several workers used standardised recording schedules which would have been unnecessary if only severe abnormality was to be noted. In studying geriatric patients, Crane and Smeets did not require to use the last two severity points on their 7 - point scale " since no patient exhibited dyskinesia of a severe nature" (Crane & Smeets 1974). As was noted Kane et al found only mild abnormality in the normal elderly they studied.

It has previously been shown (p156) that the application of

standardised, ordinal scales tends to inflate prevalence rates, though it seems improbable that different recording techniques alone could account for the wide discrepancies under discussion. While a number of those studies from which the pooled data prevalence has been computed did not use standardised methodology of this type (Mettler & Crandall 1959, Demars 1966, Siede & Muller 1967, Jones & Hunter 1969), a number did (Greenblatt et al 1968, Crane Crane & Smeets, 1974, Kane et al 1980, Kane et al 1982a),most of which also reported low prevalences.

The survey of Mettler and Crandell (1959), conducted in a mental hospital prior to the introduction of neuroleptics, is often quoted as evidence that involuntary movements in mental hospital patients were uncommon at that time in the absence of an alternative primary organic diagnosis. This study was designed to investigate the prevalence of major neurological conditions in mental hospital residents, regardless of their psychiatric diagnoses. From the authors' comments, it seems clear that 'dementia' was an important factor in allocating patients to a neurological category. Thus, with regard to schizophrenics,movement disorders were likely to have been worthy of separate note only if they occurred in the absence of such features of organicity. There is, however, growing evidence - reviewed earlier - (cf Part 1) - that 'dementia' may itself be a feature of chronic schizophrenia and that those who demonstrate it may have more movement disorder (vide-infra). Giving such patients a primary neurological diagnosis would clearly deflate the prevalence of isolated involuntary movement disorder associated with schizophrenia. Furthermore, the boundaries of the schizophrenic concept were much wider in the

United States at that time and the number of those who would now fulfill criteria for schizophrenia would have been diluted by many who would not now be considered as such. The 0.5 % prevalence of involuntary movement reported by Mettler and Crandall is likely to represent an underestimate by present standards.

Three more recent studies have reported higher prevalence rates in neuroleptic-free patients and the non-psychiatric elderly than those calculated from pooled data. Varga et al (1982) found a frequency of "not less than 10.3 %" in nursing home residents and attenders at senior citizen centres. This was in fact an underestimate, as the drug histories of all their study group were not noted. Bourgeois et al (1980), using a standardised recording system, studied residents of a retirement home and found "dyskinesias" in 18 % of the neuroleptic-free group, which were overwhelmingly orofacial, while Delwaide and Desseilles (1977), also studying a retirement home population, reported a prevalence of orofacial dyskinesia of 29 %.

These studies are difficult to evaluate. Varga et al's data were incomplete and their assessments unstandardised. Both the other groups used counting techniques but do not discuss the cut-off adopted in designating abnormality. In none is it possible to be confident that all the subjects were non-psychiatric.

The study of Delwaide & Desseilles (1977) provides further information of interest on the role of diagnosis. These authors in addition examined a group of psychogeriatric in-patients "with varying degrees of senile dementia", and found a 38 % prevalence of facial abnormality. Only 9 % of these patients had no associated neurological

signs. The point worthy of note is that this very high prevalence rate - higher than the authors' reported in another group without apparent psychiatric diagnoses - was found in patients with a specific diagnosis implying organic brain deterioration, all of whom by definition must have exhibited cognitive impairment.

7.3.1 SUMMARY

In summary, it is concluded that spontaneous involuntary movements can be found not uncommonly in severe, long-standing schizophrenic patients whose illnesses have not been modified by neuroleptic drugs. The frequency of such disorder reported here is considerably in excess of the figure suggested in the literature for heterogenous, neuroleptic-free groups and the normal elderly, and it is concluded that this increase is likely to be genuine. The prevalence found in the schizophrenics of the present study is more compatible with the high rate reported for a homogeneous diagnostic group of senile dements, than for other neuroleptic-free groups presented in the literature.

The movements found in long-standing, unmodified schizophrenia are predominantly orofacial in distribution and, in accordance with the requirements of the rating schedules used here, not of the manneristic/stereotypic variety. They are therefore identical in clinical form to movement disorders widely held to have a physical basis. None of the neuroleptic-free schizophrenics had regularly received tricyclic antidepressants or other drugs proposed - however tentatively - as being associated with the development of involuntary movements. Hence drugs cannot readily be implicated in explanation

of this abnormality.

One is left with the conclusion that involuntary movements in long-standing, neuroleptic-free schizophrenics represent the clinical manifestations of some underlying brain dysfunction. It is therefore reasonable to assume that in some cases at least, schizophrenia and involuntary movements have a pathophysiological basis in some way related, and that in the unmodified state, the latter are a pointer to the neurochemical disturbance underlying the former. Such tentative conclusions are compatible with the views expressed by a number of the early descriptive writers (Part 1 Chapter 1.4.3c), though of course not with those of Bleuler.

7.4 NEUROLEPTICS AND INVOLUNTARY MOVEMENTS

Having established the presence of involuntary movements to be a feature of unmodified schizophrenia, the second major question was concerned with how neuroleptic drugs relate to this clinical sign in such patients.

7.4.1 THE ROLE OF A HISTORY OF NEUROLEPTIC EXPOSURE

Following on from the above discussion, it is logical to begin by searching for distinctions between movements occurring in schizophrenics never exposed to neuroleptics (what might now be referred to as schizophrenic dyskinesias) and those found in patients treated with these preparations. Going back to Uhrbrand & Faurbye's concept of 'neuroleptic - caused movement disorder' (Uhrbrand & Faurbye 1960) it is reasonable to assume that differences would exist between

two groups divided on the basis of a history of neuroleptic exposure. At a clinical level this is usually taken as the validating criterion of the diagnosis of 'tardive dyskinesia' and it is certainly the assumption behind most of the published work. In this study it was not possible to separate confidently two groups of patients on the basis of the prevalence, severity and distribution of involuntary movements using solely the variable of a history of exposure to neuroleptic drugs.

Throughout this part of the work where appropriate, a 2 - tail interpretation of significance has been adopted. This stringent rule was used in accordance with the fact that no aetiological assumptions were to be drawn beforehand. If however a 1 - tail test were applied - that is, that the hypothesis under consideration allows for the difference between neuroleptic treated and free groups to be in one direction only - then certain comparisons of mean scores did achieve significance at the 5 % confidence level. With the AIMS these were comparisons of means from

a) all regions together ($t = 1.48$, $df = 409$):

b) upper limbs ($t = 1.93$, $df = 409$):

c) lower limbs ($t = 1.67$, $df = 409$). With the RS, they were

a) all regions together ($t = 1.1$, $df = 409$): and

b) lower limbs ($t = 1.76$, $df = 406$). In each case the difference was in the direction of greater means in those exposed to neuroleptics. The unique characteristics of the study population described here made it mandatory to adopt a conservative approach to data interpretation, but even if a 1 - tail analysis were adopted, the above significances were only achieved with small t - values by virtue of the large sample

size.

Thus it is concluded that the mere presence of a history of neuroleptic exposure in patients such as those studied here, is insufficient in itself to validate the assumption that these drugs have, de novo, caused involuntary movements. This in itself does not of course imply that the concept of 'neuroleptic-caused movement disorder' has no validity whatsoever, but it does suggest that if that validity is to be proven, as opposed to assumed, factors other than the neuroleptic history will require consideration. This study examined a sufficiently large sample for the relevance of several potential contributory factors to be assessed.

7.4.2 THE ROLE OF TIME AND SEX

Age is one of the major points of agreement in the literature, most, though not all, studies reporting a significant association between age and spontaneous motor activity (Chapter 1.8.2.a). If this were relevant in the present population the fact that the neuroleptic-free subjects were on average older by a decade than the treated sample could clearly have acted to decrease and even abolish any difference between them due to the drugs. The study population fulfilled Kane and Smith's criterion of spanning more than three decades of age (Kane & Smith 1982) and in line with the bulk of the literature in this situation, the prevalence of abnormality was significantly associated with increasing age.

Advancing age is, however, clearly associated with lengthening duration of illness and the relative contribution of each of these components reflecting the passage of time is unknown. In the present

work no separation of age and length of illness could be shown with regard to the severity of movement disorder. There was some indication that age may have been the more dominant part of the time component with the RS results, which would emphasise that different types of recording scale may produce totals resulting from the operation of different variables. Essentially however, age and length of illness were inextricably interwoven with regard to their relationship to the severity of movement disorder. In this context it cannot merely be that length of illness is operating as an indirect measure of the likelihood of exposure to neuroleptics in the past as previous neuroleptic exposure was accounted for. This finding, combined with those discussed in Part 1, indicates that length of illness may in itself make an important contribution to some of the deficits of chronic schizophrenia.

Although there were limitations to the analyses of individual movements, orofacial activity appears to be particularly sensitive to development with age, though unfortunately other variables of potential importance could not be assessed. The buccomasticatory lingual (BML) triad may indeed have validity as an age phenomenon as, for example, the findings of Kane et al suggest (Kane et al 1982a). It is perhaps of relevance in this regard that a number of studies, particularly earlier ones, which concentrated on facial abnormality, studied older patients.

The role of sex that emerged was not straightforward and the present work was unable to confirm the widely held impression of a simple female excess in prevalence and severity of involuntary movements. The practice of calculating figures on the basis of pooled

data is particularly inappropriate to this question in view of the interposition of modifying variables such as age. Thus the F : M ratio computed by Smith and Dunn (quoted by Kane & Smith 1982) of 1.68 from 31 different samples may reflect nothing more than the fact that females, in some studies at least, were older.

Using the technique of single symptom criteria to calculate prevalence, this study found a female excess at AIMS criterion 4 in the over 70's that is strikingly similar to that reported by Smith and Dunn (1979). These authors found a female:male ratio of 4:1 at criterion 3.5 (mean of 2 raters), while at criterion 4, 21.3 % of women over 70 rated abnormality but none of the men. In the present work, the comparable ratio at AIMS criterion of 4 was 4.31 with the prevalence in females of 15.5 % greatly outweighing the 3.6 % found in males (TABLE 2:5:5 - neuroleptic treated only to make the comparison appropriate). However it is there that the similarity ends. The present work was not able to confirm the divergent effect of age in the sexes using mean scores, which in the report of Smith et al showed a significant increase for females over 70 compared with males (Smith et al 1979b). As Fig. 2:5:9 showed, the sexes in the present study did not significantly differ in mean scores with age, including the tendency to plateau over 60 years of age - a result which was not altered by considering only those exposed to neuroleptics. Furthermore, the sexes did not differ in the mean number of movements rated in each age band, a factor not previously assessed.

The only plausible interpretation of the present findings is that elderly females have a tendency to score at the extremes while the older males are more likely to remain intermediate in severity

(i.e. a score of 6 is more likely to comprise a 4 and a 2 in the females but two 3's in the males). This finding with the AIMS data applies equally to the RS results. However while the female excess of severe AIMS - type disorder in the geriatric patients treated with neuroleptics was confined to facial items, the excess of RS - type disorder in the same patients, which was striking overall (6.34: 1) was more generally represented - i.e. in limb/trunk items as well as face.

The present work was in addition unable to attribute a role to sex in severity of abnormal movements as assessed by the numbers of patients scoring within arbitrary ranges of total scores. The only differences detectable were due to the increased age of the females compared to the males. With this accounted for, no independent role for sex in severity could be elicited with the data from either scale.

It is hard to see how the sex differences in prevalence found in this study greatly advance our understanding of involuntary movement disorder in schizophrenia. It is moreover important to emphasise that such differences as did emerge, or the incompatibility of the present findings with the conclusions drawn from the literature (Jeste & Wyatt 1981; Kane & Smith 1982), may not reflect anything more than the role of indirect modifying factors in determining the clinical presentation. They may tell us nothing about the neuropathophysiology of the condition and may be false indicators of risk.

In the present study, 17.9 % of the males over 70 years of age still had their own teeth, while the comparable figure for the females was only 3.4 %. The edentulous state was discussed as an aetiological factor in early publications in this field

(Joyston-Bechal 1965) and, while few would now accept this as the only causative factor in the context under discussion (as Paulson, quoted earlier, has stated) there equally can be little doubt that such factors can be of relevance (Sutcher et al 1971). In the present population varying states of dentition could easily account for the difference between, say, an average rating of 3 and one of 4, regardless of neuroleptic status.

Furthermore others have noted the different prescribing factors that may apply to the sexes with women tending to receive more drugs in higher doses (Degkwitz & Wenzel 1967; Jones & Hunter 1969; Fann et al 1972; Laska et al 1973; Prien et al 1975; Simpson et al 1978). In the present study only 10.3 % of the geriatric males (over 70) were receiving neuroleptics when examined, while for the females the figure was 55.9 %. By contrast, in the group assessed by Smith et al it appears that all were receiving drugs, including the geriatric patients (J.M. Smith et al 1978). Although actually being on neuroleptics when seen was shown here not to affect the prevalence of abnormal movements, it is possible that such differences at examination - or over time prior to examination which was shown to be of relevance in prevalence - may affect mean scores. Such differences could readily account for the discrepancies between the present findings and those in the literature, especially those of Smith et al, the major source of contention with the present findings. It would be an error, with variables such as these unaccounted for, to consider female sex as a primary risk factor.

It is concluded therefore that the present study was unable to attribute any noteworthy role for sex in determination of both the

prevalence and severity of spontaneous movement disorder.

The potent role of age in neuroleptic usage that has been commented on by others (J.M.Smith et al 1978; Smith et al 1979) was illustrated here. Apart from the fact that those never exposed to neuroleptics were older than those treated with these drugs, which reflects the era during which the former group was admitted, those heavily treated were significantly younger than the other exposed groups and those who had their neuroleptics commenced for the first time in the period between the two assessments were the youngest patients to have remained neuroleptic-free up to that time. This is likely to be related to the feeling among clinicians that the illness tends to "burn out" in older patients and hence that drug efficacy declines or that older patients are less able to tolerate potent, centrally-acting medication.

7.4.3 THE ROLE OF NEUROLEPTIC DRUGS

The problem posed for analysis by the age differences in the categories of neuroleptic status was mentioned earlier (Chapter 5.4). The compromise adopted means in effect that any differences in movement disorder to emerge between neuroleptic-treated and untreated groups, and between the 'some' and 'much' categories of past neuroleptic exposure, represent an underestimate as the full effects of the lower mean age of the consistently and heavily treated group (category 6) were not accounted for.

This study represents the first direct evidence in a comprehensive, homogeneous in-patient sample of a role for neuroleptic medication in determining both the prevalence and severity of

spontaneous involuntary movements. The unequivocal drug effect could be demonstrated with both a narrow and a wider definition of 'dyskinesia' as reflected in AIMS and RS data respectively.

The prevalence figures in relation to neuroleptic exposure (Figs 2:5:12 and 2:6:13) represent extremely high levels of abnormality. This partly reflects the overall prevalences reported for the whole sample. In addition however, they are calculated on an elderly (essentially over 60) population and also adopt cut-offs for normality which some might consider unduely low. Thus, Smith et al have written:

> "Since a rating of 2 (mild) on a single AIMS item could result from a variety of nervous habits, in no way should this be considered a definite indication that a patient has tardive dyskinesia"
> (J.M. Smith et al 1978).

It is important to remember that the present work was not concerned with 'tardive dyskinesia' per se, but with the generality of dyskinesia in schizophrenia, and its correlates - one of which was neuroleptic medication. The cut-offs were therefore chosen on the basis of the degree of misclassification of mild, but <u>definitely abnormal</u>, movements and not in order to arrive at a diagnosis based on aetiology, which would in any case represent a misuse of rating scales. Hence, comparisons of these specific figures with other published data are inappropriate and criticisms of the findings on the basis of over-rating or undue conservatism in defining normality, are unjustified.

The division of past neuroleptic exposure into 'some' and 'much' was arbitrary. Almost every author who has published in this field has commented on the difficulty in obtaining accurate and reliable drug histories on the study patients. The present work was no exception.

Even where clear information is forthcoming, it cannot be taken for granted that prescribed regimes bear any relationship to the amount of drug available to achieve the pharmacologically desired effect. Pharmacodynamic and kinetic variables and the simple fact that many patients have been shown not to take their medication (Willcox et al 1965) may modify the anticipated action. In recognition of such problems, the division of neuroleptic intake was purposely kept simple. Nonetheless, the arbitrary divisions adopted were felt to have validity within the limits of the quality of information on which they were based and incorporated an evaluation of both the amount of neuroleptic (in terms of daily dose) and the duration of exposure.

Whether or not neuroleptics were being administered at the time of the examination made no difference to movements of the type recorded on the AIMS, and while RS totals were similarly unaffected there was some evidence that limb movements covered by the wider Rockland concept of dyskinesia may be more influenced by this variable. Such a finding probably reflects an increase in tremor ratings in those receiving neuroleptics and is compatible with clinical experience. It is likely that such factors underly the differing correlates of limb as opposed to other body movements that have been reported over time (Kidger et al 1980). This point again emphasises the different variables that may operate with different recording techniques.

By the criteria adopted in this investigation past neuroleptic treatment was the important drug component with regard to both the prevalence and the severity of abnormal movements, the effect being noted with both scales. General conclusions would be inappropriate,

but within this older population of severe, long-standing schizophrenics, the neuroleptic effect on prevalence, although substantial and strikingly significant, was of a much lesser order than that attributed to these drugs from calculations based on pooled data. That computed indirectly is approximately 3 - 4 fold, while in the present sample, using the liberal definition of normality implicit in a higher cut-off, it is approximately 30 % with both scales (in actual fact this figure is likely to be an underestimate in view of the incompletely compensated age differences in the neuroleptic treatment categories - vide supra). This discrepancy is due entirely to the high indigenous rates of abnormality in the unmodified illness.

The findings on severity emphasise the role of neuroleptics in not only promoting the development of involuntary movements but in exacerbating their degree. AIMS results indicate that high totals are approximately 35 % commoner in those exposed to neuroleptics compared to the base-line for untreated patients, while with the RS they are 54 % more frequently found. The fact that receiving neuroleptics at the time tended to be associated with high totals on the RS is likely to again reflect the augmenting effect of these drugs on tremor-like abnormality.

Two further points raised by the findings in this study are of interest but require cautious interpretation in view of insufficient detail. The first is the effect of recently having commenced neuroleptics and the second is the effect of discontinuation.

Although onset of 'tardive dyskinesia' has been reported after 3 - 6 months of neuroleptic treatment (Degtkwitz 1969; Moline 1975;

Stimmel 1976) and sometimes even less (Chouinard & Jones 1979), the conclusion of the literature remains that 2 years or more are necessary to promote the involuntary movements. (APA Task Force 1979 and 1980). It is of note therefore that those whose neuroleptics had been commenced for the first time between examinations - that is, whose duration of treatment was less than 2 years - did not exhibit greater total abnormality than their counterparts who had remained neuroleptic-free. They did however appear to be strikingly susceptible to lower limb disturbance of the type recordable on the RS. This is again likely to be tremor-like activity or possibly restless legs. It is not due to akathisia, strictly defined (i.e. inability to sit still with a subjective drive to pace) as this is item 42 on the RS which is rated separately from the lower limb items (33 - 40) on which this analysis was conducted. The caveat to this finding is the small number of subjects on whom it is based. It nonetheless is compatible with the bulk of the literature.

As was mentioned, the idea of irreversibility appears to be incorporated in the concept of 'tardive dyskinesia' as understood by some authorities, though the question of 'persistence' versus 'reversibility' remains unclear. This study is unable to address this question properly as, in the two groups who had had neuroleptics discontinued at some time (categories 2 and 3), no information was available on precisely when the drugs were stopped, what form of preparation - oral or depot - was involved, or, of considerable importance, why drug treatment was terminated. It nonetheless remains of interest that with both scales, those whose drugs had been stopped continued to show a significant excess of movement disorder. With

the more tightly defined AIMS, that disorder in addition remained more severe.

It has been suggested that neuroleptic-related dyskinesias can be classified on their ability to resolve after discontinuation of the provoking agent (Jeste et al 1979) and that pathophysiologically, reversible and persistent syndromes may differ (Gerlach & Faurbye 1980) though how long a time is necessary before the diagnosis becomes one of 'persistent' dyskinesia is uncertain. In the present sample, the period off neuroleptics varied from months to many years, but for the majority it was at least 2 years. It is thus striking that such abnormality remains detectable, although the proportion who retain the potential to resolve is unknown. Advanced age is one of the factors that have been proposed as being associated with persistence or irreversibility of neuroleptic-related dyskinesia (Paulson 1968; Itoh & Yaji 1979; APA Task Force 1979), and the relatively old age of this analysed sub-sample of the total population is probably relevant to the continued deviation of their ratings from those of patients never on neuroleptics. However, more detailed data on the time span since stopping, type of preparation and the clinicians reasons would be required before much could be made of these findings.

Relevant to discontinuation is the general argument that past neuroleptic regimes may have been determined as much by the development of involuntary movements as by mental state and age considerations. In a cross - sectional, epidemiological study of this type, this cannot be refuted. However, many of those whose neuroleptics were discontinued had them stopped years previously - sometimes in the 1960's - at a time when 'tardive dyskinesia' was little known, far

less a cause for concern. It seems unlikely that this was a major consideration in the management decisions involving this sample at that time.

It is concluded that the present findings support the view that increasing exposure to neuroleptic drugs - by daily dose increments, duration of treatment or both - is associated with an increased prevalence and severity of involuntary movement disorder above the high base-line inherent in severe long-standing schizophrenia; that the effect may for most require more than 2 years treatment to become detectable; and that these drugs may contribute to a permanent or at least durable change. These neuroleptic effects can be detected independent of age and length of illness factors.

7.4.4 THE ROLE OF ANTICHOLINERGIC DRUGS

According to the post-synaptic dopamine receptor supersensitivity hypothesis of pathophysiology, anticholinergics, by further disrupting the cholinergic-dopaminergic imbalance in the striatum, should theoretically act to promote 'tardive dyskinesia'. Indeed, manipulation of central cholinergic systems has been suggested as a useful method of provoking 'latent' dyskinesias in those at risk (Mackay & Sheppard 1979), and of distinguishing neuroleptic-related movement disorders from other involuntary motor disorders of the face such as Meige's Syndrome (Stahl et al 1982).

It is surprising, in view of the importance of the theoretical implications and the widespread use of anticholinergics, that so

little formal examination of this question has been undertaken. Much of the advocacy for avoidance of anticholinergics in this situation is based on acceptance of a theory which, it was suggested earlier, is at best an oversimplification and at worst, quite wrong (Jeste & Wyatt 1981a).

Kane and Smith (1982) quote 5 significant findings in the literature in relation to anticholinergics, encompassing current and past use, total amount and duration of treatment, but noted 13 negative reports. Thus there is little clinical evidence from this review to support the theoretical objection to concurrent anticholinergics.

In the specific context of the present findings, Crane demonstrated a relationship between movement disorder and current anticholinergic prescription (Crane 1974), while Asnis et al (1977) and Chouinard et al (1979), both studying schizophrenic outpatients, found no association. The former group used the AIMS and the latter, their own comprehensive schedule.

The establishment of relationships between schedule scores and administration of anticholinergics in the present work depended on the scale from which data were drawn. Like Asnis et al, but in a different population, this investigation could not establish any relationships between AIMS data and anticholinergic prescription. The position with the RS data however, was somewhat different. Relationships of a significant order were found especially when a higher normality cut-off was adopted. The prevalence of movement disorder was greater and high total scores more frequent in those receiving anticholinergics when examined, the latter finding being essentially confined to females.

These findings illustrate yet again the importance of the breadth of concept employed in the study of movement disorder. The major, though not the exclusive, difference between AIMS and RS is in tremor items. The RS includes as specific items, some abnormalities conventionally referred to as parkinsonian, for example rabbit syndrome, pill-rolling, akathisia. It is likely that those receiving anticholinergics had these commenced because of the presence of parkinsonian features or general tremor-like abnormality construed by the clinician as possibly parkinsonian. This is compatible with the finding that limb abnormality - especially that of the legs - is more prevalent in those actually receiving neuroleptics when examined. Although this relationship did not reflect in RS totals, on which the anticholinergic analyses were conducted, the greater limb activity in these circumstances could, at a clinical level, have encouraged the concurrent prescription of anticholinergics. It might be anticipated in such a situation that higher scores would be more frequently noted in those receiving anticholinergic drugs, as was found.

Such an interpretation is compatible with the findings of Ezrin-Waters et al (1981), who noted that the severity of oro-buccal dyskinesia (using R.C.Smith's schedule) did not correlate significantly with anticholinergic use during the assessment period, but that total body dyskinesia did. The implication is that the difference resides in the limbs. These authors likewise attributed their findings primarily to neuroleptics,(in their case, depots in particular), anticholinergics being prescribed because of the movements rather than causing them.

Understanding any relationship between anticholinergics and movement disorder is more than establishing a statistical correlation between the two. The mere demonstration of a worsening in severity of involuntary movements following the administration of anticholinergics would not of itself allow the implication of a direct cause and effect to be drawn. A general stimulant effect of these preparations on mental state has been described (Shader & Greenblatt 1971; Jellinek 1977, Kaminer et al 1982), as also has the ability of anticholinergics to produce slight but significant exacerbation of 'positive' psychotic symptomatology (Singh & Kay 1975; Johnstone et al 1983). One point that is clear is that extra-pyramidally mediated movement abnormality can be modified by features of the mental state and the degree of the patient's alertness (Marsden et al 1975). Hence changes in movement pattern following the administration of these drugs may reflect nothing more than their ability to modify non-specific variables.

It remains possible that the appropriate explantion of the present findings is that anticholinergic drugs may themselves promote movements of the type recordable on the RS but not on the AIMS, or, with regard to the previous point, that mental state variables account for this difference. However, with the population the size of that studied here, with as much and as wide-ranging movement disorder as has been demonstrated, such non-specific effects would require to be consistently quite marked to be detected with the degree of significance reported, and the earlier explanation of the findings regarding anticholinergics seems more reasonable.

The sex differences at high cut-off also to some extent support this interpretation, as they can be explained as arising from the sort of prescribing differences noted earlier.

It can be concluded that caution must be exercised in the interpretation of drug-related data in general and anticholinergic data in particular in the study of involuntary movement disorder, but with a tight definition of both dyskinesia and normality no clear, causative relationships between administration of anticholinergic preparations and movement disorder could be established in the present work.

7.4.5 THE ROLE OF HISTORICAL AND SPECIFIC MENTAL STATE FACTORS

A large number of studies have assessed the relevance of a range of historical variables in regard to 'tardive dyskinesia', with somewhat contradictory results (cf Chapter 1.8). Surprisingly few studies on the other hand have evaluated factors related to the schizophrenic illness itself, and none have as yet looked at these questions comprehensively.

In this study, the wider range of Recorded Information items encompassing personal historical and past treatment variables shed no light on the correlates of movement disorder in severe long-standing schizophrenia. Of particular note is the absence of any relationship with past physical treatments other than neuroleptics. Apart from the Recorded Information variables of age, sex and past neuroleptic treatment reviewed earlier, there is no data in the literature suitable for comparison with the present work.

In connection with the question of organicity as a predisposing

factor, the lack of systematic enquiry and satisfactory criteria, and the resultant equivocal conclusion in the literature have been discussed (cf Chapter 1.8.2c). The present investigation established significant independent relationships between the presence of movement disorder on both assessment scales and impairment on the Withers and Hinton test battery. Indeed, it is possible that the actual relationships are stronger than those reported here (TABLES 2:5:10, 2:5:11, 2:6:10). The cognitive score ranges for purposes of analysis were chosen to balance numbers in each cell and thereby aid statistical evaluation. It is possible that the arbitrary ones used were not the most appropriate to demonstrate the relationship. These results would indicate therefore that in long-standing schizophrenics, cognitive impairment, especially that below a certain threshold, is likely to be associated with involuntary movement disorder. This conclusion finds support in the literature (Edwards 1970, Famuyiwa et al 1979) in suggesting that cognitive impairment, which is after all the mental state hallmark of organic dysfunction, is a more appropriate parameter by which to assess 'organicity' in relation to movement disorders than surgical or other historical factors, some of which bear a putative rather than a proven relationship to organic brain change.

The question remains as to whether this finding is based on an association between long-standing schizophrenia and generalised brain dysfunction, or whether the involuntary movement disorder and severe schizophrenia share in common some more localised functional or structural substrate.

Scant attention has been paid to mental state and behavioural

variables either in diagnostically heterogeneous populations or in studies concentrating solely on schizophrenics. The present study is the first comprehensive examination of these questions.

Spontaneous involuntary movements were not found to be related to the 'positive' features of the mental state. The significant relationships concern the 'negative' mental state features - that is the summated Krawiecka items for flattening of affect and poverty of speech/muteness - and in addition to behavioural deterioration in terms of overall impairment on the Current Behavioural Schedule.

There are no comparison data available in the literature, but broadly speaking, these results are in keeping with the findings reported by Ital et al (1981) and McCreadie et al (1982) referred to earlier. Mukhurjee et al on the other hand reported a significant relationship between "tardive dyskinesia" (AIMS) and a history of incoherence of speech and grandiose delusions, but information on these past events was obtained from case-note review, not direct examination of the patients (Mukhurjee et al 1982).

Kucharski et al (1980) related the discharge status of 265 "schizophrenics" (criteria as mentioned earlier in the study of Smith et al 1979b) to involuntary movement scores assessed on the AIMS two years previously, and found that those discharged had had significantly lower AIMS scores than those remaining in hospital. These authors considered several explanations of this finding including stigmatisation which, it has been suggested, impairs resocialisation (Baldessarini 1977).

Social and administrative variables are clearly relevant to a

patient's suitability for discharge from hospital, although it is of course likely that clinical factors relating to the illness itself are also important. In the case of schizophrenics, persisting psychotic features may not however be the determining clinical factors. The parallel study to the present one, reported by Johnstone et al (1981) has been mentioned previously (Part 1 - Chapter 5.2.3). As will be recalled, these authors found few differences in Assessed Abnormalities in a group of non-institutionalised chronic schizophrenics discharged from Shenley Hospital over a 5 year period, when contrasted with those of the present group (age and length of illness accounted for). The non-institutional group however produced significantly better scores on cognitive testing than the in-patients. It was suggested that deductive, problem-solving abilities may be part of what is being assessed in 'dischargability'. As movement disorder correlates negatively with cognitive performance, it could be predicted that those of an in-patient population who achieved discharge may have less movement disorder.

Kucharski et al considered the possibility of some additional factor linking AIMS disorder and discharge when they wrote that

> "it is conceivable that (their) results are due to a relationship between tardive dyskinesia, discharge, and some other factor".

Their "other factor" could relate to the type of mental state and behavioural deficits under discussion here. Thus the alternative hypothesis they offer - mainly that patients with movement disorder "may be more psychiatrically disturbed than those not so affected" - is to some extent compatible with the present findings.

On a similar theme, Chouinard et al found that their Clinical Global Impression score assessing therapeutic effect was one of the best predictors of involuntary movement abnormality and concluded that "tardive dyskinesia" was more prevalent and more severe among patients with little therapeutic improvement (Chouinard et al 1979). Bearing in mind evidence of this type and the pattern of mental state deficits associated with movement disorder in the present study, it is of interest that Jus et al (1976a) reported that "tardive dyskinesia" is more frequently found in schizophrenics with a slow, insidious onset of illness than in those with an acute onset.

Thus the present work confirms suggestions in the literature that illness-related variables may be associated with the development of involuntary movements in schizophrenics treated with neuroleptic medication. The present comprehensive evaluation of this question would indicate that the type of illness concerned is that characterised by 'negative' mental state features, cognitive impairment and general behavioural deterioration, and not the type in which 'positive' productive features predominate. This cannot be regarded as reflecting greater neuroleptic administration in those with deteriorated 'negative' states, as, within the criteria adopted this, along with age and length of illness was accounted for.

7.4.6 SUMMARY

This study has confirmed the validity of the concept of neuroleptic-caused movement disorder. The analyses have indicated however that the relationship between these drugs and abnormal

movements is complex. Neuroleptics of themselves are neither necessary nor sufficient with regard to the aetiology of spontaneous motor activity - especially in patients with long-standing schizophrenia - and a history of exposure to these preparations is on its own an inadequate parameter with which to validate the concept of tardive dyskinesia. Nonetheless with other relevant factors, particularly those reflecting the passage of time, accounted for, neuroleptic drugs are associated with both an increased prevalence and severity of spontaneous motor disorder, which may take more than 2 years to become established and which for some may persist long after neuroleptics are withdrawn.

7.5 CONCLUDING REMARKS

The question of whether the schizophrenic illness and some action of neuroleptic drugs produce motor disorders which represent the 'final common pathway' of dysfunction in different brain areas or whether the movement abnormalities arise from actions of the drugs on brain centres where the pathophysiological basis of the illness lies remains unanswered. It is worthy of note that the present findings have indicated that not only can movement disorder be associated with a specific diagnosis, but also that within this diagnosis patients with a particular pattern of deficit appear at special risk. Although the numbers of neuroleptic-free patients were too few to allow formal analysis, it is possible that the pathogenesis of 'negative' or defect type schizophrenia is associated with change which particularly encroaches on brain centres involved in the modulation of motor function.

Such illness-related change may then render these centres susceptible to a detrimental effect of drugs acting at these sites.

Jeste and Wyatt have written :

> "There are probably few clinical entities that only the man-made drugs can produce. Usually the drugs produce syndromes similar to the naturally occurring ones, although the frequency may be different"
> (Jeste & Wyatt 1981).

The case of involuntary movements in neuroleptic-treated schizophrenics may be one such example.

It is widely accepted that 'individual susceptibility' is one of the important factors with regard to the development of neuroleptic-related movement disorder (APA Task Force 1979), and most workers would agree with Simpson et al who have stated :

> ".... the TD phenomenon .... includes a sensitivity or idiosyncratic individual response to neuroleptics"
> (Simpson et al 1978).

In line with this statement the 'susceptibility' element is generally construed in drug terms. While pharmacodynamic/kinetic factors may clearly be of relevance (Jeste et al 1979; Widerlov et al 1982) especially in view of the wide variations in the individual handling of neuroleptics (Sakalis et al 1972; Wiles et al 1976), the possibility that 'susceptibility' in schizophrenics may reside primarily within the form of their illness and not their treatment requirements has not been widely discussed. The results of the present investigation would suggest that in the search for risk factors mental state and other illness-related variables require serious consideration.

PART III

RADIOLOGICAL IMAGING

"The determination to find something new and to be original is usually futile .... The first requirement is always that one must absorb what has gone before ... in its entirety. In this way tradition can be deepened and widened and our own eyes opened"

KARL JASPERS
GENERAL PSYCHOPATHOLOGY

PART III

RADIOLOGICAL IMAGING

Chapter 1 - Literature Review

1.1 PNEUMOENCEPHALOGRAPHIC STUDIES

1.1.1 INTRODUCTION

Shortly after its introduction (Dandy 1918), the technique of pneumoencephalography (PEG) was applied to the search for structural abnormality of the brain in schizophrenia. In two reports, Jacobi and Winkler (1927, 1928) described a high prevalence of cortical and subcortical abnormality in schizophrenic patients. These initial studies stimulated a number of investigations, especially in Germany and Japan, the majority of publications supporting Jacobi and Winkler's original findings. Despite serious methodological problems, this work has been treated with a neglect which is out of all proportion to its potential importance.

It is beyond the scope of the present work to review in detail this substantial literature (Haug notes "more than 40 studies" up to 1982 (Haug 1982)), though it would be a mistake to assume that modern technicological advances have rendered it irrelevant. It remains a valuable source of information. The more important and most accessible works in this field are summarised in TABLE 3:1:1.

In general, the great bulk of this literature supports the contention of Jacobi and Winkler that signs of cerebral atrophy are found frequently in long-standing 'chronic' schizophrenia. For those who have considered the question, these abnormalities are

TABLE 3:1:1

PEG STUDIES IN SCHIZOPHRENIA : THE MAJOR ACCESSIBLE WORKS

STUDY		NUMBER OF SCHIZOPHRENICS	VENTRICULAR ABNORMALITY	AGE	EXCHANGE SITE	AIR INSERTE (CC's)
JACOBI & WINKLER	1927	19	18 (94.7%)	18-49	SUBOCCIPITAL	60-145
MOORE ET AL	1933	60	25 (41.7%)	17-47	LUMBAR	115-235
LEMKE	1936	100	50 (50%)	18-62	SUBOCCIPITAL	50-60
DONOVAN ET AL	1949	19	16 (84.2%)	16-60	?	?
NOBILE & BRIZZI	1953	43	8 (18.6%)	?	?	50-70
FROSHAUG & RETTERSTOL	1956	24	4 (16.7%)	38-55	LUMBAR	20-30
BORENSTEIN ET AL	1957	134	118 (88%)	17-60	LUMBAR	35-40
HUBER	1957	190	131 (69%)	2nd-6th DECADE	LUMBAR	
NAGY	1959	226	83 (36.7%)	2nd-7th DECADE	SUBOCCIPITAL	50
BRATFOS & SAGEDAL	1960	40	17 (43%)	?	?	?
SITNIKOV	1961	50	40 (80%)	?	?	?
HAUG	1962	137	66 (49%)	19-59	LUMBAR	30
ANSINK ET AL	1963	41	10 (24.4%)	21-69	SUBOCCIPITAL	10
NAGY	1963	260	152 (58.4%)	MEAN 36.1	SUBOCCIPITAL	50-80
STOREY	1966	18	3 (16.7%)	19-45	LUMBAR	40
ASANO	1967	53	34 (64.2%)	MEAN 28.9	?	100
SIEGEL & HEIDRICH	1970	350	290 (82.9%)	15-53	LUMBAR	60-100
YOUNG & CRAMPTON	1974	36	24 (66%)	?	?	?
HAUG	1982	38	3 (7.9%)	17-36	LUMBAR	30
TOTAL		1838	1092			
AVERAGE % ABNORMALITY			59.4%			

FREQUENCY OF ABNORMALITY WITH LUMBAR METHOD (N = 951) = 67.3%
FREQUENCY OF ABNORMALITY WITH SUBOCCIPITAL METHOD (N = 646) = 48.5%

related to clinical 'deterioration', and for some (e.g. Huber & Haug), they are progressive.

It is important in the evaluation of this work to be clear about firstly, the methodological and secondly, the technical problems associated with PEG. These will be briefly summarised below. Furthermore, it is also important to appreciate that the very high prevalences of abnormality often reported partly reflect the fact that at the time when most of this work was carried out, asymmetry of the lateral ventricles was believed to represent abnormality. Many of these studies recorded this as such. It is now generally accepted however that left-right asymmetry of the ventricular system can be a normal finding in man (Last & Tompsett 1953, Lemay 1976; Galaburda et al 1978). The left lateral ventricle has been found to be larger than the right in 50 - 75 % of the normal population. Thus the true prevalence of abnormality in PEG studies in schizophrenia would probably now be reported as lower than the figures quoted in the older literature.

1.1.2 METHODOLOGICAL PROBLEMS

A number of studies were performed before standardised measures had been described in the evaluation of PEG, and hence reports were based on visual assessments. Storey (1966) has shown that interrater reliability is poorer with this method than with linear measures. If only one radiologist made the assessment, the room for variation was great. This problem was compounded by the fact that most assessments were not made blind to the subjects' diagnosis or to the purposes of the study.

In view of the considerable morbidity and small but definite mortality associated with the procedure (Whittier 1951), the American Roentgen Ray Society decreed in 1929 that it was not appropriate to use normal subjects for control purposes in PEG research (American Roentgen Ray Society 1929). Many studies in schizophrenia bypassed this difficulty by not including any comparison material, while others utilised routine encephalograms performed to exclude potential neurological abnormality but reported as normal. Unfortunately, as Lonnum has pointed out, 'normal' encephalograms are relatively rare in patient populations when strict criteria of normality are applied (Lonnum 1966).

The problem of normal controls was effectively insuperable, but some authors minimised this difficulty by using standardised techniques with blind assessments in samples of different psychiatric diagnoses, or in schizophrenics of different clinical type. Prevalences and patterns of abnormality were thus relative between diagnoses or types.

1.1.3 TECHNICAL PROBLEMS

PEG is a complex invasive procedure, the dynamics of which are even yet not fully understood. Most reports did not specify their technique but those which did showed considerable variation which may have a bearing on results. Sources of variation cited include:

Amount of CSF removed
Amount of air introduced
Site of introduction of air
Time from introduction of air to exposure of film
Position of head
Unequal filling of ventricles
Film-focus distance

It is inappropriate to discuss the details of these technical problems here, but to aid understanding of their importance, some of the major ones will be briefly mentioned.

The volumes of air introduced varied greatly between studies - from Moore et al who drained the entire cerebrospinal space and introduced an equivalent volume of air (Moore et al 1933,1935), to Hunter et al who used a modified technique involving introduction of only 8 mls (Hunter et al 1968). More importantly, the volumes in some investigations varied within their study sample with only the minimum to maximum limits quoted. While some authors used a volume for volume exchange, others introduced a greater quantity of air than CSF withdrawn.

The importance of such variations lies in the putative 'ballooning' effect of air on the ventricular system - namely, that an introduced gas, especially air at room temperature, inflates the ventricular system, an effect more marked as body temperature expands the gas (Probst 1973). The more gas introduced (large volumes) or the less room for it to expand (discrepant volumes), the greater the possible distortion of the ventricles. It has also been suggested that the possibility of this effect is greatest in the IIIrd ventricle, especially with the lumbar as opposed to the intracisternal site of exchange. Thus, studies which did not introduce a fixed and smaller amount of air in each subject at a constant site present possible sources of variation.

Although it is assumed that most films were taken immediately after the exchange, this may not be the case. With larger volumes of air, films were sometimes reported at 24 hours, especially if ventricular

filling was initially unsatisfactory. It has been demonstrated that up to 49 % of patients show an absolute increase in ventricular size in 24 hour as opposed to immediate films (Lemay 1967). This is thought to result from resolution of the periventricular oedemagenic effect of an irritant exogenous substance. It is most marked with air (all studies on schizophrenics used air) and less so with oxygen as the exchange gas, and significantly, is seen most in those with degenerative brain disorders (Lemay 1967). As the worst schizophrenics may be those in whom, by lack of co-operation, satisfactory films are least possible initially and repeats more likely, this could bias findings in favour of apparent 'dilatation' in these subjects. Thus the timing of film exposure is important. Even then, militating against the unpredictable yet contradictory effects of 'ballooning' and changes induced by local oedema requires adherence to a rigid and standardised protocol.

These points illustrate the complex dynamics of PEG and the necessity for a careful methodology that they impose. The fact that most studies were of inadequate design and execution to meet modern standards is a major criticism to acceptance of their findings. It does not however justify them being completely disregarded. The most important and carefully executed studies will be briefly reviewed. These are the works of Huber (1957), Haug (1962), Nagy (1963), Storey (1966), and Asano (1967).

1.1.4 THE MAJOR WORKS

In a series of articles from 1953 (Huber 1953,1955) culminating in his 1957 monograph, Huber described his PEG work on a total of 195 unselected schizophrenics (Huber 1957). In addition, he studied 16 "atypical schizophrenics" and 11 "cyclothymics". His sample covered all clinical subtypes with varying degrees of severity and durations of illness, and most were under 50 years of age. He found pathological changes based on standard linear measures in 68.7 % of the schizophrenics, especially in the internal liquor spaces, with the IIIrd ventricle system most affected. Twenty seven patients had abnormalities of the brain surface. When patients were divided into 4 groups on the basis of degree of deficit, ventricular enlargement occurred in 17.4 % of those without "dementia", but in 81.8 % of those with "dementia". Abnormalities were least common in catatonic patients and most frequent in what he refers to as the "body-hypochondriacal" type. The results could not be attributed to somatic treatments.

Huber himself did not conduct a formal statistical evaluation of his data but this was subsequently undertaken by Vogel and Lange (1966). Although Huber's patients were young, statistical analysis revealed an increasing prevalence of abnormality with age, especially in sulcal assessments. However, the abnormalities could not be attributed to age alone. With regard to the site of abnormality and the clinical picture, anterior horn abnormalities were significantly related to a diagnosis of "body-hypochondriacal" type. Other significant relationships were demonstrated between length of illness and increasing prevalence of severe deficit and, most importantly,

between all assessments of ventricular abnormality and increasing severity of defect - this remaining significant when the effects of age were removed.

Huber subsequently repeated the encephalograms in 27 patients, 19 of whom showed no clinical progression in the degree of their personality deterioration. The radiological appearances of these 19 were unchanged, whereas the 8 whose clinical deterioration had progressed, all exhibited progression in their PEG abnormalities. Many of the original sample had been followed for over 20 years, with ventricular enlargement being associated with a chronic illness and poor outcome.

However striking his findings, Huber was aware they appeared qualitatively at least, non-specific as he found them in his "atypical" and "cyclothymic" groups also though with much lesser frequency. Nonetheless, he considered these radiological changes as morphological signs of the brain disorder underlying schizophrenia and postulated a primary striatal/diencephalic lesion that progressed with increasing duration of illness.

The work of Haug (1962) is the most impressive of the PEG studies because of his considerable attention to detail and the relative objectivity of his methodology. He assessed the results of PEG in 278 chronic psychiatric in-patients of mixed diagnoses. He accepts this represents a biased sample, but by using inter-group comparisons his work provides noteworthy findings. Standardised radiological techniques for performing and measuring encephalograms were adhered to, the radiologist being unaware of the psychiatric status. Liberal limits of normality were adopted to minimise inclusion of "big normal variants" in the pathological groups. Each of the

conventional schizophrenic subtypes (except simplex) was represented and a "subjective evaluation" of the presence or absence of "dementia" was made.

Haug found abnormalities in 84 of his 137 chronic schizophrenics - a prevalence of 61 %. When 30 subjects were excluded because of inadequate case-note information and 1 for being over 60, the prevalence remained at 58 %. These abnormalities predominantly involved the ventricular system, cortical atrophy when present being mild and localised. All subtypes were equally affected. There was a highly significant relationship between severe clinical deterioration and definite ventricular dilatation, but no such relationship with cortical changes. While there appeared to be "a connection" between the degree of ventricular enlargement and length of illness this did not achieve statistical significance. These changes could not be attributed to age alone.

The overall prevalence of similar changes in his "non-organic" group was also high (49 %) - though two thirds of this category comprised patients diagnosed as having "reactive psychosis". Nonetheless, prevalence of IIIrd ventricular and right cella media abnormality was significantly greater in the schizophrenics. Furthermore, the form and degree of abnormality was different, the schizophrenics being characterised by a predominantly diffuse, bilateral ventricular dilatation of greater degree than the mild, focal aberrations of the "non-organic" subjects. In repeat investigations Haug too noted a pathological progression paralleling the clinical one. Like Huber, he considers in detail the possible role of shock treatments in promoting these abnormalities, but both discount this on the basis

of their findings.

The study of Nagy is of interest because of its size, though its methodology is less rigorous than the two preceding works. Nagy (1963) examined PEG's from 260 schizophrenic and 133 manic-depressive patients, all of whom were female. The selection criteria are not stated and the encephalographic technique was not standardised, though mesurements were. Of the schizophrenics, 58 % had enlarged ventricular indices, while the comparable figure for the manic-depressives was 23 %. There was a correlation between ventricular enlargement and both impaired social competence and chronicity of course.

Asano studied 53 young schizophrenics of mean age 28.9 years, using a fixed procedure (Asano 1967). This is the only encephalographic study of chronic schizophrenia to include area, in addition to linear, measures. The patients were divided on clinical parameters according to the classification of Mitsuda - 'nuclear' type (chronic deteriorating course) both mild and severe, and 'peripheral' type (episodic course) with and without deterioration.

Asano found an overall prevalence of abnormality of 64.2 % - remarkably similar to that of the 3 previously described works. When looked at by the type of schizophrenia determined from the course of illness, there was a significantly higher prevalence in the 'nuclear' than 'peripheral' groups, with the severe forms of 'nuclear' type having the highest prevalence of all (94.4 %). Abnormalities were found in only 10 % of non-deteriorated patients whose illness had run an episodic course. The ventricular system exhibited abnormalities more frequently than cortex. When strict criteria were applied, both

IIIrd and lateral ventricles showed aberrations with equal frequency, but mild abnormalities were commoner in the IIIrd. There was an identical prevalence in the under and over 45's, and Asano concurs with Huber and Haug that these findings are not merely age-related. Thus Asano demonstrated an association between the prevalence of essentially ventricular abnormalities and what are in effect measures of severity of the schizophrenic defect.

These authors all show considerable concordance and provide compelling evidence that structural brain changes, especially in the form of ventricular dilatation and distortion, may be an integral part of the schizophrenic process. They also suggest that signs of cerebral atrophy may relate to the personality deterioration of the schizophrenic defect, and if present, may augur a poor outcome.

Storey however, in a small but careful study, could not confirm these findings (Storey 1966). He examined the encephalographic data from 18 chronic schizophrenics under 45 years of age, who had spent at least 2 years in hospital. These films were compared with those of an age matched group selected from the PEG's reported as normal in the routine work of the radiology department. Measurements were linear and performed blind by two neuroradiologists.

Storey found no difference between patients and'controls'in prevalence of abnormality, and no association between PEG variants and age, duration or severity of illness or past somatic treatments.

Apart from its small size, this study is marred by the selection of 'control' PEG's which was random and not influenced by the provisional clinical diagnosis on which referral for radiological investigation was based. 'Controls' therefore had been investigated

for potential - and in some cases definite - organic brain disease such as epilepsy, and as a group are likely to have had a greater frequency of atrophic change than a normal population.

This literature, although flawed and concerned with a technique now little used, remains important and worthy of attention. While its conclusions are not unanimous, there is a striking degree of consistency in the better studies. As Bliss has written :

> "It may be that these studies are in error, but they cannot be ignored"
> (Bliss 1975)

1.2 C.T. SCAN STUDIES

1.2.1 INTRODUCTION

Computerised axial tomography (CT) was introduced by G.N. Hounsfield in 1973, as a safe, non-invasive radiological technique for visualising internal body structures. The procedure was the first to provide a clear graphic representation of soft tissue without the necessity of contrast enhancement, and soon found one of its major applications in intracranial imaging. Structures which previously could not be demonstrated in vivo could now be seen (e.g. internal capsule), and those which had hitherto required contract media for their visualisation, such as ventricles, could be clearly shown without distortion (Hounsfield 1973; Ambrose 1973). A further advantage was the ease with which investigation could be undertaken, and if necessary repeated, even in unconscious or semi-unconscious patients or those who were behaviourally disturbed. Compared to PEG, scanning required

minimal co-operation from the subjects.

CT is now firmly established as a routine investigative tool in clinical practice, including psychiatry, where it plays an invaluable role in the diagnosis of organic brain disorders. Beyond this however, it has acquired considerable importance as an investigative technique in psychiatric research. In particular, computerised tomography offered the first opportunity for the hypothesis that structural cerebral change underlies schizophrenia to be examined in life, with minimum disturbance to the patient, and with the use of adequate control groups. Hence the major limitations of PEG could effectively be overcome.

A number of groups have applied CT to the study of schizophrenic brain structure in life, and although there is some consensus in the published reports, the literature is not unequivocal. Studies up to the end of 1982 are listed in TABLE 3:1:2. The following review will focus on the findings with regard to the lateral ventricles, the brain structure most consistently evaluated. The major inferences of this work concern ventricular volume. As area ratios (specifically VBR - vide infra - Chapter 2 - Methods) correlate better with assessments of volume than linear measures (Penn et al 1978), particular attention will be paid to those studies which used area ratio or direct volume computations.

1.2.2 STUDIES APPLYING AREA/VOLUME METHODS TO THE EVALUATION OF VENTRICULAR SIZE

Johnstone et al were the first to apply CT to the study of schizophrenic brain structure in vivo (Johnstone et al 1976; Johnstone et al 1978b). They scanned 17 Feighner positive chronic

TABLE 3:1:2 C.T. SCAN STUDIES IN SCHIZOPHRENIA

STUDY	BRAIN STRUCTURE(S) ASSESSED AND METHOD	
JOHNSTONE et al 1976, 1978a	LAT. VENTS. CORTEX	AREA MEASURES (incl. VBR)
TRIMBLE & KINGSLEY 1978	LAT. VENTS.	EVAN's INDEX
WEINBERGER et al 1979a	LAT. VENT.	VBR
WEINBERGER et al 1979b	CORTEX	LINEAR MEASURES
WEINBERGER et al 1979c	CEREBELLUM	VISUAL ASSESSMENT
GLUCK et al 1980	IIIRD VENT. ANT. HORNS CORTEX	LINEAR MEASURES VISUAL ASSESSMENTS
GOLDEN et al 1980a, 1981	'BRAIN DENSITIES'	
MORIGUCHI 1981	LAT. VENT. IIIRD VENT. CORTEX	VOLUME ASSESSMENT AREA MEASURES LINEAR MEASURES
TAKAHASHI et al 1981	LAT. VENTS. IIIRD VENT. CORTEX	VISUAL ASSESSMENT LINEAR MEASURES
TANAKA et al 1981	LAT VENTS. IIIRD VENTS. QUADRAGEMINAL CISTERN CORTEX	LINEAR MEASURES
ANDREASEN et al 1982c	LAT. VENTS.	VBR
JERNIGAN et al 1982a	'VENT. AND SULCAL VOLUMES'	
NASRALLAH et al 1982	LAT. VENTS.	VBR
REVELEY et al 1982	LAT. VENTS.	VENT. AREA + VBR
WEINBERGER et al 1982	LAT. VENTS. CORTEX CEREBELLUM	VBR VISUAL ASSESSMENT
OKASHA AND MADKAUR 1982	LAT. VENT. IIIRD VENT. CORTEX	LINEAR MEASURES
FRANGOS & ATHENASSENAS 1982	LAT. VENTS. CORTEX	VBR
NYBACK et al 1982	LAT. VENTS. IIIRD VENT. CORTEX	LINEAR MEASURE RATIO VISUAL ASSESSMENT
BENES et al 1982		LINEAR AND AREA RATIOS

schizophrenic males (mean age 57.4 ± 9 years) institutionalised for many years (mean duration of hospitalisation 31.4 ± 7.5 years). Four subjects had been leucotomised. Using planimetry to calculate VBR, they demonstrated significant ventricular enlargement in this patient group compared to a normal group comprising hospital ancillary workers matched for age, sex and best occupational attainment. This finding was not attributable to past physical treatments including leucotomy, though psychosurgery was associated with ventricular dilatation. There was however no difference between schizophrenics and controls with regard to sulcal size (leucotomised patients excluded) assessed as an area measure by tracing the sulci onto millimetre square paper and counting squares. This study was in addition the first to demonstrate a relationship between impaired cognitive performance (Withers and Hinton battery) and an objective parameter of cerebral atrophy (increased VBR) in schizophrenic subjects. Cognitive impairment was also related to the presence of 'negative' schizophrenic features (Krawiecka Scale), though presence of the latter did not correlate with signs of brain atrophy.

This study was small, with subjects chosen not least by their willingness and ability to co-operate. The patients were relatively old with long hospitalisations, the ranges of both these 'time' variables in the sample being narrow. With cognitive testing, the use of control patients institutionalised for many years as a result of non-cerebral neurological disease made it unlikely that the intellectual disadvantage found in the schizophrenics could be attributed to the effects of institutionalisation, but these controls were not scanned. Thus the contribution of age to CT appearance and

the contribution of long-term institutional care to the CT differences in the schizophrenics could not be adequately assessed. Likewise, the small sample size precluded a precise evaluation of the role of past physical treatments (except leucotomy shown to be associated with significant cerebral damage). Finally, the specificity of the findings to schizophrenia could not be determined.

In a subsequent series of publications, Weinberger and colleagues have confirmed and extended the findings of Johnstone et al. They studied a total of 73 psychiatric patients defined by Research Diagnostic Criteria (Weinberger et al 1979 a). Apart from 4 diagnosed as schizoaffective and 3 as affective (there was also one case of "mental retardation (aetiology unknown)") the sample comprised 65 RDC schizophrenics under 50 years of age. Assessing ventricular size using VBR measured by planimetry, these workers found a highly significant difference in lateral ventricles between chronic schizophrenic patients and controls (schizophrenics $>$ controls). Indeed, 53 % of their chronic schizophrenic group had ventricular enlargement that was greater than 2 SD of the control mean, and 40% were completely outside the control range. Age, race, length of illness and duration of hospitalisation were not correlated with VBR. Those with a history of ECT did show a greater degree of ventricular dilatation than those with no such history, but this did not account for the basic finding.

Weinberger et al also reported that a significantly larger proportion of their schizophrenics compared with controls demonstrated some cortical atrophy (Weinberger et al 1979 b). Cortical abnormality was defined in terms of linear measures exceeding stated values for maximal width of the Sylvian fissure and interhemispheric

fissure and mean width of the three largest sulci, though the particular cut-off values for normality were arbitrarily adopted. The cortical findings were less consistent than those for ventricle. Thirty two percent of patients demonstrated abnormality by their criteria on one of the above measures while only two (3.3 %) were outwith their stated normal range on all three. The commonest abnormality was in the area of the Sylvian fissure. Cortical abnormality did not correlate with the presence of ventricular dilatation.

One of the major criticisms of this work lies in the choice of controls, which were selected from material generated by other studies in the same hospital (National Institute for Mental Health and St. Elizabeth's Hospital, Washington D.C.). Of 56 controls, 48 were first degree relatives of patients suffering from Huntington's Disease. Although these controls were described as "healthy" and "asymptomatic" insufficient is known about the CT scan appearances associated with preclinical Huntington's Chorea and of the genetic carrier state for such controls to be accepted with equanimity. In addition, it is likely that Weinberger et al's patients presented a particularly severe form of illness. Half the sample came from the research wards of NIMH, which has a national commitment and hence is likely to attract unusual cases presenting particular management problems. The other half were patients from a "general psychiatric unit" serving a designated catchment area. Although no statistical differences emerged between the VBR's of the two sets of patients, such a general comparison could deflect from very real differences in clinical presentation, course of illness, treatment patterns and demographic factors, any or all of

which could relate to VBR in either group. Such relationships would be masked by combining the groups. It is hard to imagine that the unique position of NIMH in American psychiatric research would not attract somewhat idiosyncratic patients to its wards.

This group have reported extensively on a number of variables that they found to be correlated with CT scan abnormalities in chronic schizophrenics and have proposed that enlarged ventricles in particular may be a meaningful basis on which to define a distinct subgroup of the illness. This is founded on increased ventricle size being associated with poor premorbid adjustment (Weinberger et al 1980b), poor response to neuroleptic drugs (Weinberger et al 1980 a), increased prevalence of reversed cerebral asymmetries (Luchins et al 1979), and the presence of 'soft' neurological signs (Weinberger and Wyatt 1982). This group's published results on cognitive performance have been mentioned earlier (cf Part 1). While such a concept is clearly of interest the findings on which it is based require replication, which, with regard to some variables - e.g. reversed asymmetries - has not been possible to date (Andreasen et al 1982a; Jernigan et al 1982b).

Golden and co-workers also reported on brain abnormalities in young (mean age 32 $\pm$ 6 years) chronic schizophrenics fulfilling DSM - III criteria (Golden et al 1980a). The technique of scan assessment used by this group was somewhat novel in that they did not utilise polaroid pictures but rather calculated directly from the print-out of attenuation numbers. Using data from the maximal ventricular cut and adjacent two rostral cuts, they counted every fourth Hounsfield number (omitting a rim around the skull to reduce

artifactual radiological interference) and computed the mean value for each hemisphere which they referred to as "brain density". They found the mean "density" values for their schizophrenics to be significantly lower than (radiology departmental) controls (Golden et al 1980 a) and further that this reduction was greatest in the left frontal area (Golden et al 1981). However, greater "densities" overall were found in the left than in the right hemisphere.

This technique has not been widely used in schizophrenia research, though Reveley et al reported findings using the print-out as opposed to photograms (vide infra). By using 'raw' data from print-outs many of the assumptions implicit in constructing the pictorial analogue are avoided. However, the technique gives to analysis a degree of exactitude which is unlikely to be justified. The CT system is very precise, being able to measure absorption coefficients to an accuracy of 0.5%. Hence very small differences in tissue "density" can be detected, though the basis of variability is poorly understood. Coefficients attributed to adjacent pixels can differ widely within discrete brain areas, even when pictures may show relative homogeneity. Thus mean attenuation values calculated for either hemisphere or any part of a hemisphere are to some extent influenced by chance. The differences reported by Golden et al are slight, as they themselves point out, and although reaching the 5 % significance level for most comparisons, are likely to fall within the variance of the method. As the authors note, a difference of 1 Hounsfield Unit would have been sufficient to eliminate one of their statistically significant findings. It could be proposed that sampling every third or every fifth pixel may have

produced different results. Moreover, not only is the validity of this method in doubt, but recently its reliability has been seriously questioned (Levi et al 1982).

Criticisms of this work also arise from the choice of controls which were taken from radiology departmental scans reported as normal. While CT is more likely to be undertaken than PEG, the same objections apply to this type of control - especially when the differences being sought are subtle and the mode of evaluation open to question.

Thus while the work of the Nebraska group can be taken as broadly in line with that reviewed previously in showing abnormality of the schizophrenic brain, it must be interpreted with some qualification.

In a large but rarely quoted study from Japan, Moriguchi compared the scans of 55 schizophrenics (criteria unspecified) with those of 65 controls who had migraine, epilepsy and neurotic diagnoses (Moriguchi 1981). Scan pictures were comprehensively evaluated. Cortical indices and third ventricle were measured linearly, the area of the anterior horns calculated, and an assessment made of lateral ventricular volume by summating areas on all relevant pictures.

Only with the number of parietal sulci did no difference emerge between schizophrenics and controls, though with a number of comparisons differences only achieved significance by omitting epileptics from the control sample. This illustrates the unsatisfactory nature of such organic diagnostic groups in work of this kind. The author also noted that enlargement of the interhemispheric fissure and increase in lateral ventricular volume both correlated with

length of illness but not age of onset. Two independent psychiatrists made an assessment of the degree of deterioration in the schizophrenic patients but this did not correlate with any of the indices of cerebral damage.

This study is of some interest and worthy of greater attention. The major problems associated with it refer to the unspecified inclusion criteria for schizophrenia and as mentioned the choice of controls, some of whom appear to have been very young (11 years). Most importantly, it is not clear from the author's presentation whether or not the age effects demonstrated on all indices except interhemispheric size and third ventricle width were accounted for in the statistical analyses.

Andreasen et al used VBR to assess ventricular size in a study of 52 young (mean age 30 $\pm$ 10.6 years), DSM - III and RDC type schizophrenics who were not institutionalised (Andreasen et al 1982 c). They concurred that their schizophrenic group had a significantly larger mean VBR than controls, though the magnitude of the difference was not great, and the considerable schizophrenic/ control overlap and the wide variance of the experimental group were emphasised. Age effects are not commented on, and although the distribution of VBR's is taken to show a "trend" towards bimodality, no statistical confirmation of this is presented. ECT was the only physical treatment assessed but was not found to be a contributory factor. As none of the patients were chronically institutionalised this could not account for the findings. The controls comprised matched scans from radiology files which had been reported normal, though the authors acknowledge the difficulties associated with this. They further illustrate graphically the importance of the

controls used and the criteria for dilatation adopted.

Almost one-third of their sample had a history of either alcohol or drug abuse "at some time in the past", though the authors discount this as the relationship established between substance abuse and VBR was a negative one. The type of abuse relevant to their sample is not mentioned but a tendency towards a negative relationship between indices of atrophy and opiate abuse has been reported (Hill and Mikhael 1979). As drug history in the controls could not be assessed, it is impossible to say whether such an effect was tending to mask even greater differences in VBR between the groups than that found.

In a related publication, Andreasen et al explored the relationships between VBR changes in their schizophrenic patients and the presence of "negative symptoms" * (Andreasen et al 1982b). They compared the 16 schizophrenics who had "the greatest ventricular enlargement" with the 16 who had the smallest with regard to their "positive and negative symptoms". The authors concluded that "patients with ventricular enlargement tend to have a preponderance of negative symptoms.... while patients without ventricular enlargement tend to have a predominance of positive symptoms" and state that their investigation "provides support for a new way of subtyping schizophrenic disorders as negative (or defect) versus positive(or florid)".

These statements represent a somewhat emphatic interpretation of the authors' data. None of the five items comprising "negative symptoms" was significantly different between the groups and of the five "positive symptoms" only bizarre behaviour was significantly

* The difference between Andreasens "positive and negative symptoms" and the 'positive' and 'negative' features used in the present work has already been emphasised (cf Part 1).

less common in the large ventricle group. As the probability values for none of the other nine items were less than 0.1, it is hard to interpret these data objectively as showing even the "trend" in the direction the authors suggest.

It is possible that the schizophrenic subjects of Andreasen et al were too young or had been ill for insufficient a period or were not 'chronic' enough to achieve sufficiently high ratings to demonstrate a relationship between ventricular enlargement and specific 'negative' characteristics. It is of interest to note however that in failing to find such a relationship that conforms to conventional significance, yet demonstrating a significant correlation between cognitive impairment and ventricular dilatation, these workers have reproduced the original findings of Johnstone et al in an entirely different schizophrenic population (vide supra).

Recently, Jernigan et al have utilised a new technique to assess ventricular size in a group of 30 chronic, relatively young (mean age 32.4 $\pm$ 8.2 years) schizophrenics defined by DSM-III criteria (Jernigan et al 1982 a). These workers have developed a semi-automated method for quantifying cerebrospinal fluid volumes by applying computerised measurement algorithms directly to the attenuation matrices produced by the scan computer. The analysis uses a simple volume-averaging model to estimate the CSF content in local subsegments of the intracranial space. By summing throughout particular sets of subsegments, estimates of total ventricular volume and sulcal fluid volume can be obtained.

This study could demonstrate no difference in ventricular volume or sulcal volume between the chronic schizophrenic patients and a group of normal healthy controls who had been scanned as part

of a previous study. Although the mean age of the controls was greater than for the patients (age having been demonstrated by this technique to be a significant determinant of ventricular size in normals) statistical analysis took account of both age and cranial size.

In view of their novel technique of analysis the authors conducted a parallel investigation into the comparability of their method with the more conventional planimetry adopted in the literature. They submitted coded sets of films to the NIMH group and the Nebraska group for planimetric assessment of VBR. While the means achieved by each group differed widely (by approximately 100 %) no difference could be demonstrated between schizophrenics and controls using either groups' measurements.

This study is of considerable interest, not least for the fact that it included 16 subjects who were scanned as part of the study reported by Golden et al (cf Part 1, Chapter 1.3.3.) correlating ventricular enlargement with impairment on cognitive testing (Golden et al 1980 b). This latter work was an intra-group study of schizophrenics and used no normal controls. Despite the novel evaluation technique with its dependence on attenuation values and the inherent problems of this, visual measurement by planimetry by two other groups did not alter the findings.

This discrepancy with the published literature described above could result from selection factors. Of their 30 subjects, 10 were outpatients who represented "all consenting outpatients seen over the study period". They do not say what proportion of outpatients this figure represents. It is reasonable to suggest however that this apparently small number of consenting patients may

represent the most amenable and best preserved of that group. Thirteen of the inpatients came from a research ward whose protocol included withdrawal of medication. Thus only those in whom this could be achieved were referred for scanning. A further 25 patients who came through the research facility were lost to scanning because medication could not be withdrawn (refusal or clinical deterioration including patients being transferred to a locked ward), or because the patients discharged themselves against medical advice etc. Thus those scanned represent one-third of the possible sample who permitted medication to be discontinued and who survived long enough (? how long) in a drug-free state to allow a scan to be performed. The seven remaining subjects were from "other wards" and were selected "only for their willingness" to be scanned. It seems likely therefore that the sample of Jernigan et al is biased in favour of young schizophrenics with relatively little behavioural disturbance.

Nasrallah et al (1982) used planimetry to assess VBR in a group of 55 consecutive male admissions who conformed to DSM-III criteria for schizophrenia. All were under 45 years (mean 29.9 years). There was a strikingly significant difference (in terms of magnitude, the greatest in the published literature) between the mean VBR of the schizophrenics and that of controls in the direction of enlargement in the former group. The authors reported that 35 % of their schizophrenics had VBR's that lay outwith 2 SD's of the control mean.

The clarity of this finding is unfortunately dimmed by the authors' choice of controls. In an attempt to avoid exposing normal

individuals to radiation while keeping the selection of controls random, they chose for comparison the scans of 27 consecutive, age-matched males investigated immediately following motor vehicle accidents. It is unlikely that CT scan parameters are unchanged following closed head injury in view of the variable cerebral oedema developing in these situations. This will be particularly so in cases where the injury is of sufficient degree to require radiological investigation, the effect being to decrease the ventricular representation and hence reduce the 'control' mean VBR. On the other hand, if the injury is severe enough and scanning not immediate, ventricular enlargement may develop (Levin et al 1981). The position is further complicated by the possible role of intoxicating drugs in road traffic accidents and the effect of these on ventricular size. The objections inherent to such a group used for control purposes greatly outweigh the advantages of ramdom selection. Thus while these findings are in line with most of those discussed so far, acceptance of at least the magnitude of the difference if not the basic finding itself must be qualified.

Nasrallah et al subdivided their schizophrenic population into paranoid, non-paranoid hebephrenics and non-paranoid undifferentiated subtypes using the Tsuang-Winokur criteria. All three major subtypes of schizophrenia had significantly increased cerebral ventricular size compared to the head injury patients. However, ventricular enlargement was significantly greater in the paranoid and non-paranoid hebephrenic subtypes than in the non-paranoid undifferentiated group, although no difference emerged between the first two groups. There were no differences between the Tsuang-Winokur

subtypes in terms of premorbid history, duration of illness, severity determined by the number of hospitalisations, or response to medication to account for these findings.

These results imply that schizophrenics who exhibit ventricular dilatation do not belong to any one clinical type, at least in terms of the Tsuang-Winokur criteria, and that studies using a high proportion of 'non-paranoid undifferentiated' subjects may show less striking degrees of enlargement than those using other types. The authors suggest that the lack of a difference in mean VBR between their paranoid and non-paranoid hebephrenic patients casts doubt on any direct relationship between ventricular enlargement in chronic schizophrenia and factors such as poor premorbid adjustment, poor response to neuroleptics, neuropsychological impairments, and 'negative' symptoms, all supposedly less common in paranoid subjects. While this conclusion is noteworthy, it does extend the results of the study which referred to 'paranoid' specifically defined. It is of interest however that no difference could be demonstrated in ventricular size between patients conventionally viewed as in general having different patterns of deficit.

An interesting and important variation on the above studies was reported by Reveley et al (1982) who examined the scans of 11 healthy monozygotic and 8 dizygotic twin pairs and those of 7 pairs of monozygotic twins discordant for schizophrenia. Their findings confirmed that the schizophrenics of twin pairs have significantly larger ventricles than their non-affected co-twins and controls. This was the case in 6 out of 7 of their discordant pairs. Furthermore,

they showed that while ventricular size is strongly under genetic control there is greater variability of size in MZ twins discordant for schizophrenia, implying to the authors the imposition of some external environmental factor in the genesis of both the ventricular enlargement and, subsequently, the schizophrenia. They speculate that perinatal complications may be relevant in this regard.

1.2.3 STUDIES APPLYING LINEAR/VISUAL ASSESSMENT METHODS TO THE EVALUATIONS OF VENTRICULAR SIZE

A number of other studies have appeared in the literature which used either visual assessment or linear measures to evaluate CT scan images. Owing to the limitations of these techniques (which have been mentioned and which will be discussed in Chapter 2 below) these studies will be reviewed in less detail than those previously.

Shortly after Johnstone et al's original publication, Trimble and Kingsley (1978) reported an uncontrolled evaluation of scans from 11 schizophrenics aged from 17 to 66 years, using Evans' Index. Although one patient had been leucotomised and 2 had histories of coincidental epilepsy, with all their subjects the Evans' Index "fell within the normal range (<0.3)". In view of the methodological inadequacy, its findings must be viewed as anecdotal.

Gluck et al (1980) used a "prolective trohoc" analysis technique to assess the difference in linear measures of maximal IIIrd ventricle width, maximal anterior horn distance and sulcal enlargement on the scans of 68 chronic schizophrenics (criteria unspecified) and 180

matched controls from radiology departmental records. The unusual statistical procedure was adopted to take account of the fact that in a number of scans the chosen parameters were too small to be measured, though the exact number to which this applied or whether it applied to other than IIIrd ventricle is not stated. No differences could be detected between the schizophrenics and controls on any of the selected measures.

In the largest CT study in schizophrenia, Takahashi et al (1981) examined the scans of 280 patients tightly defined by both Carpenter's Flexible Diagnostic System and a series of strict exclusion criteria. The 234 controls comprised both normal volunteers and neurotic patients, matched for age, sex and educational status. The matching was close for 169 pairs. The study sample was young (mean age 27.9 years) and had been ill for a relatively short period (mean 6.5 years). Scans were evaluated by a visual assessment, by straight linear measurements, and by ratios of linear brain measures to internal skull diameter. Both lateral and IIIrd ventricle were examined, as was cortex, both in general and by areas.

The authors reported significantly more overall cerebral abnormality in their schizophrenics than in controls using visual assessment. However, using linear measures, only IIIrd ventricle width was significantly greater in the schizophrenics. It was recognised that the CT abnormalities found were slight.

Having taken considerable care with the selection of patients and controls, this work is deeply flawed by the inadequate scan assessment technique. Furthermore, in aiming for a large sample size, the authors adopted a multicentre approach with scans performed on

different machines. Data from different machines, especially earlier models,are not necessarily comparable and the practice of pooling results is questionable, especially when no comparability analysis is performed on findings from different centres.

Also from Japan, Tanaka et al (1981) reported on the scans of 49 schizophrenic patients (criteria unspecified), of mean age 35 years. No detail on length of illness is provided or on whether or not the patients were institutionalised. Their control group comprised 38 cases investigated mainly for headache " who showed neither neurologically abnormal findings nor any specific lesion except ventricular enlargement and cortical atrophy in CT findings". This presumably means that the presence of ventricular and/or cortical atrophy were not exclusion criteria for controls.

The authors found no difference in those under 40. In the 41 - 60 age group, schizophrenics had larger measures on left and right septum-caudate distances, maximal quadrageminal cistern, IIIrd ventricle and interhemisphere width, maximum width of hemispheric sulci and maximum distance between Sylvian fissure and inner skull.

Apart from the use of linear measures, unspecified diagnostic criteria and presentation of scant clinical detail, it is hard to accept the control group in this study without comment. In a randomly selected group of normal, healthy volunteers signs of atrophy could not be reasonably used for exclusion from a control group. However, in this study the population were not randomly selected, normal, healthy individuals by virtue of suffering cranial symptomatology of sufficient degree to warrent CT investigation.

Okasha and Madkour (1982)provide the only report in this

area from a Third World country (Egypt). They studied 43 chronic schizophrenics (criteria unspecified) of mean age 33 years who had been ill for at least 5 years. However, as the youngest of the sample was 15, it is doubtful if they would be considered representative of schizophrenia in most western countries. Seventy five per cent were hospitalised. They had as controls 39 patients (mean age 33 years) "with peculiar symptoms in the head and needing reassurance by CT".

The authors conclude that their results show that there were "no significant differences between chronic schizophrenics and controls" in cortical assessments, but that "a highly significant difference was obtained on IIIrd ventricle and cella media index", both indicating atrophy in the schizophrenics. As no statistical analysis is presented, the use of the word "significant" with regard to these findings is inappropriate, though the differences were in the predicted direction.

In Greece, Frangos and Athanassenas (1982) compared the VBR's from scans of 70 Feighner positive schizophrenic in-patients (mean age 40 years) ill continuously for at least 2 years (mean length of illness 13 years), with the normal VBR values published by Barron et al, and found significant ventricular enlargement in their patients, even when age was accounted for. As was shown by Jernigan et al (vide supra) the practice of comparison of absolute values in the literature is unacceptable.

In addition the same authors also found significantly larger mean VBR's in their paranoid patients compared with hebephrenics and a trend in the same direction between paranoid and undifferentiated types, these types being defined according to ICD - 9 criteria.

Age was not considered to underly these findings. Using a different definition of 'paranoid' these authors concur to some extent with Nasrallah et al (vide supra) though there is discordance between the studies on the relative placings of hebephrenics and undifferentiated patients in the hierarchy of ventricular size.

Nasrallah (1982) has published a further study on the paranoid - non-paranoid distinction using CT. This investigation used radiology department scans done "as part of the workup for headache" as controls and assessed pictures by means of linear measures. It is not clear if the study sample are the same schizophrenics reported in their previous work reviewed earlier. While describing a number of trends, the only significant findings concerned a greater mean bicaudate distance in paranoids aged 20 - 30 years compared with controls and more paranoids than non-paranoids with bifrontal or bicaudate diameters that exceeded the control mean by more than 1 SD. In contrast to the author's previous study this work provides little objective support for the validity of a paranoid - non-paranoid dichotomy on the basis of CT changes.

Nyback et al (1982) scanned 46 patients of mean age 32 years admitted to the Karolinska Hospital, Stockholm, with "acute psychosis". Of these, 28 conformed to the RDC for 'definite schizophrenia', a further 13 being classified as 'probable'. Nineteen were first admissions. As controls, 46 healthy volunteers were scanned. Using linear indices involving frontal horns they found significant enlargement in patients compared with controls, which was true of comparisons involving all patients, only those under 45 years of age,

RDC schizophrenic and all schizophrenics under 45 with no history of drug/alcohol abuse. No differences emerged between all schizophrenics with no history of substance abuse compared with controls. Mean IIIrd ventricle measures were also greater in all patients under 45 compared with controls. Although cortical atrophy (visually assessed) was stated to be "more frequent" in the patient group, no statistical analysis is provided and it must be assumed that no significant differences emerged. Age correlated with both measures of ventricular size in the volunteers but only with IIIrd ventricle size in the patients, leading the authors to suggest that schizophrenia may be associated with a process which obscures normal ageing in the lateral ventricles.

This is one of the better studies using linear measures in evaluation, though there is some evidence that the results may have been partly influenced by failure to exclude 10 subjects (22 % of the sample) with a history of drug or alcohol abuse.

Benes et al (1982) examined scans of "schizophrenics" and controls, all of which came from radiology records. Thus, even the "schizophrenics" were scanned for reasons that were not routine. The authors state these patients were investigated for "varying degrees of cognitive impairment". It is relevant that of 40 schizophrenics scanned, only 11 conformed to Feighner criteria, and of these, only 4 did so without a history of drug or alcohol abuse. The diagnostic criteria to which the other patients conformed are not stated. Controls, (mean age 29 years) were considerably older than patients, and had been scanned as part of the investigation of headache and dizziness. Patients were young (mean age 21.2 $\pm$ 5.5 years) with an average of 4.5 years of illness, and had spent just over one

year in hospital. The authors, calculating ratios based on both linear and area measures, found no differences between the experimental subjects and controls, and felt that the very short time the former had spent in hospital was relevant in this result, though this is speculative. They make no comment on the possibility that differential age effects could have obliterated subtle patient-control differences. Apart from their young age and the relatively 'mild' form of illness they suffered from, it is highly doubtful that these subjects would be accepted by most workers as typical schizophrenics suitable for research purposes.

Thus the original work of Johnstone et al has stimulated great interest, and although some consistency in findings has emerged, studies using the CT technique of imaging also present fundamental methodological problems.

1.3 SUMMARY OF THE LITERATURE ON RADIOLOGICAL IMAGING IN SCHIZOPHRENIA

In summary, the literature on radiological imaging of brain structure in schizophrenia indicates the following:

1) In some cases, schizophrenia is associated with structural brain changes. The most consistent positive findings relate to enlargement of the lateral ventricular system, which has been demonstrated with both PEG and, more recently, with CT in studies using different methodologies and control groups. The literature is not however unequivocal.

2) CT studies, which have produced numerical data and which allowed the use of control groups, show that "ventricular enlargement" refers to a statistical difference between patient and control group mean values. In general, the variance is greater in schizophrenic groups than controls and the degree of overlap is considerable.

3) There is no evidence of a characteristic or pathognomonic appearance in the schizophrenic brain using either PEG or CT, and nothing as yet to support the view that a distinct subgroup of patients can be identified solely on the basis of radiological findings.

4) The specificity of the structural changes is unknown

5) The clinical correlates of ventricular enlargement remain unclear. PEG suggests that 'deterioration' is associated with brain change. There is as yet no substantial evidence from CT that 'deterioration' defined in terms of the 'negative' or 'defect' state is particularly associated with ventricular enlargement, and suggestions that particular clinical subtypes may be more affected or that early environmental assaults may be relevant, remain speculative.

6) Other parameters of cerebral atrophy have either not been widely studied (e.g. IIIrd ventricle) or have produced inconsistent or unreliable findings (e.g. cortex).

1.4 THE PRESENT STUDY

1.4.1 GENERAL COMMENT

This review demonstrates the extent of work carried out in the field of radiological imaging of the schizophrenic brain in vivo. In addition, it illustrates the ongoing difficulties of methodology and interpretation of data in what remains a highly complex field of investigation. The newer CT system is precise in recording attenuation data, so minor variations in technique may reflect in results - for example, whether the patient is scanned parallel to the orbitomeatal line, as is customary in Europe, or at 20 ^{o} to it as in the U.S. Furthermore, the attenuation data themselves are subject to a range of effects dependent on the physics of x-rays - for example, effects such as beam hardening (Dichiro et al 1978), linear drift (Thaler et al 1979), the energy dependence of the values (Zatz and Alvarez 1977) etc. Hence, the technicological problems inherent in PEG have been replaced by different problems of a subtler order associated with the new technology. When the changes being sought are unlikely to be gross in degree or characteristic in type there is all the more need for close attention to the selection of both experimental and control subjects in application of CT to clinical psychiatric research.

1.4.2 THE SPECIFIC QUESTIONS

This part of the work was concerned with determining whether structural brain change can be attributed to schizophrenia using in vivo radiological imaging (CT). Specifically, four main questions

were addressed, exploration of the last three being dependent on an affirmative answer to the first.

These questions were :

1) Is schizophrenia associated with lateral ventricular enlargement ?

If so:

2) How specific is this to schizophrenia ?

3) Are past physical treatments of relevance ?

4) What are the clinical correlates ?

In general, the literature on brain imaging reviewed above, could be taken as suggesting that ventricular enlargement is to be found in this condition in association with what are in effect parameters of severity - i.e. 'deterioration', the need for long-term hospital care, referral to research wards, poor premorbid functioning, poor response to neuroleptic drugs etc. Hence the present population seemed ideally suited to answering these questions.

In order to answer the questions posed in this part of the work, patients selected from within the basic population of 510 were scanned and the results compared with scans from several control groups.

The following diagnostic groups were studied :

a) chronic schizophrenic in-patients
b) discharged (non-institutionalised) schizophrenics
c) first episode schizophrenics
d) manic depressives receiving long term in-patient care
e) manic depressive outpatients

2.1 SELECTION OF THE CHRONIC SCHIZOPHRENIC IN-PATIENTS

Matched groups comprising 112 cases were selected for scanning from the total group of 510.

2.1.1 THE DEFECT STATE

PEG work described earlier (Chapter 1.1.4) indicated that increased ventricular size in schizophrenia was associated with deterioration as assessed by global clinical judgement. In Part 1, it was noted that other elements of deterioration or defect, namely impaired behavioural performance, 'negative' schizophrenic features and neurological signs of an extra-pyramidal type, were all associated with cognitive impairment, though deficits in none of these areas correlated with the presence of 'positive' mental state features. As presented in the literature review, cognitive impairment has frequently been correlated with increased lateral ventricular size (Part 1, Chapter 1.3.3). Such findings are consistent with the concept

that the clinical presentations characterised by predominantly 'positive' and 'negative' features represent relatively independent dimensions of pathology. It has been postulated that structural brain changes are more likely to be associated with 'negative' or 'defect' features. For this part of the study, the term 'defect state' was defined as in Part 1 (Chapter 4.3). Patients with and without a 'defect state' were matched on each of the following variables :

Age
Sex
Length of illness
Past academic record
Gross ('other') neurology
Past treatment with: Insulin coma
ECT
Neuroleptic drugs

Past physical treatments were also matched in terms of 'none', 'some', 'much', as defined previously (Part 1).

Seven identically matched pairs were scanned.

2.1.2 PAST PHYSICAL TREATMENTS

The question of the relationship between ventricular size and past exposure to physical forms of treatment, for which this population was particularly suitable, was examined in two ways. Firstly, a sample who had received no insulin, ECT or neuroleptic treatment was compared with a matched sample * who had been heavily treated by physical means. It was not possible to match those who had never received physical treatment with subjects heavily treated with all

* In this Part, the term "a matched sample" refers to one comprising subjects matched for age, sex, and length of illness.

three modalities. Thus a numerical value of 1 - 3 was arbitrarily attributed to the 'none', 'some' and 'much' categories respectively for each form of treatment. Those with no history of physical therapy were matched with subjects scoring at lease 6 on this arbitrary system. These latter subjects had thus been heavily treated in at least one modality or had received moderate degrees of exposure to all three. The two groups comprised a total of 16 subjects.

Secondly, the relevance of individual treatments was assessed by comparing matched samples who had had equal exposure to treatments other than the one under consideration. For each modality in turn subjects never exposed were compared with those heavily exposed. Thus, for example, matched subjects never treated and heavily treated with insulin were compared, their exposure to ECT and neuroleptics being equal. For each treatment modality, 8 separate pairs were available.

2.1.3 COGNITIVE FUNCTIONING

It was not possible to assess the relationship between premorbid intelligence, 'defect state' and structural brain change because, of those with higher premorbid attainment or potential, only 2 had the 'defect state' as currently defined. This undoubtedly reflects the strong correlation between premorbid and current cognitive ability. In addition matching of the higher academic group with others was complicated by a number of the former patients having had leucotomies.

In order to study patients in whom there could be little doubt that present poor cognitive performance represented a decline, those higher academic patients who achieved more than the mean Withers and

Hinton score for the total population were compared with a matched sample who achieved less than the mean. Even this comparison proved difficult however, yielding only 4 matched pairs. In order to increase the numbers the length of illness criterion was widened to allow matching of subjects one band above or below the ideal. If this was unsuccessful, the age criterion was likewise widened. In this way a total of 22 patients were made available.

In a similar fashion a group of higher academic subjects was compared with subjects in either of the other ranges of cognitive performance (average or poor), age and length of illness being controlled as closely as possible in the above mentioned way.

2.1.4 CATATONIC PATIENTS

As was described in Part 1, patients with a PSE designation of catatonic syndrome tended to have particularly severe deficits and might be predicted to show particularly marked ventricular enlargement. Patients in CS $^{+}$ Catego subclasses (N = 16) were therefore compared with a matched sample in either NS $^{+}$ or DS $^{+}$ subclasses.

2.1.5 UNDER - 45's

Restricting the scanned subjects to those fulfilling these formal criteria would have resulted in a rather elderly study group. In order to assess lateral ventricular size over a reasonably wide age range, a number of patients under 45 years of age were also included. Fifteen such patients were scanned, an additional 8 having been done as part of the above comparisons.

2.1.6 SELECTION

Computer print-outs generated groupings of the patients (by code number) in terms of the major variables and detailed matching was made by hand. For those under 45 years and the CS $^{+}$ patients, random lists were drawn up and every fifth and every alternate subject respectively was considered. The number of potentially suitable patients in other groups was so small that all who fulfilled the criteria (and consented) were included. Before consent was sought, the nursing staff and the consultant in charge of the patient's care were asked for their views on the suitability of the patient for inclusion in the CT part of the study. In no case was a request for inclusion opposed. The patients were asked for permission having had the procedure explained. Where a patient refused an attempt was made to find an alternative match, or, where this was not possible, the pair was dropped. Those under 45 years or with CS $^{+}$ subclasses who refused, were replaced with the next patient on the random lists. For mute patients unable to give their verbal consent, a joint decision regarding suitability was made by both medical and nursing staff. In such cases, ward staff often accompanied the patient and remained with them throughout the procedure.

2.2. SELECTION OF THE CONTROL GROUPS

The control groups (except the first episode schizophrenics) were chosen to match the in-patient schizophrenics for sex and, as closely as possible, for age.

The non-institutionalised chronic schizophrenics were drawn

from patients with a case-note diagnosis of schizophrenia, discharged from Shenley Hospital during the years 1970 - 1974 inclusive (Johnstone et al 1981). Of these 210 patients, 120 conformed to the Feighner criteria for schizophrenia. One hundred and two were traced and 79 examined in a manner similar to that adopted for the present study. From these, a sample was selected which in addition to matching the in-patients on age, sex and length of illness, also approximated in terms of exposure to insulin, ECT and past neuroleptic drugs. Eighteen matched out-patients, whose mental state permitted and who lived in reasonable proximity to the hospital, co-operated in scanning.

The first episode schizophrenics were a small group of 8 patients admitted with their first illness during the course of the study. All were placed in Catego Class S following PSE assessment.

The manic depressive in-patients were chosen from the 29 patients of the total in-patient population (1227 cases) of Shenley who conformed to Feighner criteria for primary affective illness and had been receiving continuous in-patient care for at least one year. Eleven such patients could be closely matched with the in-patient schizophrenics and were scanned.

Out-patient manic depressives and neurotic subjects were drawn from individuals attending the outpatient clinics of Northwick Park Hospital. The former fulfilled the Feighner criteria for primary affective illness while the latter conformed to Feighner criteria for anxiety neurosis or undiagnosed psychiatric illness. The scanned out-patient manic depressive group comprised 22 subjects and the neurotic group 19.

2.3 PROCEDURE

All scans were performed on the same EMI 5005 whole body scanner at 120 Kv, with a 65 second scan time, and with patients in the supine position. Sedation was avoided where possible but in the 11 patients in whom it was required (all schizophrenic in-patients) intravenous diazepam was used. The scans were examined by the collaborating radiologist using an EMI Mk 11 independent viewing console and bromide pictures obtained of the axial cut showing maximum lateral ventricular size. The window width at which these bromides were taken may affect the assessment of ventricular size on CT - increasing window width resulting in increasing representation of ventricle. For all scans a standard window width of 30 was adopted, as the radiologist considered this to give the best representation of ventricular margins. Unfortunately, with the machine being used, that window width giving the best presentation of ventricular margin often gave a blurred image of brain/skull interface. A second bromide was therefore taken of the same maximal ventricular cut but at a window width of 100, this value giving a clear delineation of brain and skull. Window level - a less influential variable on ventricular representation - was kept as near to 15 as was compatible with the clearest ventricular appearances.

The pictures were presented in random order by the collaborating radiologist, the clinician being blind to the identities and diagnostic categories of the patients. Measurements were made using the Joyce-Loebl Magiscan Image Analyser, where areas were calculated from boundaries. Margins of the lateral ventricles were outlined manually

with a light pen, while those of brain were detected automatically by an edge-tracking computer programme. Areas were thus determined for brain and lateral ventricle, using the cuts of maximal ventricular size at window widths of 100 and 30 respectively. Ventricular size was expressed as the ratio of ventricular area to brain area as a percentage (Ventricular/Brain Ratio or VBR). All scans were examined twice and the average of the two halves were taken as the VBR for each patient. The test-retest reliability was 0.97 . In addition, alternate scans in the first half and in the latter half of the series were examined by a second and a third clinician respectively and the inter-rater reliabilities of the method were high, ranging from 0.91 to 0.99.

2.4 STATISTICAL NOTE

The same basic principles were adhered to as stated for the analysis of movement disorder data (Part II, Chapter 3.2.3). Specific procedures will be mentioned as they arise.

Chapter 3 - Results

3.1 GENERAL

A total of 198 subjects were successfully scanned. All of these films were considered technically adequate for assessment. Two subjects, whose original scans were contaminated by artifact, allowed the investigation to be repeated, the original scans being discarded. With only 2 patients (both chronically hospitalised schizophrenics) did the procedure require to be aborted before completion. These patients were substituted by the next ones on their respective lists. Sedation prior to commencing the scan sequence was necessary to settle 11 subjects, all of whom were long-stay schizophrenic in-patients. This was achieved by administration of intravenous diazepam to the point of inducing light sleep. The amount required ranged from 10 - 70 mgms (mean 37.3 $\pm$ SD 20.4 mgms).

Eleven scans were excluded from assessment and analyses. The reasons for these exclusions and the actual numbers analysed in each diagnostic category are shown in TABLE 3:3:1. The presence of unsuspected organic pathology was only considered a justifiable basis for exclusion if there was reasonable evidence that such pathology may exert a direct bearing on ventricular size. Thus, the 3 patients referred to in TABLE 3:3:1 as being excluded for non-operative organic reasons, all had signs of ventricular distortion or mid-line shift. As will be referred to subsequently, several other subjects demonstrating unsuspected organic pathology (mainly isolated peripheral infarction) were not excluded as their lesions did not impinge on the central liquor spaces. Maintaining these subjects in the study did not alter

TABLE 3:3:1 NUMBERS OF SUBJECTS SCANNED AND EXCLUSIONS IN EACH DIAGNOSTIC CATEGORY

DIAGNOSTIC CATEGORY	NUMBER SCANNED	NUMBER EXCLUDED	REASONS FOR EXCLUSION	NUMBER ANALYSED
CHRONIC SCHIZOPHRENIC IN-PATIENTS	118	8	LEUCOTOMY 6 SUBDURAL HAEMATOMA 1 PORENCEPHALIC CYST (BIRTH TRAUMA) 1	110
OUT-PATIENT SCHIZOPHRENICS	18	0	-	18
FIRST EPISODE SCHIZOPHRENICS	8	0	-	8
IN-PATIENT AFFECTIVES	11	1	NON-FULFILLMENT OF DIAGNOSTIC CRITERIA 1	10
OUT-PATIENT AFFECTIVES	24	2	(L) POSTERIOR QUADRANT ARTERIOVENOUS MALFORMATION 1 NON-FULFILLMENT OF DIAGNOSTIC CRITERIA 1	22
NEUROTICS	19	0	-	19
				187

the basic findings (vide infra).

3.2 COMPARISONS OF VENTRICULAR SIZE IN DIFFERENT DIAGNOSTIC GROUPS

3.2.1 STRAIGHT INTER-GROUP COMPARISONS

The distributions of VBR's in the total sample of 187, and in each diagnostic category separately, are shown in Figs 3:3:1 and 3:3:2 respectively. There is clearly considerable overlap in all groups. The mean VBR of the schizophrenic patients (long-stay in-patients, out-patients and first episodes combined) was 11.87 $\pm$ SD 3.42, while that for the non-schizophrenics (in-patient manic depressives, out-patient manic depressives, neurotics combined) was 10.87 $\pm$ SD 2.34. This difference only narrowly missed conventional statistical significance (ANOVA: F - value (1,185) = 3.66, P = 0.057). Analysis of variance of the group means reveals that this was due entirely to a significant difference between the mean VBR of the long-stay schizophrenic in-patients compared to that of the neurotics (TABLE 3:3:2). No other comparisons between the groups reached significance and there were no noteworthy trends.

3.2.2 AGE

Such an analysis does not however take account of the possible effects of age on VBR. Although not all workers have been able to establish a significant contribution to ventricular enlargement from increasing age, there is evidence in the literature that such a relationship exists, at least in normal samples.

FIG 3:3:1

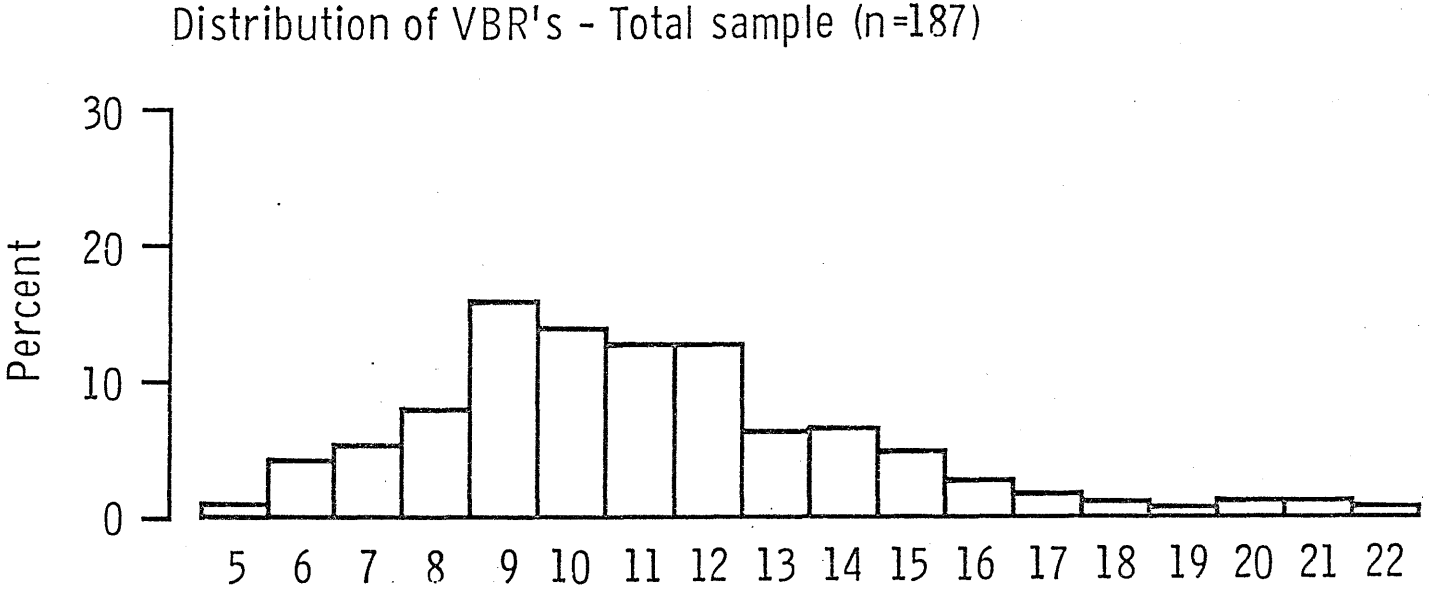

Distribution of VBR's - Total sample (n=187)
Percent
30
20
10
0
5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22

FIGURE 3:3:2 VENTRICULAR-BRAIN RATIOS IN EACH DIAGNOSTIC GROUP (WITH GROUP MEAN ± S.D.)

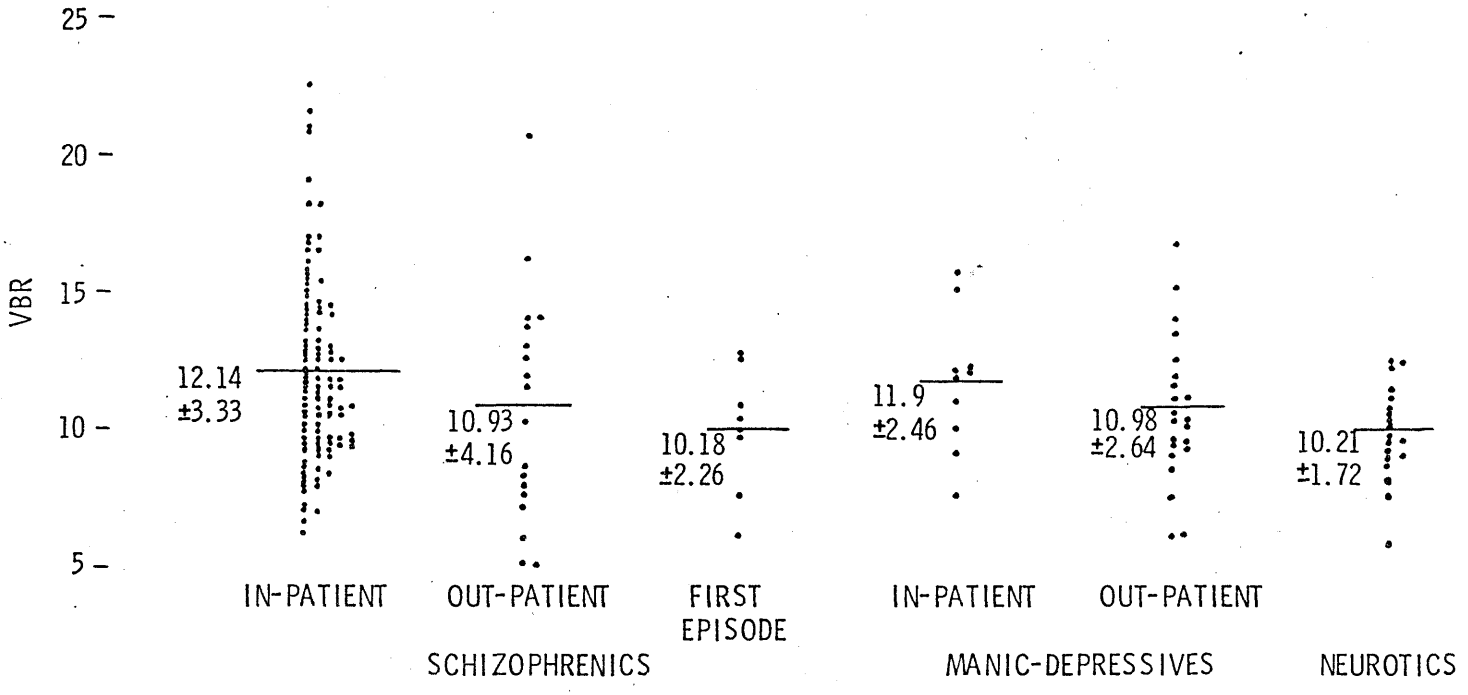


TABLE 3:3:2 T-TEST MATRIX FOR GROUP MEANS (df = 181) - AGE NOT ACCOUNTED FOR

	IN-PAT. SCH.	OUT-PAT. SCH.	NEUROTICS	IN-PAT. AFF.	OUT-PAT. AFF.	1st EPISOI SCH.
IN-PAT. SCHIZ.	0.00					
OUT-PAT. SCHIZ.	-1.49	0.00				
NEUROTICS	-2.45*	-0.70	0.00			
IN-PAT. AFF.	-0.22	0.78	1.37	0.00		
OUT-PAT. AFF.	-1.55	0.05	0.78	-0.77	0.00	
1st EPIS. SCHIZ.	-1.69	-0.56	-0.02	-1.15	-0.62	0.00

* p = 0.015

The distribution of age in the total sample of 187 subjects and in each diagnostic group separately, is shown in Figs 3:3:3 and 3:3:4 respectively. The mean age of the scanned subjects was 55.99 $\pm$ SD 12.7 years (range 22 - 87 years). As TABLE 3:3:3 demonstrates, the groups differed markedly in their mean ages, the in-patient manic depressive group being older and the first episode schizophrenics younger than the others. As would be anticipated by the nature of the constituent patients, the groups also differed markedly in mean lengths of illness (TABLE 3:3:3).

In the total sample of 187, the relationship between age and VBR is shown in Fig. 3:3:5. This was highly significant ($F(1,184) = 38.8$, $P < 0.0002$). The above inter-group comparisons of VBR were thus repeated accounting for the effects of age.

3.2.3 INTER-GROUP COMPARISONS - AGE ACCOUNTED FOR

With age covaried, the mean VBR of the schizophrenics remained significantly greater than that of the non-schizophrenics, the probability value decreasing considerably ($F(1,184) = 6.1$, $P = 0.015$). Comparison between the six groups confirmed that with age effects accounted for, this difference was again due to the long-standing schizophrenic in-patients having a significantly larger group mean VBR than the neurotics (TABLE 3:3:4). The age adjusted group mean VBR's ($\pm$ SE's) are shown in TABLE 3:3:5.

As was mentioned above this result was not altered by omitting those patients with incidental intracranial pathology not impinging on the ventricular system (chronic schizophrenic in-patients v neurotics $t = 2.27$, $df = 171$, $P < 0.025$).

FIG 3:3:3

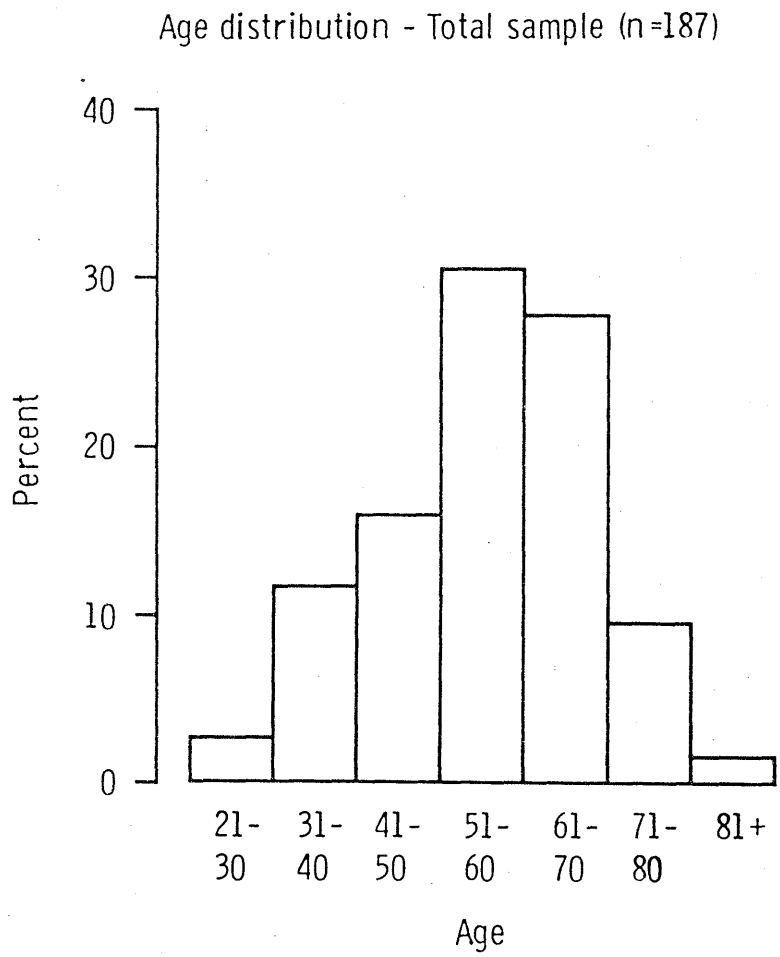

Age distribution - Total sample (n=187)
Percent
40
30
20
10
0
21-30
31-40
41-50
51-60
61-70
71-80
81+
Age

FIG 3:3:4

Age distribution for each diagnostic group

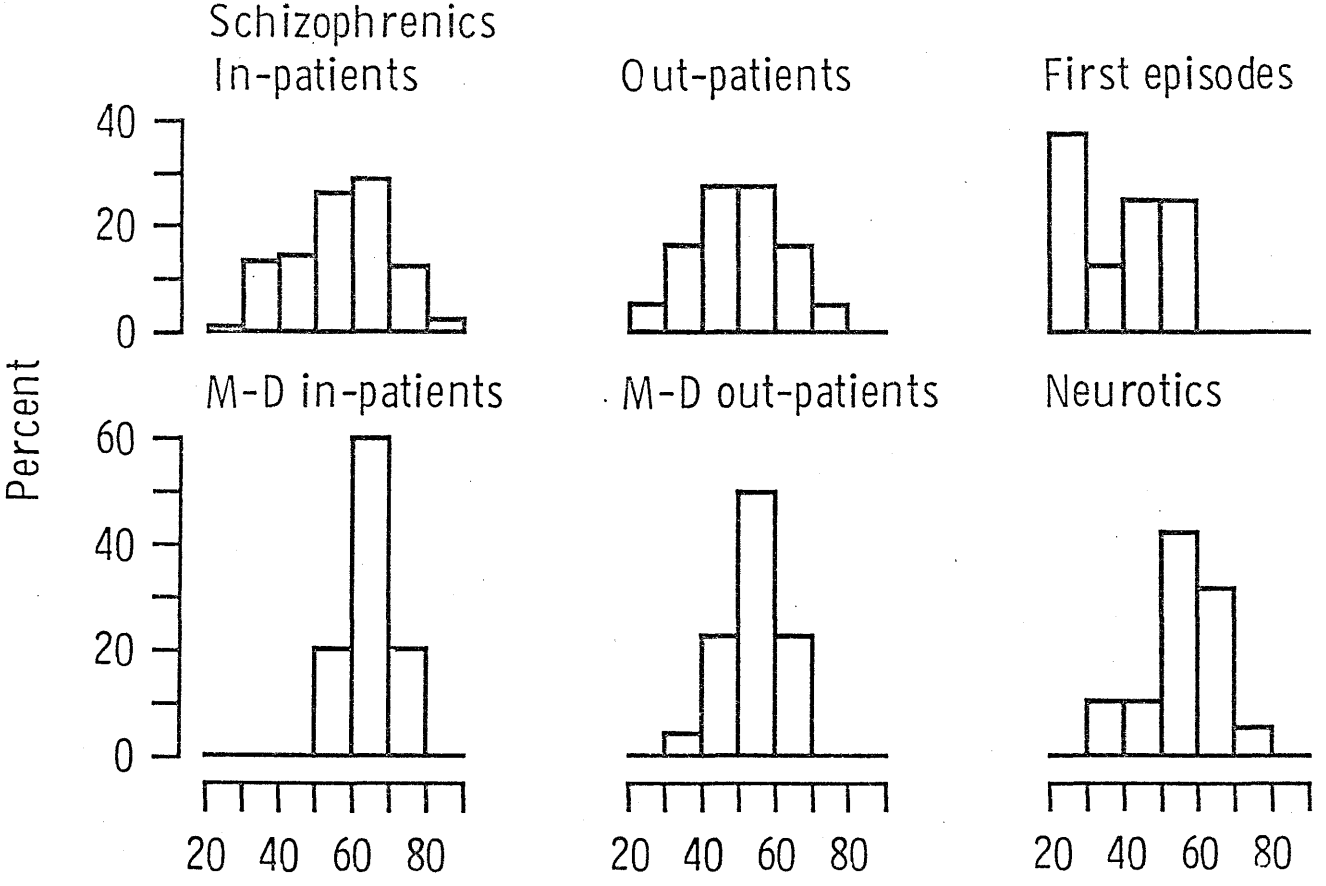


TABLE 3:3:3 MEAN AGES AND LENGTH OF ILLNESS OF TOTAL SCANNED SAMPLE (N = 187)

DIAGNOSTIC CATEGORY		NUMBER SCANNED MALES	FEMALES	TOTAL	MEAN AGE ± SD (YEARS)		MEAN LENGTH OF ILLNESS ± SD (YEARS)*	
SCHIZOPHRENICS	IN-PATIENTS	71	39	110	58.2 ± 12.8	55.5 ± 13.9	31.9 ± 10.6	28.5 ± 12.9
	OUT-PATIENTS	6	12	18	49.8 ± 11.9		21.9 ± 10.7	
	FIRST EPISODES	4	4	8	39 ± 13.2		-	
NON SCHIZOPHRENICS	MANIC-DEPRESSIVE IN-PATIENTS	2	8	10	65.2 ± 6.4	57.2 ± 9	28.3 ± 14	18.1 ± 13.8
	MANIC-DEPRESSIVE OUT-PATIENTS	11	11	22	54.7 ± 6.9		22.7 ± 12.4	
	NEUROTICS	9	10	19	56 ± 10.4		6.5 ± 6	

* SEE TEXT FOR DEFINITION

FIGURE 3:3:5 RELATIONSHIP BETWEEN AGE AND VBR

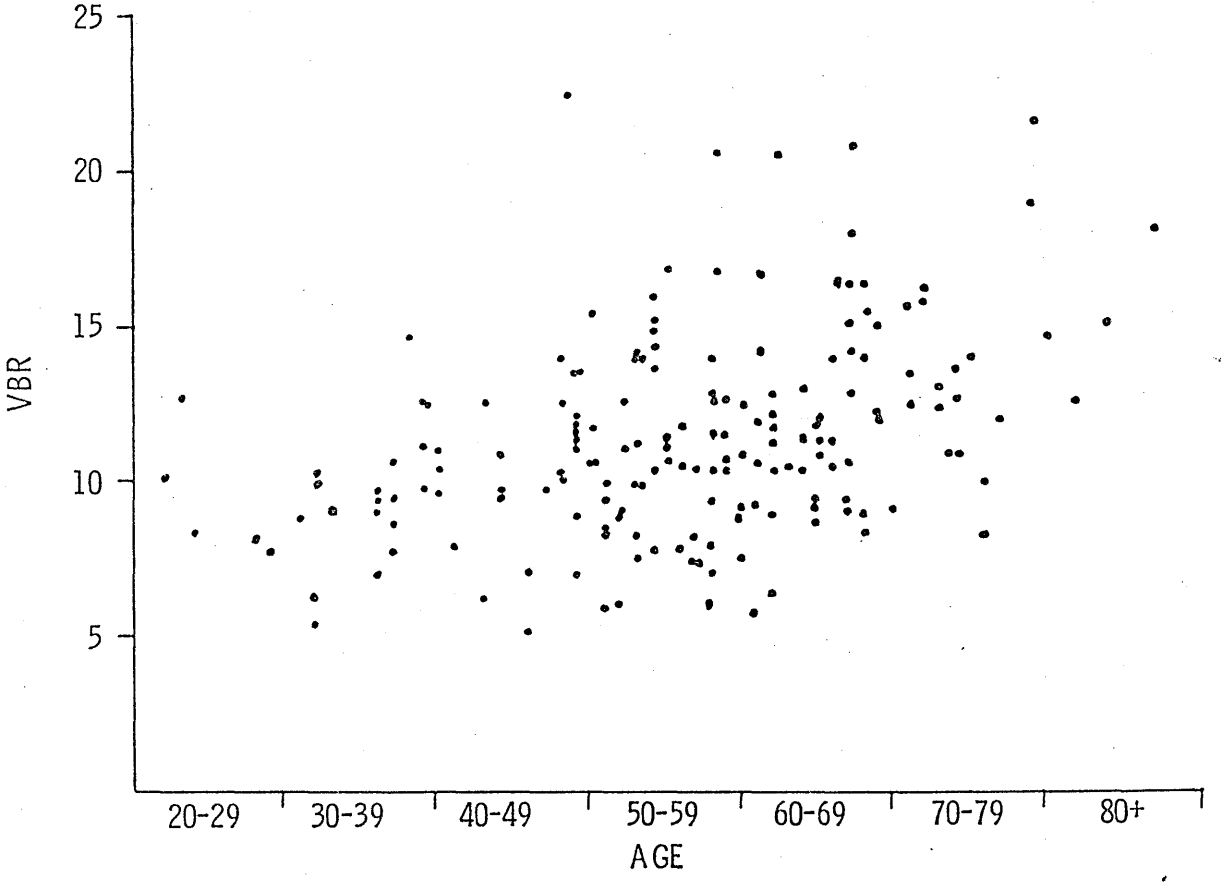


TABLE 3:3:4 T-TEST MATRIX FOR GROUP MEANS (df = 180) - AGE ACCOUNTED FOR

	IN-PAT. SCH.	OUT-PAT. SCH.	NEUROTICS	IN-PAT. AFF.	OUT-PAT. AFF.	1st EPI. SCH.
IN-PAT. SCHIZ.	0.00					
OUT-PAT. SCHIZ.	-0.44	0.00				
NEUROTICS	-2.32*	-1.40	0.00			
IN-PAT. AFF.	-0.97	-0.51	0.65	0.00		
OUT-PAT. AFF.	-1.14	-0.48	0.99	0.14	0.00	
1st EPIS. SCHIZ.	0.02	0.29	1.35	0.66	0.65	0.00

* p = 0.021

TABLE 3:3:5

AGE CORRECTED GROUP MEAN VBR's (± S.E.'s)

LONG-STAY SCHIZOPHRENIC IN-PATIENTS	11.97 ± 0.28
SCHIZOPHRENIC OUT-PATIENTS	11.56 ± 0.69
FIRST EPISODE SCHIZOPHRENICS	11.90 ± 1.07
MANIC-DEPRESSIVE IN-PATIENTS	10.96 ± 0.93
MANIC-DEPRESSIVE OUT-PATIENTS	11.11 ± 0.62
NEUROTICS	10.20 ± 0.67

3.2.4 LENGTH OF ILLNESS AND SEX

In keeping with previous Sections, length of illness was also evaluated as a separate component of the effect of the passage of time. By the nature of the comparison population in the present Section, the term 'length of illness' could not be consistently defined for each group. For the chronic schizophrenic in-patients and out-patients it was calculated as in Parts 1 and 11 - i.e. length of time since first admission. For the first episode schizophrenics it was clearly zero, as fractions of a year were not considered. For the other groups the term was defined as the time since first psychiatric contact (TABLE 3:3:3).

Using these definitions, analysis of covariance was conducted with age and length of illness as covariates and VBR as dependent variable. This showed a highly significant effect of all covariates - i.e. of time factors ($F_{2,182} = 20.05$, $P<0.0001$). However, this relationship was entirely due to the striking effect of age alone ($F_{1,182} = 14.77$, $P = 0.0002$). There was no significant independent effect of length of illness ($F_{1,182} = 1.77$, $P = 0.19$).

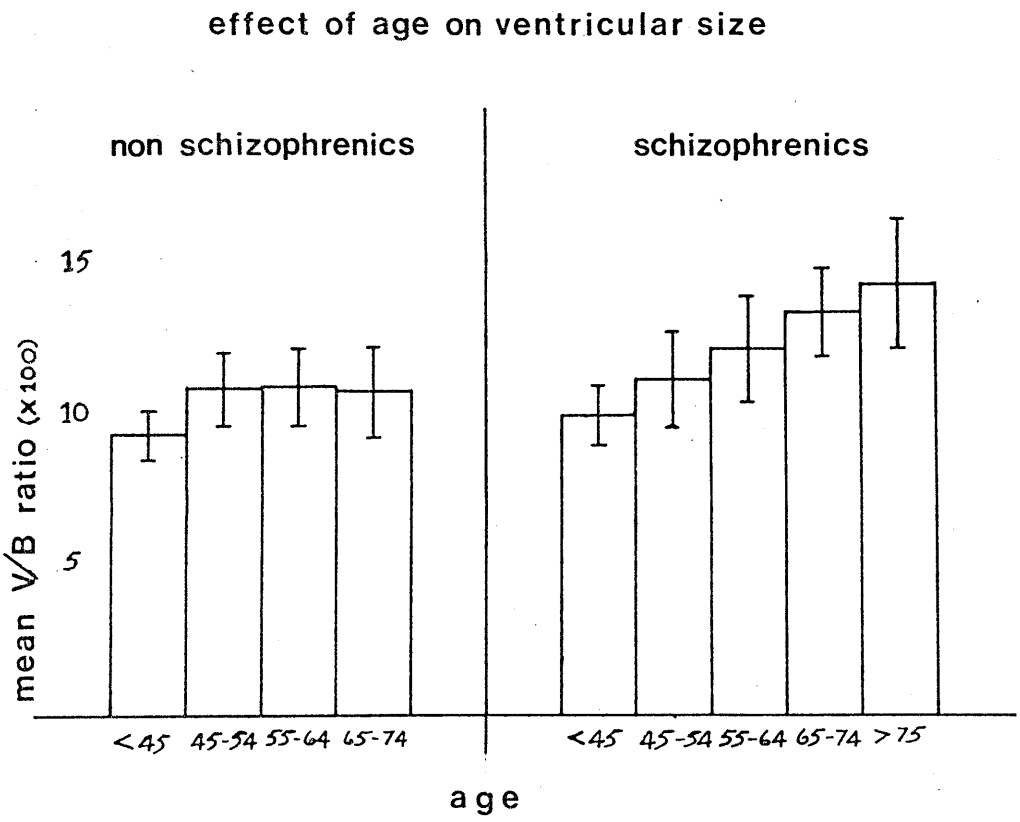
Sex likewise was not significantly related to VBR ($F_{1,182} = 0.95$, $P = 0.33$).

3.3 THE NATURE OF THE RELATIONSHIP BETWEEN AGE AND VBR

Having established a strong association between age and ventricular size as assessed by VBR, the nature of this relationship was explored further.

The relationship between age and VBR in non-schizophrenics and schizophrenics separately is shown in Fig. 3:3:6. There is a definite

FIG 3:3:6


effect of age on ventricular size
non schizophrenics
schizophrenics
mean V/B ratio (x100)
15
10
5
<45
45-54
55-64
65-74
<45
45-54
55-64
65-74
>75
age

implication of a greater and premature effect of age in those with schizophrenic diagnoses. However, in statistical terms, no significant difference could be demonstrated in the equality of slopes for the age/VBR relationship when either the non-schizophrenics were compared with the schizophrenics ($F\ 1,183) = 0.4$, $P = N/S$), or when the relationship within each diagnostic group was evaluated ($F\ 5, 175) = 0.99$, $P = N/S$). This suggests that the positive relationship between age and VBR is in fact consistent in schizophrenics and non-schizophrenics alike, and within the limits set by the relatively small number in some groups, in each diagnostic category likewise.

Further, however, there is evidence that such age effects as are demonstrable on the VBR's of non-patient groups may only become manifest in middle life, ventricular size remaining fairly constant until approximately the 6th decade. Polynomial regression analysis was performed to determine the form of the best fit relationship between age and VBR in this mixed patient sample, with the expectation that the relationship would accelerate with increasing age.

Polynomial regression produces 3 coefficients. The coefficient of degree 1 is the linear coefficient; that of degree 2 is the quadratic coefficient; and that of degree 3 the cubic coefficient. Only the coefficient of degree 1 (linear) reached conventional significance (t - value $= 6.01$, $df = 183$, $P = 0.001$). However this analysis did show a non-significant trend to significance for the quadratic coefficient of degree 2 (t - value $= 1.37$, $df = 184$, $P < 0.08$). Thus, although the quadratic component is not significant by conventional criteria, the best fit curve does show accelerating function with age.

The plots of observed and predicted values for the coefficients

with age for coefficient of degree 1 (linear)

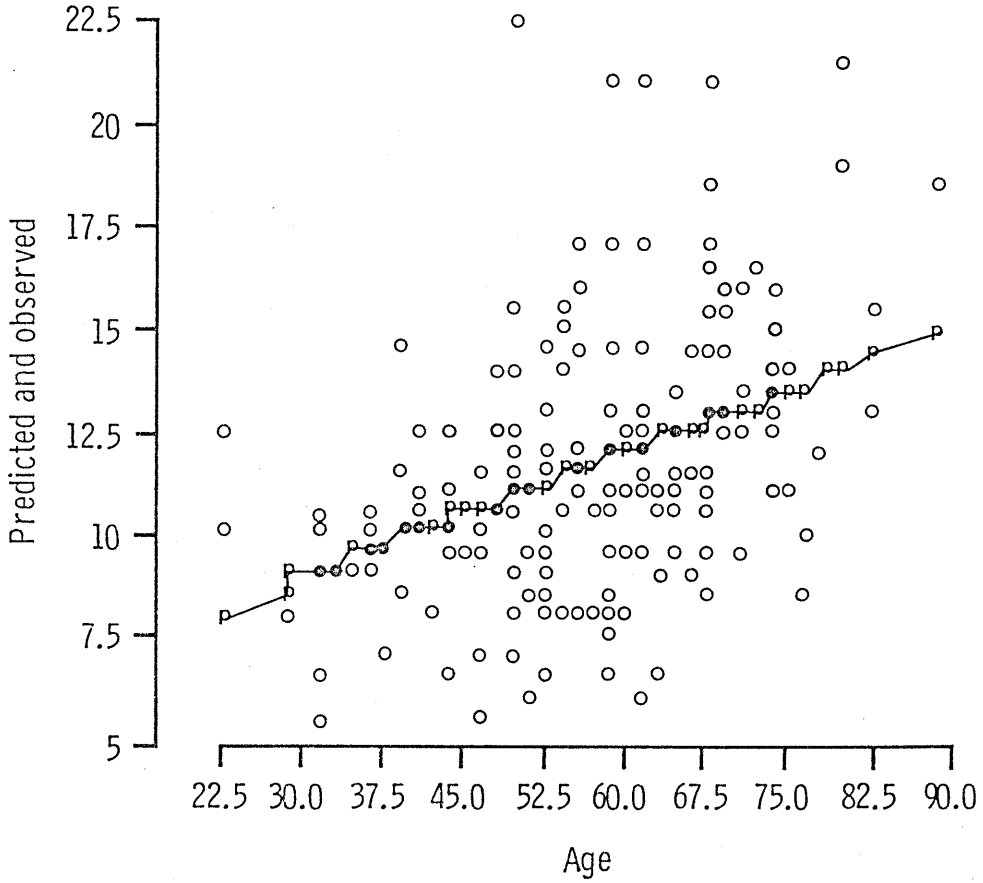
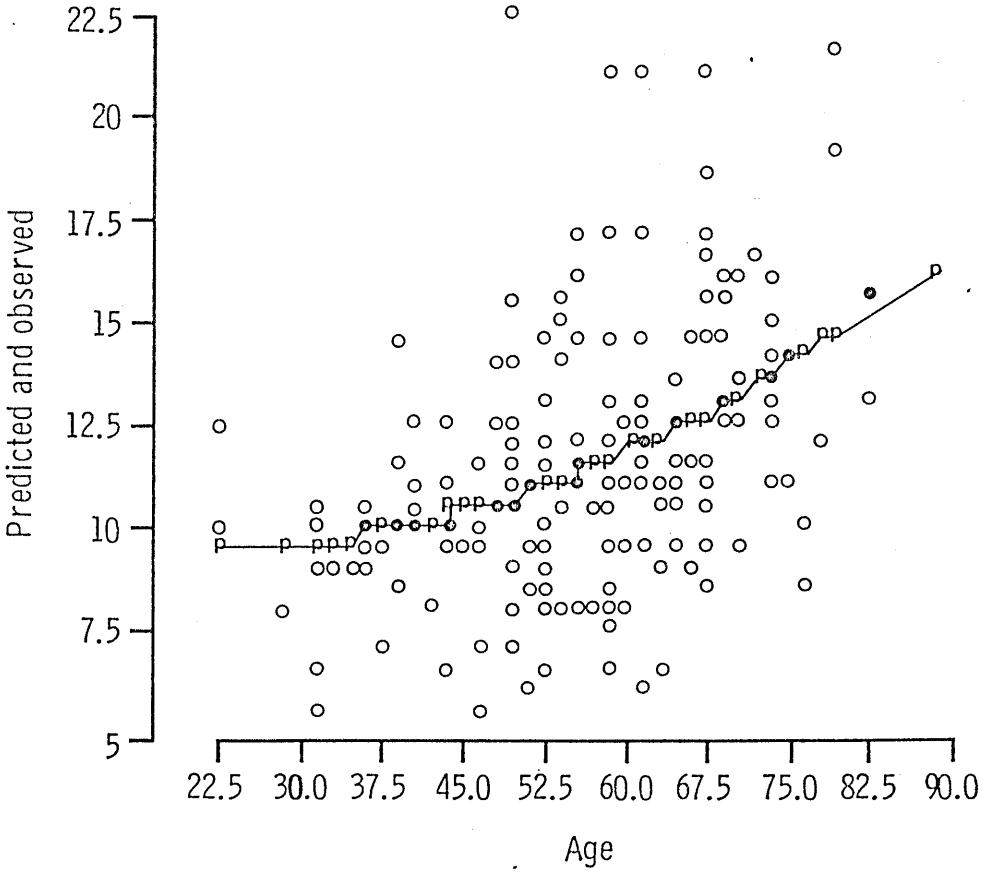


FIG 3:3:8 Polynomial regression: observed and predicted VBR's with age for coefficient of degree 2 (quadratic)



of degrees 1 and 2 are shown in Fig 3:3:7 and 3:3:8. These suggest that the age relationship may differ below the early part of the 5th decade compared to later in life. This trend to non-linearity may thus reflect a flatter, plateaued relationship of VBR to age in those in the present sample who were under approximately 40 years of age, while after this, the relationship becomes stronger and linear. This quadratic (degree 2) relationship may have failed to reach significance because of the relatively small proportion of the study sample under 40 years of age (14.4 %). Because of this bias towards older subjects and the relatively small numbers in diagnostic groups, it was felt that data from the present study could not be used with any reliability to explore this question further within subgroups of the total population.

Thus while no definite premature or accelerated age effects could be demonstrated in schizophrenics as compared to non - schizophrenics in this study, it may be that ventricular appearances associated with age may occur earlier - up to one decade - in patients with functional psychiatric diagnoses than in the general, non-patient, population. Hence the present comparison may not be the appropriate one to demonstrate premature age differences in schizophrenia, which are likely to emerge only when patients with long-standing schizophrenia, representing a wide age range, are compared with appropriate normal controls.

3.4 DISTRIBUTIONS OF VBR's

3.4.1 SKEWNESS/KURTOSIS

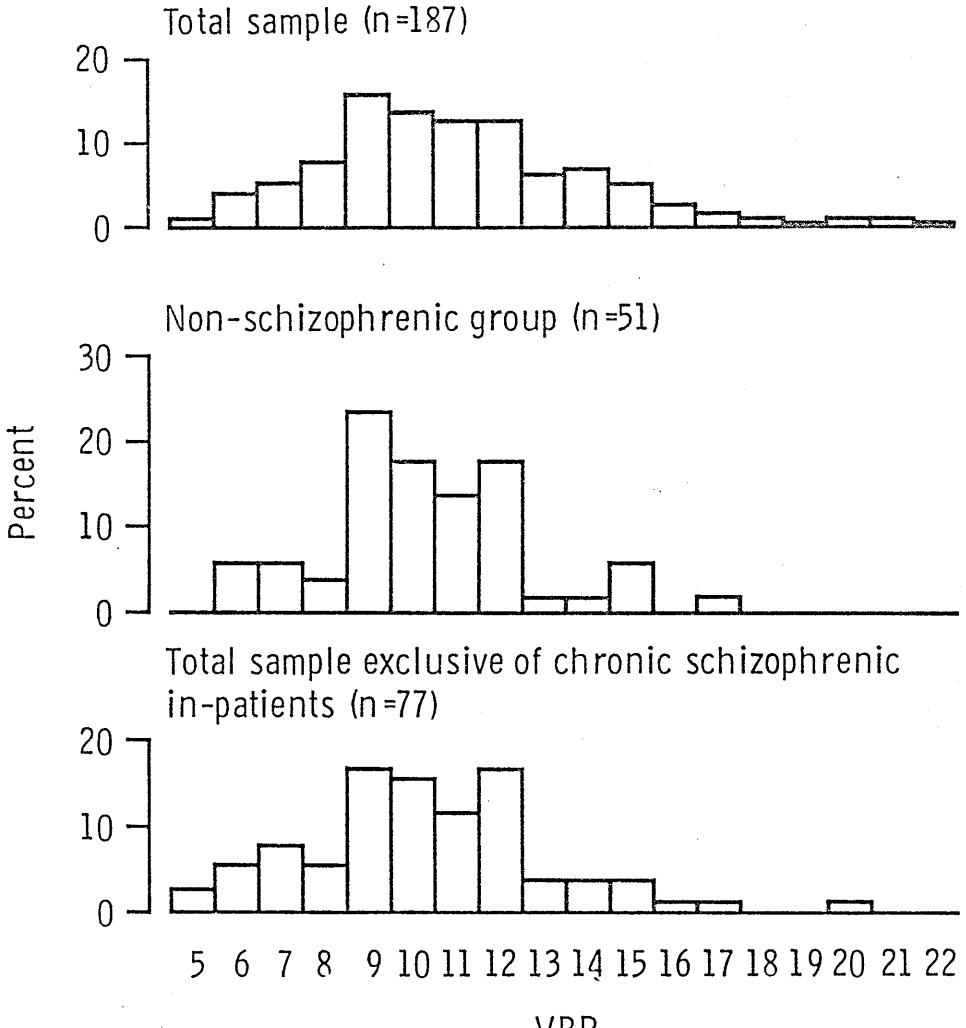
The distributions of VBR and of age in the total sample were illustrated in Figs 3:3:1 and 3:3:3 respectively. While age would appear to conform approximately to a normal distribution, that of the VBR's clearly deviates from normality. The distributions of VBR for different groupings of the total sample are shown in Fig 3:3:9. Statistical evaluation of the deviation or otherwise from normality of the distributions within these groups was performed by calculations of skewness and kurtosis for both VBR and age. The combinations shown in the figure were adopted to examine where the major source of the deviation lay, as some of the pure diagnostic categories contained too few subjects for tests of skewness and kurtosis to be reliably conducted directly. Skewness is a measure of asymmetricality of the deviation from normal, while kurtosis is a measure of symmetrical deviation.

As TABLE 3:3:6 shows, the highly significant skew in the distribution of the total sample is due to a significant positive skew in the schizophrenic patients, and this in its turn, emanates from an excess of long-stay schizophrenic in-patients with large VBR's. These deviations are not the result of skew in the age distributions.

The significant kurtosis of the VBR distribution in the total sample reflects the high proportion (55.6 %) with VBR's between 9.0 and 12.99 (Fig 3:3:9).

FIG 3:3:9

Distributions of VBR in different patient groupings



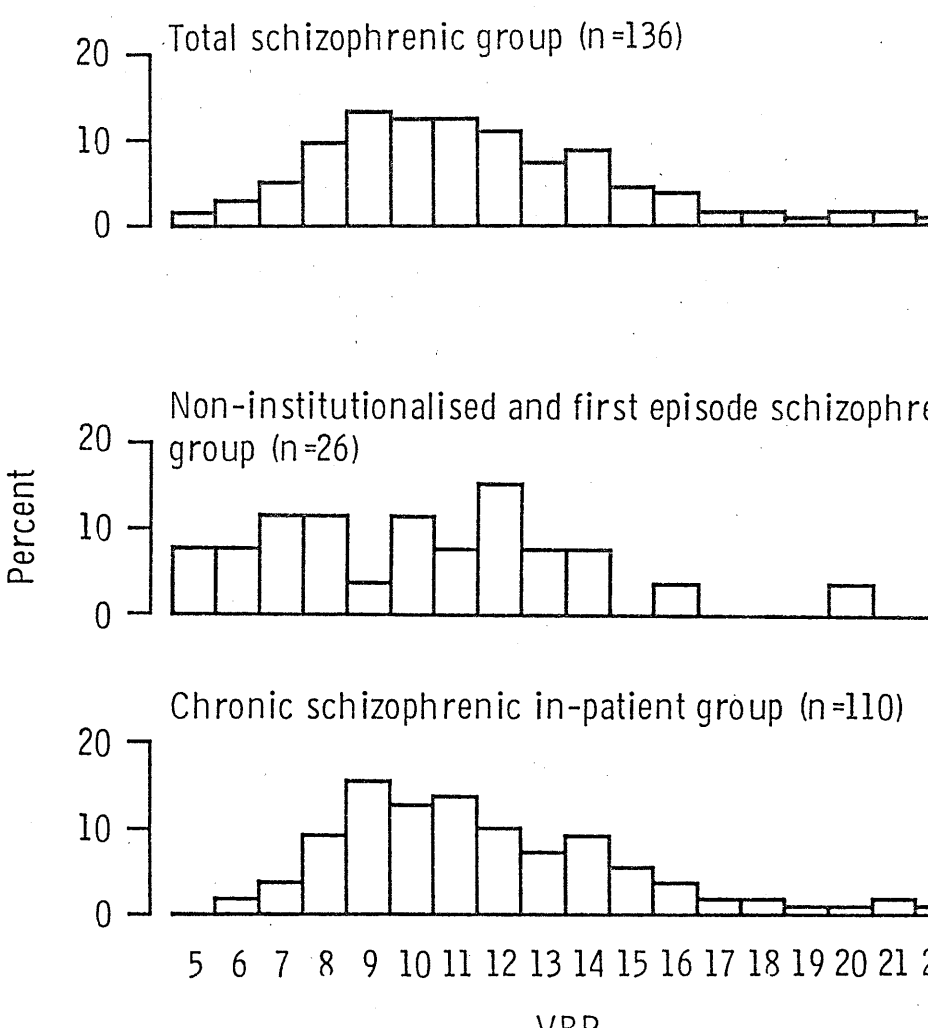


TABLE 3:3:6 ANALYSIS FOR SKEWNESS AND KURTOSIS OF DISTRIBUTIONS OF VBR AND AGE IN DIFFERENT DIAGNOSTIC GROUPINGS

		SKEWNESS						KURTOSIS					
		FOR VBR			FOR AGE			FOR VBR			FOR AGE		
PATIENT GROUPING	N	VALUE	VALUE S.E.	SIGNIF.	VALUE	VALUE S.E.	SIGNIF.	VALUE	VALUE S.E.	SIGNIF.	VALUE	VALUE S.E.	SIGNI
TOTAL SAMPLE	187	0.82	4.57	p<0.001	-0.31	-1.73	N/S	0.99	2.76	p<0.01	0.19	0.52	N/S
NON-SCHIZOPHRENIC GROUP	51	0.36	1.05	N/S	-0.56	-1.64	N/S	0.15	0.22	N/S	0.1	0.15	N/S
TOTAL SAMPLE EXCLUSIVE OF CHRONIC SCHIZOPHRENIC IN-PATIENTS	77	0.54	1.94	N/S	-0.73	-2.63	p<0.02	0.94	1.68	N/S	0.14	0.26	N/S
TOTAL SCHIZOPHRENIC GROUP	136	0.74	3.53	p<0.001	-0.21	-1.02	N/S	0.59	1.40	N/S	-0.48	-1.14	N/S
NON-INSTITUTIONALISED AND FIRST EPISODE SCHIZOPHRENIC GROUP	26	0.61	1.27	N/S	-0.27	-0.56	N/S	0.19	0.2	N/S	-0.88	-0.91	N/S
CHRONIC SCHIZOPHRENIC IN-PATIENT GROUP	110	0.86	3.69	p<0.001	-0.2	-0.84	N/S	0.62	1.33	N/S	-0.58	-1.24	N/S

It has been suggested that a VBR of greater than 2 SD's above the control mean is indicative of abnormality in schizophrenia studies (Weinberger et al 1979a), and hence that analysis based on distribution is valid. Although this criterion was adopted empirically, it has been used in a number of studies. The previous analysis would tend to support the use of distribution in the further study of VBR and its correlates. However, in view of the strong and possibly complicated association between age and ventricular size, it is necessary to make a specific age correction before proceeding further.

3.4.2 CALCULATION OF AGE - CORRECTION

The regression coefficient of VBR with age was 0.102. That is, for each year of variation in age, VBR varied approximately by 0.102. Applying this term to the mean VBR of the neurotic group and calculating from their mean age, an age-corrected mean VBR or predicted value for neurotics at all ages was derived. A range of variance for 1 and 2 standard deviations above and below these age-corrected or predicted VBR's was calculated from the observed standard deviations of the neurotic group at their mean VBR and group mean age. The observed VBR's were then categorised in terms of their relationship to those predicted, age-corrected means and standard deviations based on the neurotic sample.

Inherent in this procedure are two assumptions. Firstly it is assumed that age bears a linear relationship to VBR. While in the present study this is statistically so, the tendency to a signficant quadratic relationship is ignored in the above calculation. Secondly is the assumption that standard deviation does not vary with age.

This may not be strictly correct, but the present study did not furnish sufficient data to allow resolution of this question. Any possible margin of error issuing from these two assumptions would however be small, and the likelihood of misclassification slight.

3.4.3 AGE-CORRECTED DISTRIBUTIONS

The VBR distributions relative to these age-corrected predicted values are shown in Figs 3:3:10 and 3:3:11, which illustrate each diagnostic group separately and the same groupings of the population which were referred to previously. These distributions were compared with the theoretical number that would be expected with a normal distribution.

The distribution of the total population differed significantly from normality ($X^2 = 353.14$, $df = 4$, $P < 0.00001$). This deviation from normality is reflected in the distributions of both the non-schizophrenic ($X^2 = 26.83$, $df = 4$, $P < 0.001$) and the schizophrenic ($X^2 = 319.16$, $df = 4$, $P < 0.00001$) subsamples. Furthermore the pattern of distribution in the schizophrenics was significantly different from that of the non-schizophrenics (Kolmogorov-Smirnov two-sample test : $X^2 = 7.42$, $df = 2$, $P < 0.025$) (Fig 3:3:11).

These findings result from an excess of patients with ventricles greater than 2 SD's above the age-corrected, predicted mean. Thus while both non-schizophrenic and schizophrenic subsamples had more patients with large ventricles than would have been expected by chance, the excess of such patients among the schizophrenics was strikingly greater than that found in those with non-schizophrenic

FIG 3:3:10

Distributions of VBR relative to age-corrected predicted values - Diagnostic groups separately

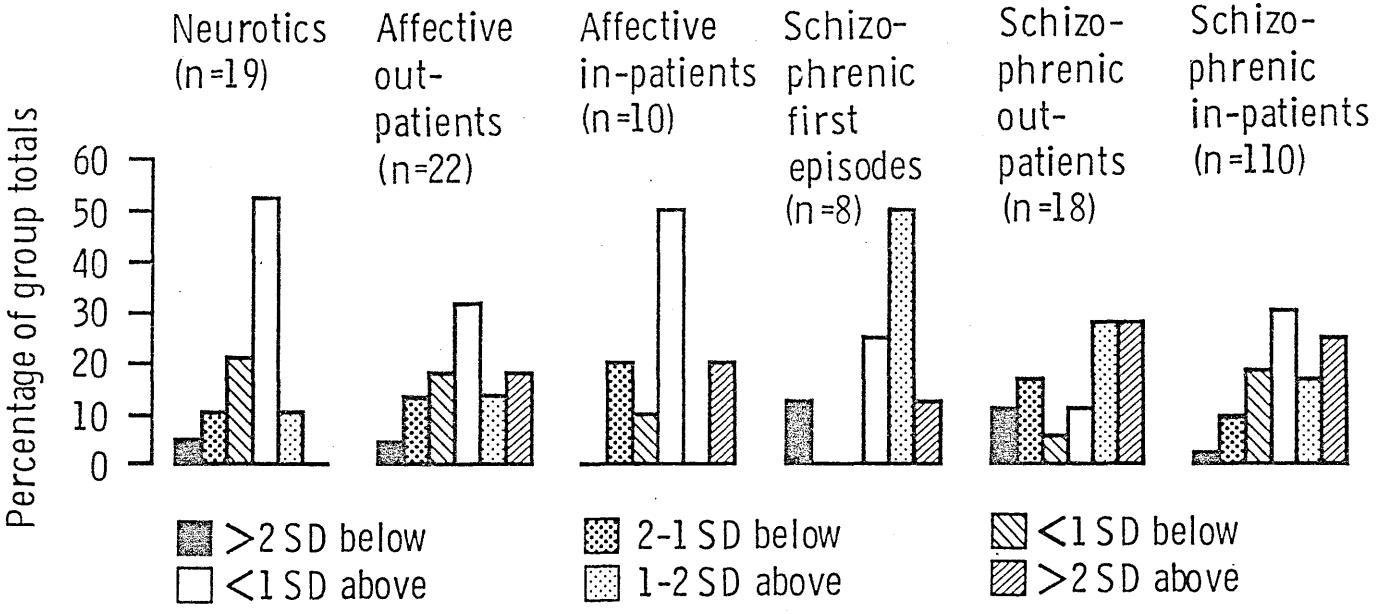
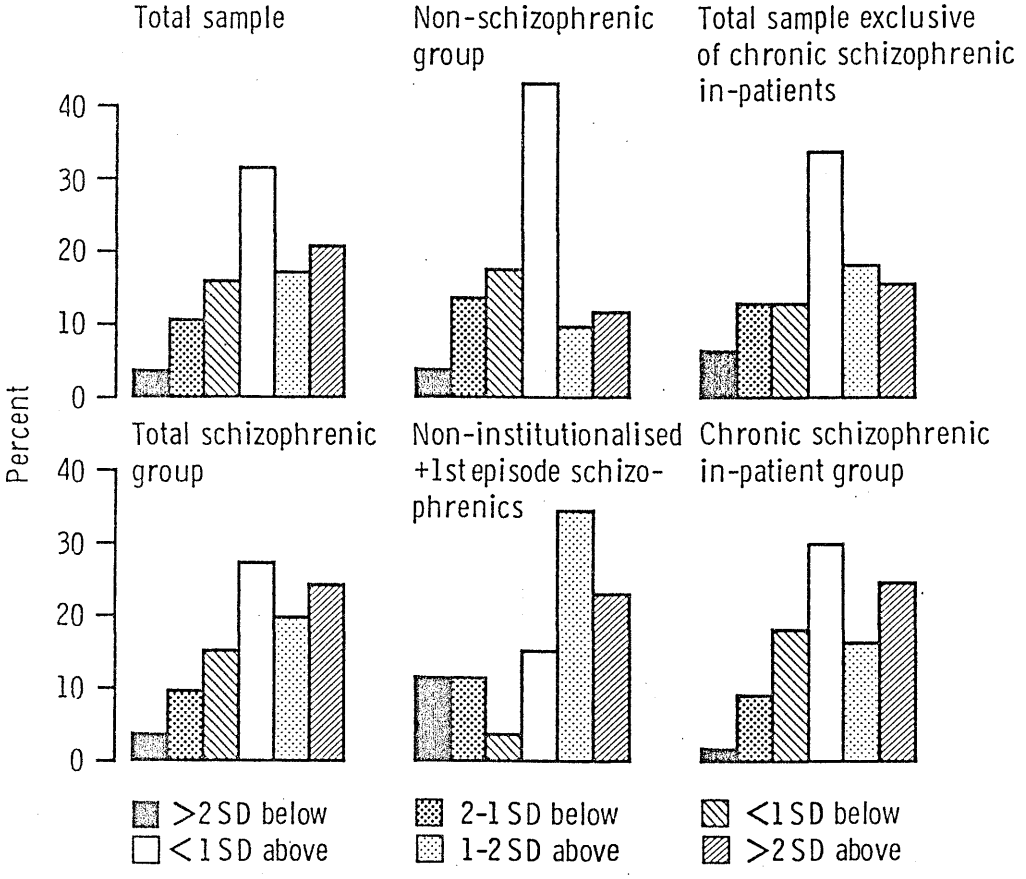


FIG 3:3:11

Distributions of VBR relative to age-corrected predicted values - Various patient groupings



diagnoses.

One further finding to emerge related to the distribution at the small end of the range. While neither all the schizophrenics considered together, nor the chronic in-patients alone appeared to differ from a normal pattern at the left-hand side of their distributions, the non-institutionalised and first episode schizophrenics considered as a single group, did. This group not only had an excess of subjects with large ventricles (greater than 2 SD's above mean), but also had an excess in the smallest range (smaller than 2 SD's below mean). Analysing normality with small numbers becomes of dubious validity, though with 26 subjects represented it is unlikely that small numbers alone are the cause of unreliability in this result. Three (11.5 %) of these patients had ventricle sizes in the smallest category, as opposed to the single one (in actual fact 0.5) predicted.

Thus, assessed in two different ways, the distribution of VBR's in the present sample is markedly different from what whould be expected if ventricular size is normally distributed in the general population, and analysis of scanned data that are based on distribution appear to have some justification. The striking finding is the great excess of ventricle sizes outwith 2 SD's in schizophrenic patients.

3.5 THE CLINICAL CORRELATES

3.5.1 ANALYSIS OF MATCHED PAIRS

The matched pairs differed only on the single variable under consideration. The ventricular size of those in whom the variable was present was compared with that of those in whom it was absent, analysis being by paired t - tests.

The results are shown in TABLE 3:3:7. No significant differences emerged in the ventricular sizes of the matched pair groups.

3.5.2 RELATIONSHIPS BETWEEN VENTRICULAR SIZE AND ITEMS OF RECORDED INFORMATION AND ASSESSED ABNORMALITY

a) GENERAL

Correlations were sought between ventricular size (VBR) and items of Recorded Information and Assessed Abnormality. As was shown earlier, only the long-stay schizophrenic in-patients had a group mean VBR that was significantly greater than that of the neurotics. Hence in searching for predisposing or promoting factors associated with ventricular enlargement, it was appropriate to restrict these analyses to the long-stay schizophrenics only.

The VBR's of the 110 long-stay schizophrenics were categorised with reference to the age-corrected means and standard deviations described earlier.

TABLE 3:3:7 ANALYSIS OF MATCHED PAIRS

VARIABLE			MEAN VBR ± SD
DEFECT STATE		PRESENT	10.59 ± 1.97
		ABSENT	12.35 ± 3.49
PAST PHYSICAL TREATMENTS		NONE	13.13 ± 3.68
		HEAVY	11.46 ± 2.67
	INSULIN	NONE	13.36 ± 2.01
		MUCH	11.37 ± 4.81
	ECT	NONE	12.56 ± 2.12
		MUCH	13.01 ± 3.28
	NEUROLEPTICS	NONE	14.84 ± 3.97
		MUCH	12.97 ± 3.5
PAST ACADEMIC RECORD	HIGHER: H&W ABOVE MEAN		12.65 ± 3.01
	H&W BELOW MEAN		13.2 ± 4.8
		HIGHER	12.77 ± 3.55
		AVERAGE/BACKWARD	13.1 ± 2.74
CATATONIC SYNDROME		PRESENT	12.59 ± 4.15
		NS/DS PRESENT	11.39 ± 1.23

This produced six categories :

a	smaller than 2 SD below predicted value	: 2 subjects
	2 - 1 SD below predicted value	: 10 subjects
b	within 1 SD below predicted value	: 20 subjects
c	within 1 SD above predicted value	: 33 subjects
d	1 - 2 SD above predicted value	: 18 subjects
e	greater than 2 SD above predicted value	: 27 subjects

In view of there being only 2 subjects where VBR was outwith 2 standard deviations below the predicted value, the smallest two categories were combined (i.e. category a - 12 subjects).

Statistical evaluation was by unified analysis of variance by ranks (analysis of trends), which allows for significance to be assessed across adjacent categories collapsed in any combination. For trends that were in the direction of prediction, a 1 - tail interpretation of significance was adopted. Where no prior prediction had been formulated or where findings went in a direction contrary to prediction, a 2 - tail interpretation was used.

b) RECORDED INFORMATION

The Recorded Information variables for which correlations with ventricular size were sought were :

i) A family history of schizophrenia
ii) A history of birth trauma and/or head injury
iii) A history of fits
iv) Past academic record (as defined in Part 1)
v) PSE subclasses
vi) Past physical treatments : insulin coma
ECT
neuroleptic drugs

Physical treatments were considered in terms of the amount of past treatment - i.e. 'none', 'some', 'much', as defined previously. Leucotomy, known to have a bearing on subsequent ventricular size and configuration (Bydder et al 1980; Naeser et al 1981) was not

considered in these analyses. The CT appearances of the leucotomised patients who were scanned will be described separately (vide infra Chapter 3.6).

No a priori hypotheses were formulated with regard to possible relationships between VBR and items of Recorded Information.

The only consistent significant relationships to emerge concerned family history and past insulin treatment (TABLE 3:3:8 and 3:3:9). The relationship between categories of ventricular size and family history is illustrated in Fig 3:3:12. No subjects in the two smallest categories of ventricular size (i.e. those with ventricles smaller than 1 standard deviation below predicted mean) had a definite family history of schizophrenia. The difference between these groups and the prevalence found in VBR categories above the predicted mean value was highly significant ($z = 3.06$, $P = 0.0026$). This remained the case when comparison was restricted only to those with a definitely positive family history and those with a definitely negative history, doubtful ('possible') cases being omitted ($z = 2.99$, $P = 0.0032$). Thus, by collapsing adjacent categories and analysing for relationships of an essentially linear type, ventricular enlargement was associated with a positive family history of schizophrenia. However, as TABLE 3:3:8 and Fig 3:3:12 show, only about 12 % of those with the very largest ventricles ($>$ 2 SD above predicted mean) had a definite family history of schizophrenia. Fig 3:3:12 does not point to any relationship being of a linear type. In statistical terms the strongest relationship with the family history variable was the comparison between those at the extremes of ventricular size ($<$ 1 SD below and smaller and $>$ 2 SD's above) with

TABLE 3:3:8 RECORDED INFORMATION: DISTRIBUTIONS (%) IN RELATION TO VBR CATEGORIES

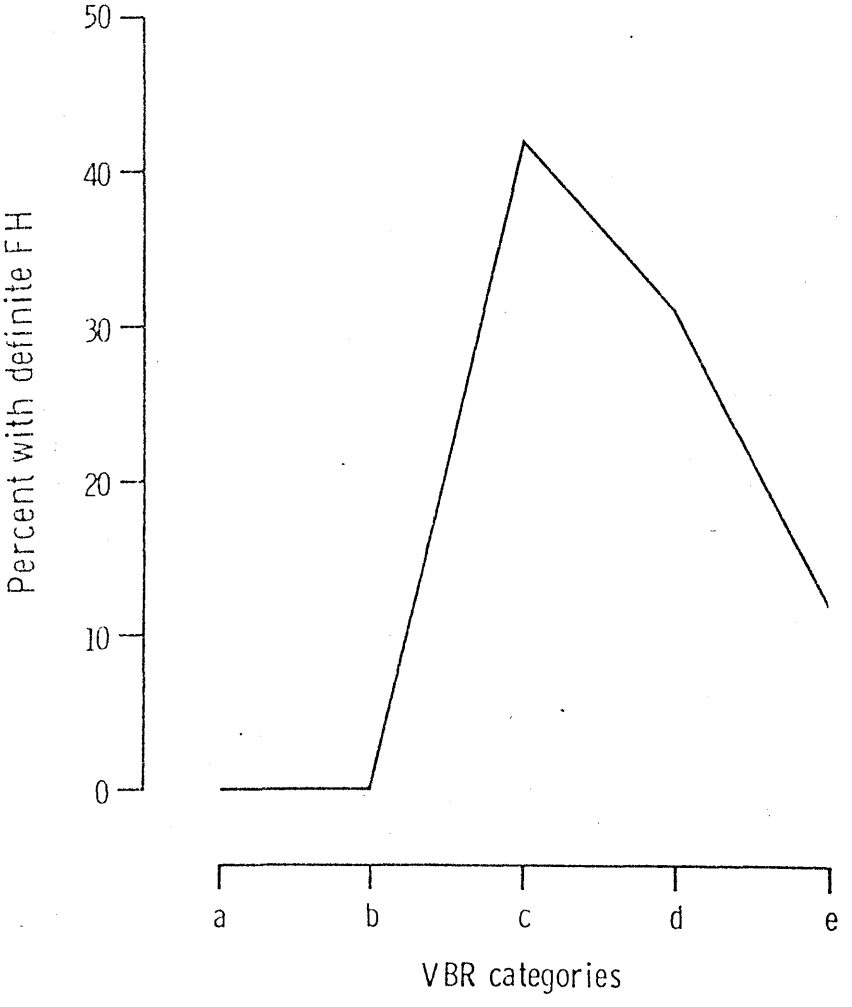
		>2 SD BELOW	2-1. SD BELOW	<1 SD BELOW	<1 SD ABOVE	1-2 SD ABOVE	>2 SD ABOVE
TREND CATEGORIES		a		b	c	d	e
FAMILY HISTORY	% WITH NONE	70		73	46	54	56
	% WITH POSSIBLE	30		27	12	15	32
	% WITH DEFINITE	0		0	42	31	12
BIRTH TRAUMA/ HEAD INJURY	% WITH POSITIVE HISTORY	18		57	25	30	17
FITS	% WITH POSITIVE HISTORY	9		17	20	9	15
PAST ACADEMIC RECORD	% WITH 'GOOD'	10		11	18	14	14
	% WITH 'AVERAGE'	80		68	61	79	64
	% WITH 'POOR'	10		21	21	7	23
P.S.E.	% NS+	33		35	33	33	22
	% DS+	42		20	45	11	48
	% NSDP	0		0	3	6	0
	% DP+	0		5	0	11	0
	% CS+	17		20	9	11	15
	% MISC.	0		0	3	11	0
	% POSSIBLE	8		20	6	17	15

TABLE 3:3:9 PAST PHYSICAL TREATMENTS: PERCENTAGE DISTRIBUTIONS IN RELATION TO VBR CATEGORIES

		>2 SD BELOW	2-1 SD BELOW	<1 SD BELOW	<1 SD ABOVE	1-2 SD ABOVE	>2 SD ABOVE
TREND CATEGORIES		a		b	c	d	e
INSULIN COMA	% WITH 'NONE'	73		63	76	71	56
	% WITH 'SOME'	9		21	12	6	15
	% WITH 'MUCH'	18		16	12	23	30
E.C.T.	% WITH 'NONE'	45		84	69	53	67
	% WITH 'SOME'	36		11	31	35	22
	% WITH 'MUCH'	18		5	0	12	11
NEUROLEPTICS	% WITH 'NONE'	8		25	15	17	22
	% WITH 'SOME'	25		10	21	33	26
	% WITH 'MUCH'	67		65	64	50	52

FIG 3:3:12

Relationship between VBR categories and the presence of a definite family history of schizophrenia



those in roughly average categories of ventricular size - i.e. a curvilinear type of comparison having the form 1-1-2-2-1 ($z = 3.24$, $P = 0.0016$). In this way, a family history of schizophrenia was significantly more common in those with normal ventricle sizes, while patients at the extremes of ventricle size (both large and small) were much less likely to have a positive family history.

As TABLE 3:3:9 shows, a higher proportion of those in the two largest ventricular categories had received many insulin comas in the past. Accepting the medical prediction that hypoglycaemia predisposes to brain damage and hence adopting a 1 - tail interpretation, this finding is significant ($z = 1.75$, $P = 0.038$). With a more stringent 2 - tail interpretation it represents a non-significant trend. As the evidence on which to base a firm prediction is poor, the latter criterion was applied. Furthermore, an association between heavy past insulin treatment and a parameter of brain damage in the most general sense, would be somewhat at odds with the clinical findings reported in Part 1, where it was noted that certain deficits were less severe in those treated with insulin coma.

No other relationships emerged between ventricular size and items of Recorded Information.

c) ASSESSED ABNORMALITIES

i. GENERAL

The Assessed Abnormalities for which correlations with ventricular size were sought were :

a) Cognitive performance
b) 'Positive' mental state features : Withers and Hinton totals
c) 'Negative' mental state features : Krawiecka scale
d) Behavioural performance : Current Behavioural Schedule totals
e) Spontaneous involuntary movement disorder : AIMS and RS totals

The mean scores on Assessed Abnormality variables for the basic study population of 510 and for the scanned subsample of 110 are shown in TABLE 3:3:10. This shows that the subgroup selected for scanning did not significantly differ from the total population from which they were drawn in terms of their assessed clinical deficits, except that the scanned patients had a significantly higher mean score for 'negative' mental state features than the total sample. This reflects the predominant hypothesis that CT scan abnormalities would be related to features of 'deterioration' or 'defect', typified characteristically in this study by 'negative' features.

The problems of analysing total scores from multi-item rating scales apply here as elsewhere. In Part II (Chapter 5.7) cut-off points were chosen largely on statistical considerations, and were based on the numbers of subjects available for analysis. With a sample size in the present section of only 27 % that of the group studied in Part II, use of the cut-offs which ensured equity of distribution in the previous part of the study may not have produced a like effect in this smaller, selected group. For this reason arbitrary comparison cut-offs for the Assessed Abnormality variables were redefined for this section of the study. Although essentially arbitrary, attempts were made to relate these cut-offs to definite findings in the patient sample.

For those variables in which an increasing total represents increasing abnormality - 'positive' and 'negative' mental state features, AIMS and RS - the comparison cut-off was progressively raised from unequivocal normality (0 - 1) to the mean score of the scanned group. For those variables where a decreasing total represents increasing impairment - Withers and Hinton and Current Behavioural Schedule - the comparison cut-off started from the group mean value and was progressively lowered to a limit of 1 standard deviation. The means and standard deviations are shown in TABLE 3:3:10.

It was assumed that ventricular enlargement is evidence of brain damage and as such, it was predicted that ventricular enlargement would correlate with :

a) cognitive impairment
b) the presence of 'negative' but not 'positive'mental state features
c) behavioural deterioration
d) the presence of spontaneous involuntary movement disorder

The distributions for each Assessed Abnormality variable in relation to VBR categories are shown in TABLE 3:3:11.

ii COGNITION

Using the mean Withers and Hinton for the scanned group (approximately 45) as the first cut-off, a relationship of a linear type was established between cognitive performance and ventricular size. This was such that cognitive impairment was more common in those in the two smallest categories of ventricular size (i.e. below the mean) than in those above the mean ($z = 2.13$, $P = 0.032$, 2 -tail). This relationship persisted down to a Withers and Hinton cut-off of 31, and especially rested on the very high prevalence of severe

TABLE 3:3:10

MEAN SCORES ON ASSESSED ABNORMALITY VARIABLES FOR TOTAL STUDY POPULATION AND SCANNED SUBGROUP

	TOTAL SAMPLE		SCANNED SUBGROUP		SIGNIFICANCE
	MEAN (± SD)	N	MEAN (± SD)	N	
AGE	59.2 ± 13.9	510	58.2 ± 12.8	110	N/S
LENGTH OF ILLNESS	31 ± 11.1	510	31.9 ± 10.6	110	N/S
F : M RATIO	0.89	510	0.55	110	-
'POSITIVE' MENTAL STATE FEATURES	3.6 ± 3.5	458	3.39 ± 3.52	109	N/S
'NEGATIVE' MENTAL STATE FEATURES	2.4 ± 2.3	458	3.01 ± 2.59	109	p=0.015
COGNITIVE PERFORMANCE	44.6 ± 25.3	407	49.03 ± 30.39	100	N/S
BEHAVIOURAL PERFORMANCE	34.7 ± 8.3	501	35.88 ± 8.18	109	N/S
MEAN AIMS TOTAL	4.26 ± 4.64	411	3.7 ± 4.17	110	N/S
MEAN R.S. TOTAL	8.63 ± 8.29	411	8.18 ± 7.89	108	N/S

		>2 SD BELOW	2-1 SD BELOW	<1 SD BELOW	<1 SD ABOVE	1-2 SD ABOVE	>2 SD ABOVE
TREND CATEGORIES		a		b	c	d	e
WITHERS AND HINTON	% WITH TOTAL 0-45	75		50	37	38	42
	% WITH TOTAL 0-38	58		50	30	25	38
	% WITH TOTAL 0-31	58		44	23	25	38
	% WITH TOTAL 0-24	42		39	20	25	38
	% WITH TOTAL 0-17	25		33	13	12	26
'POSITIVE' FEATURES	% WITH TOTAL 0-1	50		45	27	47	37
	% WITH TOTAL 0-2	67		55	39	53	52
	% WITH TOTAL 0-3	67		55	48	59	59
	% WITH TOTAL 0-4	75		65	70	65	74
'NEGATIVE' FEATURES	% WITH TOTAL 0-1	25		30	33	35	37
	% WITH TOTAL 0-2	25		50	45	59	56
	% WITH TOTAL 0-3	42		60	67	65	63
	% WITH TOTAL 0-4	50		60	76	76	67
CURRENT BEHAVIOURAL SCHEDULE	% WITH TOTAL 0-34	36		50	39	33	48
	% WITH TOTAL 0-32	18		35	33	22	41
	% WITH TOTAL 0-30	9		20	27	17	33
	% WITH TOTAL 0-28	0		20	18	11	26
	% WITH TOTAL 0-26	0		15	15	11	26
AIMS	% WITH TOTAL 0-1	33		40	52	44	22
	% WITH TOTAL 0-2	42		50	70	44	22
	% WITH TOTAL 0-3	75		70	73	44	33
	% WITH TOTAL 0-4	75		85	79	56	48
ROCKLAND	% WITH TOTAL 0-1	30		25	15	11	19
	% WITH TOTAL 0-2	50		30	48	17	26
	% WITH TOTAL 0-4	60		45	64	33	33
	% WITH TOTAL 0-6	70		55	70	33	41
	% WITH TOTAL 0-8	90		65	73	41	56

cognitive impairment in those with the smallest ventricular sizes (category a).

This result is surprising and quite contrary to prediction (hence the 2 - tail interpretation). However, the findings raise the possibility that the relationship between ventricular size and cognitive impairment in patients such as these may not be a straightforward linear one. Fig. 3:3:13 is a graphic representation of the data presented in TABLE 3:3:11, and shows the percentage of those in each VBR category who score within each Withers and Hinton cut-off range - i.e. impairment increasingly severely defined. This once again strongly suggests a curvilinear relationship, especially with increasingly severe degrees of cognitive impairment.

Additional trend analyses were conducted to evaluate the significance of such an interpretation. In these, the extreme VBR categories were compared against three different combinations of intermediate categories. Hence the additional comparisons were :

1 - 2 - 2 - 2 - 1
1 - 2 - 2 - 1 - 1
1 - 1 - 2 - 2 - 1

Only the latter comparison produced significance (TABLE 3:3:12). While, with a 2 - tail interpretation, only comparisons at Withers and Hinton cut-off 31 and 24 are significant at less than 5 %, the trend is clear.

Thus, the present findings support the view that a relationship exists between cognitive performance and ventricular size but strongly suggest that this relationship is not straightforward. The data support the view that in patients such as these cognitive impairment may be associated with <u>both</u> large and small ventricle sizes.

FIG 3:3:13

Relationship between VBR categories and cognitive impairment at varying W&H cut-offs

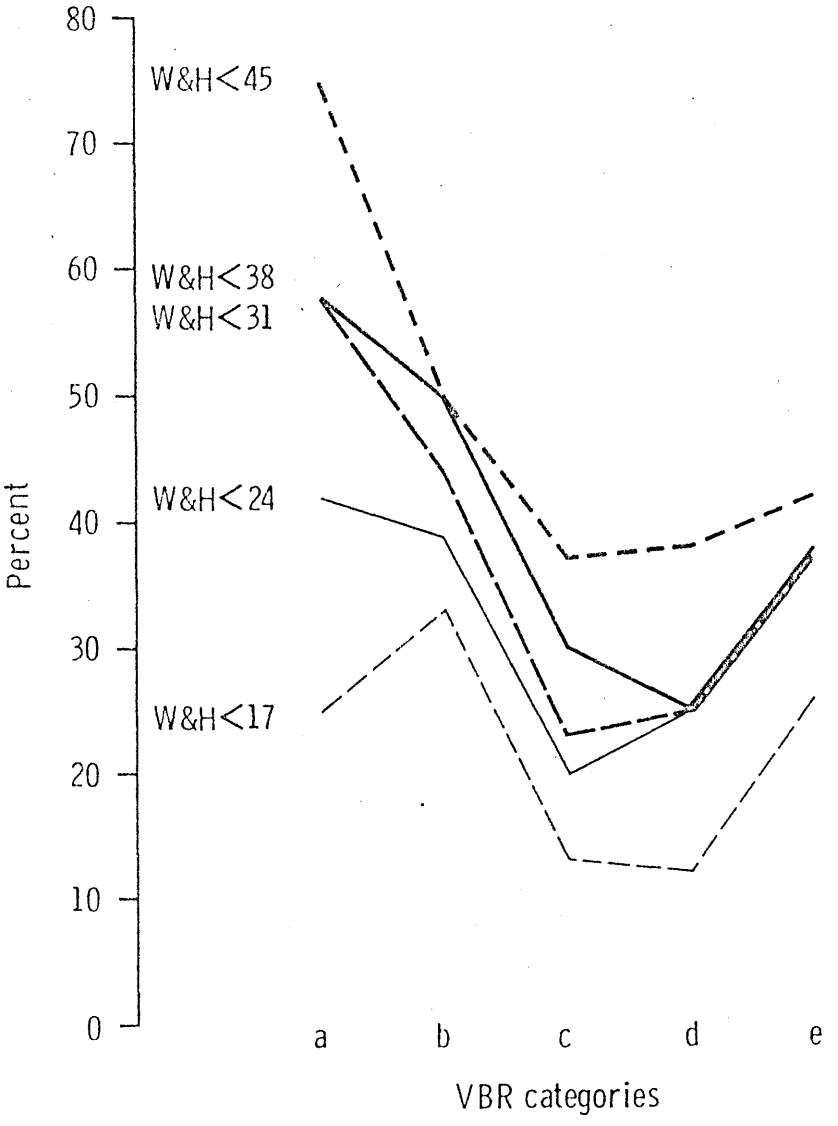


TABLE 3:3:12 COGNITION-ANALYSIS OF TRENDS: COMPARISON 1-1-2-2-1

H & W TOTAL	45 or LESS	38 OR LESS	31 OR LESS	24 OR LESS	17 OR LES
Z-VALUE	1.48	1.84	2.13	1.84	1.99
P-VALUE (1-TAIL)	0.067	0.031	0.015	0.031	0.022

iii. 'POSITIVE' MENTAL STATE FEATURES

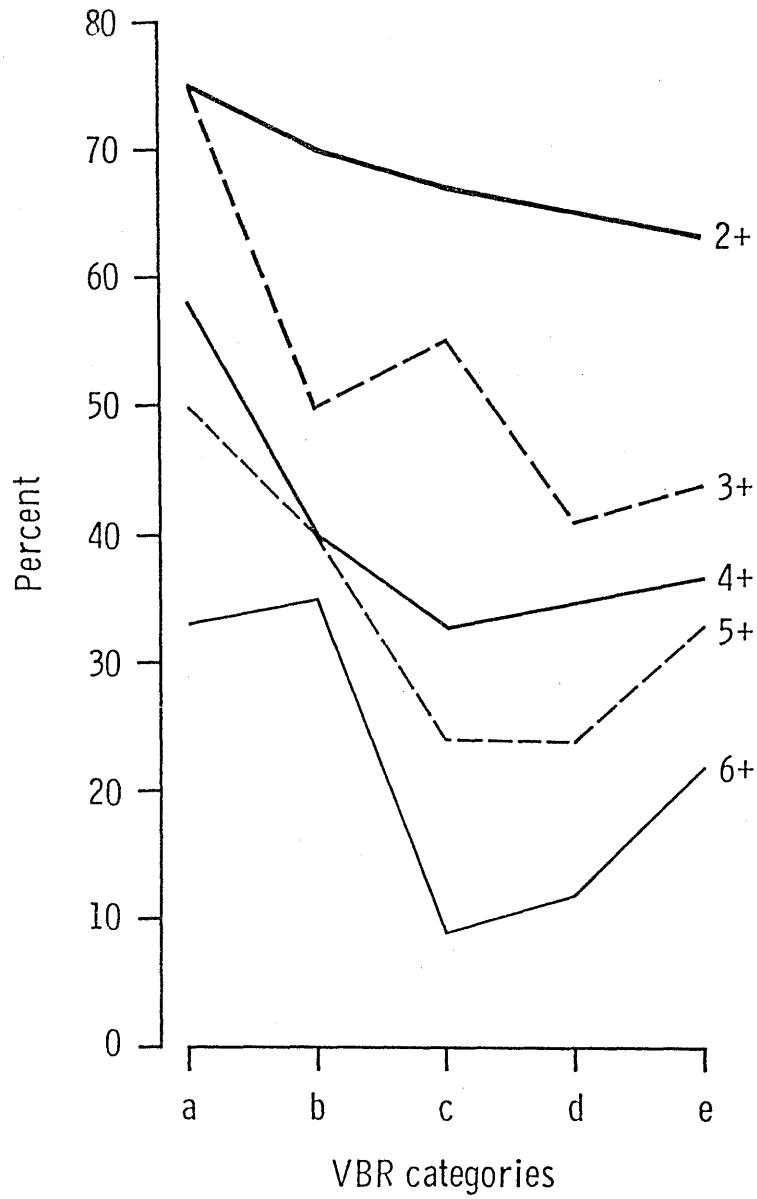
No relationships emerged between ventricle size and 'positive' features of the mental state at any cut-off.

iv. 'NEGATIVE' MENTAL STATE FEATURES

The position regarding 'negative' mental state features and VBR categories was also complicated. Fig. 3:3:14 illustrates these relationships. (For comparability the figure is based on the complimentary percentages to those in TABLE 3:3:11 - i.e. it shows the relationship between VBR and increasingly severe degrees of impairment in terms of 'negative' feature scores). If those with no 'negative' scores whatsoever (total 0 or 1) were compared with the rest (i.e. - those scoring 2 or more) no relationship emerged. Increasing the cut-off (0 - 2 v 3 +) produced a trend to significance for a relationship of linear type (Fig 3:3:14), especially when VBR categories b/c and d/e were combined ($z = 1.88$, $P = 0.028$). This was considered as only a trend as it was in the opposite direction from prediction. When increasing severity of abnormality was considered, the 'U - shaped' relationship noted with Withers and Hinton scores again emerged. On a 1 - 1 - 2 - 2 - 1 curvilinear comparison, a trend towards significance emerged at a cut-off of 5 +, though this reached significance at a cut-off of 6 + ($z = 2.42$, $P = 0.014$, 2 - tail). That is, 'negative' feature scores of 6 or more were significantly more common at both extremes of ventricular size than in roughly average size VBR categories.

FIG 3:3:14

Relationship between VBR categories and 'negative' features at varying cut-offs (krawiecka scale 'negative' ITEMS)



v. BEHAVIOURAL PERFORMANCE

Ventricular enlargement was increasingly associated with declining behavioural performance (CBS total cut-off 34 - 26) though conventional significance was only reached with the lowest behavioural score ($z = 2.07$, $P = 0.043$). Most striking was the linear relationship comparing the smallest VBR category (a), the three intermediate categories (b - c - d) and the largest (e) at total cut-off 26 ($z = 2.07$, $P = 0.018$). This was in line with prediction.

vi. MOVEMENT DISORDER

The most striking statistical relationships established in these analyses (and indeed some of the most striking established in the entire study) were between increasing ventricular size and the presence of spontaneous involuntary movement disorder recorded on the AIMS and RS. The prevalence of movement disorder, defined by increasing the AIMS and RS cut-offs for normality in each category of ventricular size is shown in Fig 3:3:15.

At cut-off 0 - 1, no significances were found with the RS, and those with the AIMS amounted mainly to trends. However, at all other cut-offs significance was of a consistently high order with both sets of data, and in line with prediction. Furthermore, when AIMS and RS totals were arbitrarily divided into three ranges representing increasingly severe abnormality, more severe movement disorders were progressively found in the two largest VBR categories (d and e). This was especially true with the RS data representing the wider concept of involuntary movement. TABLE 3:3:13 presents a summary of these results

FIG 3:3:15

Relationships between increasing ventricular size [a - e] and prevalence of involuntary movements at increasing cut-offs for normality

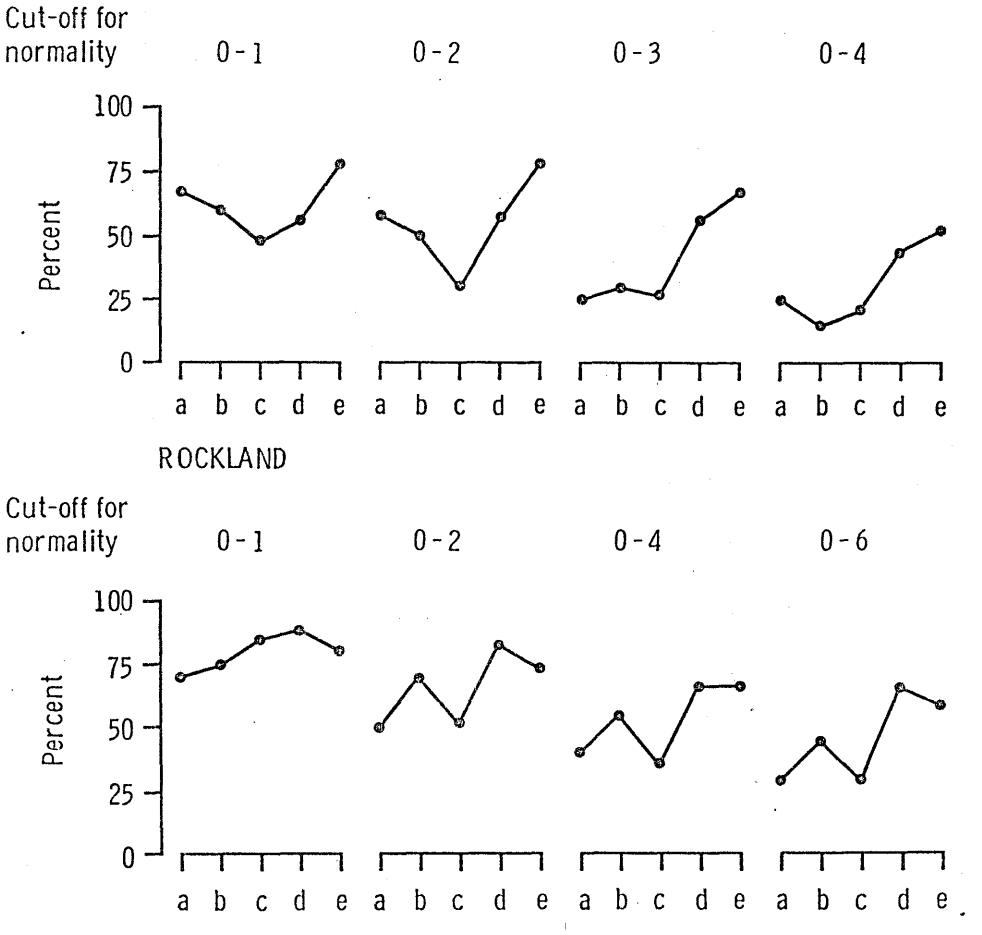


TABLE 3:3:13

SIGNIFICANCE LEVELS OF SELECTED COMPARISONS FOR RELATIONSHIP BETWEEN VBR AND INVOLUNTARY MOVEMENTS

	TREND	COMPARISON CUT-OFF	1 2 3 4 5	1 1 1 2 3	1 1 1 2 2	1 1 1 1 2
AIMS	PREVALENCE	0-1 v 2+	P=0.15	P=0.029	P=0.076	P=0.019
		0-2 v 3+	P=0.025	P=0.001	P=0.0026	P=0.0016
		0-3 v 4+	P=0.0007	P=0.0003	P=0.0003	P=0.0015
		0-4 v 5+	P=0.0025	P=0.001	P=0.0009	P=0.005
	SEVERITY	0-1 v 2-6 v 7+	P=0.082	P=0.021	P=0.035	P=0.027
ROCKLAND SCALE	PREVALENCE	0-1 v 2+	N/S	N/S	N/S	N/S
		0-2 v 3+	P=0.056	P=0.033	P=0.012	P=0.15
		0-4 v 5+	P=0.033	P=0.01	P=0.007	P=0.046
		0-6 v 7+	P=0.016	P=0.0076	P=0.0027	P=0.058
	SEVERITY	0-2 v 3-10 v 11+	P=0.0067	P=0.004	P=0.0019	P=0.029

to illustrate as Fig 3:3:15 shows, that the major differences lay in the two largest VBR categories.

vii. INDIVIDUAL COMPONENTS OF THE KRAWIECKA SCALE AND CURRENT BEHAVIOURAL SCHEDULE

Correlations were next sought between VBR and the individual items comprising the Krawiecka Scale and the Current Behavioural Schedule.

The distributions of those scoring at increasing cut-offs on each item of the Krawiecka Scale, are shown in TABLE 3:3:14 (depression and anxiety received high ratings too infrequently for other than a single comparison to be performed). Analysis of trends produced significance only with hallucinations. The nature of this is shown in Fig 3:3:16 (complimentary percentages from TABLE 3:3:14). A linear relationship could be established such that hallucinations were less frequent in those with the largest ventricles ($z = 2.29$ $P = 0.01$). This would be compatible with the prediction that ventricular enlargement is associated with 'defect state', where this is defined in predominantly 'negative' terms.

However, Fig 3:3:16 once again suggests a curvilinear relationship. With a 1 - 2 - 2 - 2 - 1 comparison, hallucinations were significantly less frequently found at <u>both</u> extremes of ventricular size ($z = 2.24$, $P = 0.024$, 2 - tail).

In addition to these fairly consistent associations of hallucinations, incoherence of speech was significantly more common in those with the largest ventricles ($z = 2.05$, $P = 0.038$). This occurred as an isolated finding on comparison of category e with the

		>2 SD BELOW	2-1 SD BELOW	<1 SD BELOW	<1 SD ABOVE	1-2 SD ABOVE	>2 SD ABOVE
TREND CATEGORIES		a		b	c	d	e
DEPRESSION	% WITH SCORE 0-1	92		75	88	100	85
ANXIETY	% WITH SCORE 0-1	92		85	88	94	93
AFFECTIVE FLATTENING	% WITH SCORE 0-1	25		35	36	35	52
	% WITH SCORE 0-2	50		55	64	71	74
	% WITH SCORE 0-3	83		80	91	88	89
AFFECTIVE INCONGRUITY	% WITH SCORE 0-1	100		90	88	82	85
	% WITH SCORE 0-2	100		95	91	88	85
	% WITH SCORE 0-3	100		95	97	94	93
PSYCHO-MOTOR RETAR-DATION	% WITH SCORE 0-1	42		55	64	65	63
	% WITH SCORE 0-2	83		70	88	94	85
	% WITH SCORE 0-3	100		100	100	94	96
DELUSIONS	% WITH SCORE 0-1	67		70	48	82	70
	% WITH SCORE 0-2	75		75	61	88	74
	% WITH SCORE 0-3	83		90	73	88	78
HALLU-CINATIONS	% WITH SCORE 0-1	75		60	67	65	89
	% WITH SCORE 0-2	75		65	73	65	89
	% WITH SCORE 0-3	75		75	76	71	89
INCO-HERENCE OF SPEECH	% WITH SCORE 0-1	75		75	79	88	59
	% WITH SCORE 0-2	92		85	94	88	85
	% WITH SCORE 0-3	100		95	100	94	93
POVERTY OF SPEECH	% WITH SCORE 0-1	42		55	67	65	52
	% WITH SCORE 0-2	67		65	82	88	63
	% WITH SCORE 0-3	92		90	91	94	85

FIG 3:3:16

Relationship between VBR categories and the presence of hallucinations (krawiecka scale 2+)

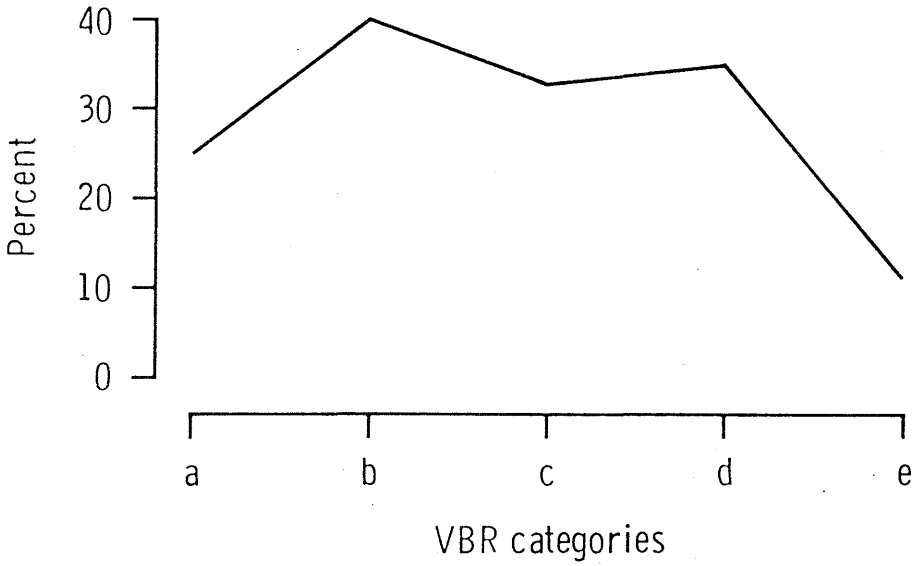
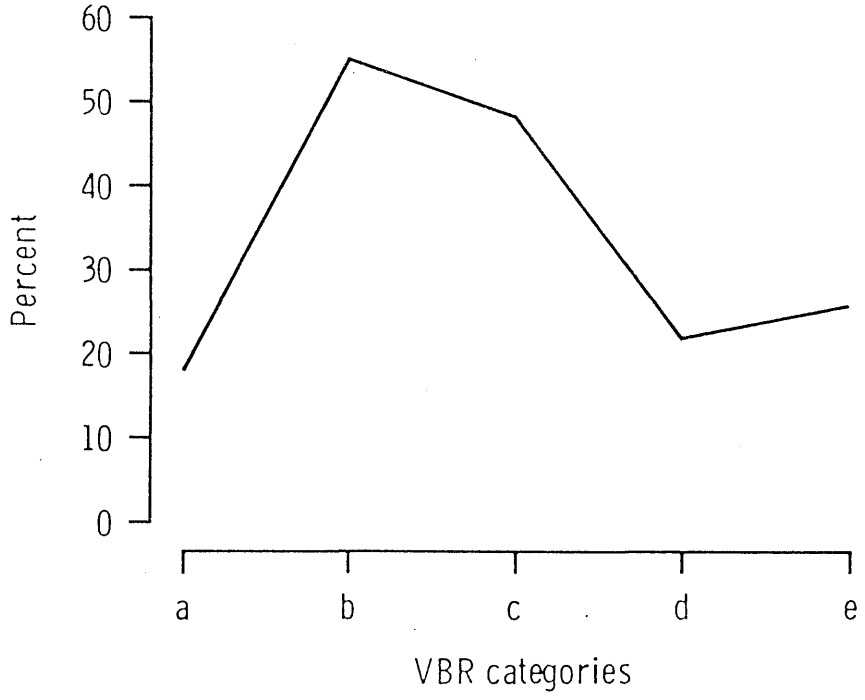


FIG 3:3:17

Relationship between VBR categories and the presence of antisocial behaviour (CBS)



rest, with no consistency or trends showing in other comparisons. It is contrary to prediction with incoherence classified as a 'positive' feature and may represent a random result in the context of multiple comparisons.

The 'negative' feature, flattening of affect, tended to be more common in those with small ventricles, in opposition to prediction, while poverty of speech tended to be more common at both extremes of ventricle size - though neither of these significances reached the 5 % level.

The constituent items of the Current Behavioural Schedule were organised under six main headings :

Social Behaviour
Activities
Exhibited Abnormal Behaviour
Antisocial Behaviour
Incontinence
Stability of Behaviour

For the purposes of analysis, the total possible for each of the first three constituents was simply halved, those scoring less than half being compared with those scoring more than half the maximum. For the last three constituents, which comprised essentially single items, presence of the feature was compared with absence (TABLE 3:3:15).

In accordance with prediction, low scores on social behaviour, activities and exhibited behaviour were significantly associated with increasing ventricular size in a generally linear fashion. The major comparisons throwing light on the basis of the relationships (TABLE 3:3:16), indicate that low scores on each of these three items were much less common in category a (smallest ventricles) than in category e (largest ventricles), with the intervening categories being

TABLE 3:3:15

COMPONENTS OF CURRENT BEHAVIOURAL SCHEDULE: DISTRIBUTIONS (%) IN RELATION TO VBR CATEGORIES

		>2 SD BELOW	2-1 SD BELOW	<1 SD BELOW	<1 SD ABOVE	1-2 SD ABOVE	>2 SD ABOVE
TREND CATEGORIES		a		b	c	d	e
SOCIAL BEHAVIOUR	% WITH SCORE 0-8	18		25	21	17	44
	% WITH SCORE 0-7	18		15	12	11	33
ACTIVITIES	% WITH SCORE 0-5	9		35	30	33	48
	% WITH SCORE 0-4	9		10	15	22	30
EXHIBITED BEHAVIOUR	% WITH SCORE 0-6	9		10	12	6	26
	% WITH SCORE 0-5	0		10	9	6	19
ANTISOCIAL BEHAVIOUR	% WITH SCORE 0-4	18		55	48	22	26
INCONTINENCE	% WITH SCORE 0-2	9		20	9	28	15
STABILITY OF BEHAVIOUR	% WITH SCORE 0-1	18		25	27	17	22

TABLE 3:3:16

SIGNIFICANCE LEVELS OF SELECTED COMPARISONS FOR RELATIONSHIP BETWEEN VBR AND CONSTITUENTS OF CURRENT BEHAVIOURAL SCHEDULE

TREND	COMPARISON CUT-OFF	1 2 3 4 5	1 1 1 2 3	1 1 1 1 2	1 2 2 2 3
SOCIAL BEHAVIOUR	0-8 v 9+	P=0.045	P=0.022	P=0.0076	P=0.014
ACTIVITIES	0-4 v 5+	P=0.021	P=0.023	P=0.039	P=0.038
EXHIBITED BEHAVIOUR	0-6 v 7+	P=0.068	P=0.046	P=0.017	P=0.031

approximately intermediate in prevalence. The presence of incontinence and a stable behavioural pattern were not related to VBR categories. The position of antisocial behaviour was again atypical, in that the form of its relationship with VBR was curvilinear (Fig 3:3:17). Less antisocial behaviour was recorded in those at the extremes of ventricular size (a, d and e), than in those in intermediate positions ($z = 2.99$, $P = 0.0032$, 2 - tail).

3.6 THE STRUCTURAL CONSEQUENCES OF LEUCOTOMY

Of the 118 chronic schizophrenic in-patients successfully scanned, 6 had previously had leucotomy performed. It is of interest to note briefly the CT findings in these patients (TABLE 3:3:17). All the operations were bilateral and five were of the prefrontal type. The sixth patient - the only one to have had the procedure carried out in the more modern era of stereotaxic standardisation - had had a bimedial leucotomy. Burr holes were readily seen in the 5 prefrontal cases. In the bimedial operation, the approach was higher with holes placed on the superior convexity of the mid-frontal region. In the axial cuts of the standard CT series, these may not show.

The striking feature of these scans was the great variability and irregularity of the lesions produced by the surgical intervention. Low-density lesions seen on CT varied in size, from 3.8 x 1.2 cms to 0.7 x 1.5 cms, and also in shape, some forming distinct crescents, others being rounder. They extended to varying depths and were often continuous with the frontal horns of the lateral ventricles, to which they bore anything from an anterior to a posterolateral relationship.

TABLE 3:3:17 SUMMARY OF CT FINDINGS IN LEUCOTOMISED PATIENTS

PATIENT AGE/SEX	LENGTH OF ILLNESS (YRS)	LEUCOTOMY TYPE/YEAR	TIME FROM LEUCOTOMY TO CT SCAN (YRS)	OTHER PHYSICAL TREATMENTS	C.T. FINDINGS
1 62/F	34	BILATERAL PREFRONTAL IN 1949 NO FURTHER DETAILS	30	INSULIN ECT NEUROLEPTICS	BILATERAL, CRESCENT, LOW-DENSITY REGIONS 3.6 x 1.2 cms ON LEFT AND 3.4 x 1.6 cms (R)
2 63/F	40	BILATERAL PREFRONTAL IN 1948 "CUT MADE 5 cms DEEP IN PLANE 13 mm ABOVE NASION"	31	ECT NEUROLEPTICS FOR MANY YEARS	LEFT CRESCENT, LOW-DENSITY 3.8 x 1.2 cms, RIGHT LOW-DENSITY AREA 2.6 x 6.3 cms IN FRONTO-PARIETAL AREA AND 1.5 x 2 cms AREA IN POSTERIOR PARIETAL AREA BILATERAL BURR HOLES
3 62/M	35	NO OPERATION DETAILS 1953	26	INSULIN-48 ECT-28 NEUROLEPTICS	RIGHT 3 x 1 cm LESION OPPOSITE JUNCTION OF FRONTAL HORNS AND BODY OF LATERAL VENTRICLES. LEFT 0.7 x 1.5 cm LESION IN SIMILAR POSITION WITH 1.5 cm LESION AT TIP OF FRONTAL POLE BILATERAL BURR HOLES
4 60/F	30	BIMEDIAL LEUCOTOMY 1963	16	ECT-44 NEUROLEPTICS SINCE 1956	BILATERAL LESIONS 2 cm in DIAMET ON RIGHT AND 2.5 cm IN DIAMETER (LEFT, ANTERIOR TO FRONTAL HORNS (LATERAL VENTRICLES. UNILATERAL BURR HOLE
5 67/M	46	BIFRONTAL - 1946 "ON THE LEFT SIDE THE ANTERIOR PART OF THE VENTRICLES WAS FAR FORWARD. A VESSEL ON THE SURFACE OF THE HEMISPHERE NEEDED CONTROLLING WITH DIATHERMY. THERE WAS NO INCIDENT ON THE RIGHT	33	INSULUN-78 BARBITURATES SINCE 1950's NEUROLEPTICS SINCE 1967	SYMMETRICAL 1.5 x 2 cm LESIONS LATERAL TO AND COEXTENSIVE WITH THE FRONTAL HORNS EXTENDING TO BURR HOLES. SULCAL WIDENING BENEATH BURR HOLES. BILATERAL BURR HOLES
6 59/F	40	PREFRONTAL - 1947	32	ECT FOR 18 MONTHS NEUROLEPTICS SINCE 1960	BILATERAL SYMMETRICAL 3 x 1.2 cm LESIONS ANTEROLATERAL TO FRONTAL HORNS AT MEAN DEPTH OF 3 cms BELOW CORTEX. BILATERAL BURR HOLES

MODIFIED FROM BYDDER G.M. ET AL (1980)

In all cases, small, superficial, low density lesions were visible immediately beneath the burr holes, and were usually associated with widening of the cerebral sulci. However, no significant frontal lobe atrophy was noted. All the patients had been heavily treated by other physical means. (For examples, see Appendix VIII).

One case showed very extensive, low-density areas occupying a large part of the right hemisphere in the distribution of the middle cerebral artery, and which were compatible with post-operative infarction (Appendix VIII). It is of interest to note that this patient had no localising neurological signs, achieved one of the highest scores on cognitive testing in the series, and was one of only 4 out of the 510 subjects of the basic study who managed to work independently in competitive (open) employment outside the hospital.

Thus these six scans demonstrated two main findings. Firstly, the brain lesions consequent upon leucotomy were very heterogeneous, varying considerably in size, shape and position. They often varied also from one side to the other in the same patient. Secondly, the size of the lesion could not be suspected clinically. Very considerable damage could ensue without any objective clinical evidence of its presence.

3.7 UNSUSPECTED INTRACRANIAL PATHOLOGY

A variety of intracranial pathologies, unsuspected clinically, were revealed during the CT part of the study. For the most part these did not necessitate removal of the patient from the investigation and as was noted above their inclusion did not alter the findings. The

TABLE 3:3:18

CT DIAGNOSES IN CASES OF UNSUSPECTED PATHOLOGY IN SCANNED SAMPLE (187 PATIENTS)

C.T. DIAGNOSIS	NO. OF CASES
CEREBRAL INFARCTION	7
PORENCEPHALIC CYST	1
SUBDURAL HAEMATOMA	2
ARTERIOVENOUS MALFORMATION	1
CYSTIC ENLARGEMENT OF PINEAL	1

CT diagnoses are shown in TABLE 3:3:18 and the cases summarised in TABLE 3:3:19. Some examples are illustrated in Appendix VIII.

All but one of these unsuspected abnormalities were found in chronic schizophrenic in-patients. One manic depressive outpatient, on long term lithium carbonate, was found to have an extensive left posterior quadrant lesion believed to be an arteriovenous malformation. This could not be confirmed at the time as the patient refused to have the procedure repeated with contrast enhancement. * Intermittent episodes of headache and vomiting had been attributed clinically to lithium intoxication though serum levels were always normal. On the basis of his gross CT changes, he was excluded.

In the planning of the CT part of the study a non-institutionalised schizophrenic who had been considered suitable in terms of matching criteria was admitted in florid relapse, and could not therefore be scanned as part of the project. She is thus not noted in TABLES 3:3:18 or 3:3:19. Investigations done as part of the routine clinical work-up in this situation revealed her to have a 2 x 1.8 cm left frontal meningeoma.

* Diagnosis subsequently confirmed.

TABLE 3:3:19 CLINICAL FINDINGS, TREATMENT AND CT FINDINGS IN PATIENTS WITH UNSUSPECTED INTRACRANIAL PATHOLOGY

PATIENT NO	SEX AGE (YR)	AGE AT FIRST ADMISSION (YR)	DURATION OF CURRENT ADMISSION (YR)	HISTORY OF CEREBRAL TRAUMA	PREVIOUS TREATMENT			MENTAL STATE	NEUROLOGICAL FINDINGS	CT FINDINGS
					NUMBER OF INSULIN COMAS	NUMBER OF ECTs	EXPOSURE TO NEUROLEPTICS			
SCHIZOPHRENICS										
1	F66	26	40	Nil	0	0	No	Withdrawn. Emotionally flat stable course	Akinesia and rigidity	Bilateral parietal infarcts 2 x 2 cm on left and 2 x 1.5 cm on right. Bilateral triangular 3 x 2 cm occipital infarcts.
2	F67	20	47	Unknown	0	44	Yes	Withdrawn. Stable course	Spontaneous movements of face and upper limbs. Akinesia and posturing of fingers	2 x 1.5 cm infarct in left parietal region. 1.5 x 1.5 cm infarct in right occipital lobe.
3	F58	32	26	Nil	99	10	Yes	Occasional ill-sustained ideas of influence. Minimal emotional flattening. Stable course.	Mild spontaneous movements of lower limbs. Akinesia.	1.5 x 1.5 cm infarct in right posterior parietal region. 2 x 1.7 cm infarct in right temporal lobe.
4	F76	39	37	Nil	0	0	Brief	Marked withdrawal. Emotional flattening and fluctuating course.	Rigidity	2 x 2 cm right parietal infarct.
5	M49	16	8	Minor head injury as child	0	0	Yes	Constant hallucinations and delusional ideas. Stable course.	Nil	2 x 2 cm right frontal infarct.
6	M49	21	28	Nil	0	0	Yes	Partial delusions. Stable course.	Nil	1 x 1 cm left frontal infarct lateral to the head of the caudate nucleus.
7	M58	21	33	Nil	114	8	Yes	Gross affective flattening and withdrawal stable deteriorated condition.	Rigidity and flexed posture Spontaneous movements of lips and stereotyped rocking.	Moderate ventricular dilation and cortical atrophy. Follow-up 4 years later showed increased cerebral atrophy and a 3 x 2 cm left fronto-parietal infarct.

TABLE 3:3:19 continued

PATIENT NO	SEX AGE (YR)	AGE AT FIRST ADMISSION (YR)	DURATION OF CURRENT ADMISSION (YR)	HISTORY OF CEREBRAL TRAUMA	PREVIOUS TREATMENT			MENTAL STATE	NEUROLOGICAL FINDINGS	CT FINDINGS
					NUMBER OF INSULIN COMAS	NUMBER OF ECTs	EXPOSURE TO NEUROLEPTICS			
8	F46	20	9	No specific mention of birth difficulty but mild left hemiparesis from birth	89	3	Yes	Constant hallucinatory experiences.	L hemiparesis	5 x 3 cm right parieto-temporal porencephalic cyst. Mild right cerebral atrophy.
9	M62	25	37	Road traffic accidents 6 weeks prior to CT scan	0	16	Yes	Regular intense hallucinatory experiences. Fluctuating course.	Spontaneous "frowning" movements of face. High myopia.	0.8 - 1 cm low density between skull and fronto-parietal surface of the left hemisphere with slight displacement of the midline to the right and flattening of the cerebral sulci on the left. Follow-up 4 weeks later show decrease in thickness to 0.3 - 0.5 cm.
10	M65	26	39	Nil	0	0	No	Emotional flattening retardation social and withdrawal. Stable course.	Rigidity. Mild pescavus.	0.7 - 1 cm thick low density lesion over left fronto-parietal cortex with slight displacement of the midline to the right.
11	M41	11	10	Nil	0	0	Yes	Partial delusions and intermittent hallucinations.	Nil	1.5 cm cystic pineal body with calcification in the wall.
NON-SCHIZOPHRENIC										
12	M		Out-patient	Nil	0	0	Yes	Normal (see text)	Nil	Multiple nodular calcifications in L occipital region and the region of superior colliculus with posterior displacement of the quadrigeminal cistern on that side.

4.1 METHODOLOGICAL ISSUES

Certain methodological questions require comment.

4.1.1 SELECTION OF EXPERIMENTAL SUBJECTS (LONG-STANDING SCHIZOPHRENIC IN-PATIENTS)

The long-stay schizophrenic in-patients who were scanned, were selected from the total pool of 510 who have formed the basis of this study. Thus, to begin with they represent a particular type of schizophrenia which may not nowadays be representative of the majority of schizophrenics in this country. It is known from the deficits described in Part I, that, regardless of the reasons for their remaining in the institution they represent schizophrenia in a severe form. That the subgroup scanned is in its turn slightly unrepresentative of the in-patients as a whole is reflected in the fact of their mean 'negative' features score being significantly higher than that of the total sample (TABLE 3:3:10). As mentioned, this undoubtedly reflects the dominant hypothesis running through the selection procedure - namely, that ventricular enlargement, if present, would be likely to be associated with 'deterioration' or 'defect'. Hence although the institutionalised schizophrenic group who participated in this part of the study have been clearly defined, it is important to emphasise that they represent severe, long-standing schizophrenia - and severe long-standing schizophrenia biased somewhat towards a particular pattern of clinical deficit. From what has been published using radiological imaging in the study of schizophrenia, it was

reasonable to postulate that this pattern of deficit would be the most likely one associated with CT scan change.

4.1.2 SELECTION OF CONTROL GROUPS

The choice of the best control group for studies of this kind is difficult, as reflected in the diverse groups used in the literature - e.g. 'non-affected' relatives of patients with Huntingtons's Chorea (Weinberger et al 1979a), scans reported as normal by radiology departments (Andreasen et al 1982c), the victims of road traffic accidents (Nasrallah et al 1982a) and 'normal volunteers' obtained largely from hospital staff (Jernigan et al 1982a). Problems arise with all these groups as was mentioned in the Introduction to this Section. Truely normal asymptomatic volunteers would be the ideal, if they could be matched with the experimental sample for age and other factors of possible relevance such as social and academic background, and - most importantly - if a reliable and detailed history of possible CNS disease, alcohol and drug intake and family history of psychosis could be obtained. There may however be strong motivation to deny such facts, especially if the volunteers are colleagues.

In this study, all patients shared in common referral to, and management by, the specialist psychiatric services. Patients with neurotic illness were felt to be the most suitable basic control group. No patient in the neurotic group had a family history of schizophrenia, and full details of life-time ingestion of psychotropic drugs and alcohol were sought in every case. Patients in whom alcohol abuse and drug ingestion were felt to represent problems, were not included. In the 19 selected, alcohol intake was said to be low, but all had been

prescribed psychotropic drugs in the past, mainly benzodiazepines and tricyclic antidepressants. However, in none could a history of abuse be established.

It could be argued that the use of a control group of neurotics, many of whom had received anxiolytics, would act to minimise the extent of the ventricular enlargement in other groups, as they themselves would have a degree of enlargement greater than what would be predicted in a normal population. A recent report has suggested an association between ventricular enlargement and benzodiazepine ingestion (Lader et al 1984). Because of this argument, it is not claimed that the neurotics are equivalent to normals, only that they are likely to approximate to normals, and certainly are closer to the general population than the other groups studied. However, the distinction in the present study may be largely semantic. The range of VBR's in the neurotic sample was small and their distribution normal, suggesting that abnormally large ventricles are not found or are infrequently found in this group.

4.1.3 ASSESSMENT OF VENTRICULAR SIZE

In this study an area estimate of ventricular size from bromide films was used in preference to direct use of attenuation values, the reliability of which is uncertain (Levi et al 1982). Linear measures correlate relatively poorly with computer estimates of volume whereas area assessments correlate well, the relationship only breaking down at very large ventricular sizes (Penn et al 1978).

The use of a ratio eliminates the need to consider the minification factor inherent in the production of bromides and hence

removes another source of error, and VBR has become a commonly used measure for assessment of ventricular size. Whether or not it represents the best measure is however uncertain. It is worthy of note that one of the better studies reviewed earlier (Jernigan et al 1982a) which obtained a negative result, in addition to examining 'milder' subjects, used an alternative evaluation procedure, and it should be considered that this is the basis of the negative findings, rather than (or in addition to) factors of sample selection.

Partial volume effects are insurmountable with CT and are undoubtedly the basis of the widely differing acceptance of what is ventricle by different groups of workers, and hence the variability in absolute values, which Jernigan et al have demonstrated (Jernigan et al 1982a). These effects are likely to be less with greater degrees of ventricular enlargement where the normal slope of the lateral ventricular wall (the structural basis of the partial volume effect) is lost and a more vertical form has developed. Nonetheless with all sizes of ventricle the problem is considerable. In ignoring partial volume effects completely one is placing undue reliance on the measured cut being the maximal one.

VBR is strictly speaking the 'VBR for that cut' and the maximal VBR is the 'maximal VBR for the scan series'. What is maximal in any series depends where the beam scans through the ventricular system, which in turn, depends on the accurate positioning of the patient, their co-operation, and the relative size and shape of the skull, brain and ventricular system - of which the first (positioning) is of major importance. The assumption is that even if the majority of series have missed the true or anatomical maximal point, deviations above and below this will be randomly distributed throughout the sample - both

patients and controls. This statistically reasonable assumption would not take account of the fact that the room for variation in one diagnostic group may be much greater. In the present work, the impression was gained that the institutionalised schizophrenics were in general more difficult to position satisfactorily and had to be more strenuously encouraged to maintain their position than other groups, even their out-patient counterparts.

In this study attempts were made to accommodate partial volume effects in recognition of the fact that the maximal cut for the series may not represent the anatomical maximum. Simple guidelines were defined beforehand and agreed with those involved in reliability measures. The very high reliabilities obtained confirm the value of this procedure. However, it did mean that the absolute VBRI's obtained in the present study were considerably larger than those published by other workers. For this reason, ventricular enlargement is relative within studies and defining cut-off points for normality for general use (e.g. Weinberger et al 1982) is a misleading and inadviseable exercise. Moreover, variability in absolute VBR values internationally may be also contributed to by different scan positions adopted especially between the United Kingdom and the United States. In this study all patients were scanned parallel to the orbito-meatal line, as is customary in the U.K.

Considerable care was taken in the present study to ensure that all bromides were taken at comparable window widths as this variable can considerably alter ventricular representation. Most studies do not comment on this and whether window width is held constant is in general unknown. The present method of using two bromides at different window widths to define ventricle and brain is novel, but

is believed to be valid.

4.2 GENERAL FINDINGS

4.2.1 AGE

Age was a major contributing factor to VBR in this large sample of psychiatric patients. Although the significant association between these two variables was linear, there was also a non-significant quadratic relationship and it is likely that the association between ventricular size and age is not straightforward. Had the sample contained a greater proportion of younger subjects (i.e. under 45 years) it is possible that the quadratic relationship would have reached significance. Nonetheless, the results still indicate a lesser effect of age up until the 5th decade after which the age effects become more striking.

The idea of a non-linear relationship between ventricle size and age has support in the literature from the study of normal subjects using different methods of scan evaluation. Barron et al (1976) found a "gradually progressive" increase in VBR through the first six decades followed by a "dramatic increase" thereafter. Meese et al (1980) reported relative consistency in a number of linear measures and ratios up to 60 years of age followed by an increase with age - a tendancy they "encountered rather often" with different measures of the CSF spaces. Zatz et al (1982) computed intracranial fluid volumes and found that ventricular and sulcal volumes remained constant to 60 years after which both "increase at an increasing rate". Other workers have confirmed the stability of ventricular indices up to middle life

(Haug 1977; Cala et al 1981).

This relative constancy of ventricular size in younger patients provides the likely explanation for an absence of age effects on VBR reported in a number of studies reviewed earlier. Most of these groups purposely sought to investigate only younger subjects within a narrow range of age in order to overcome the problem of contamination with interposing dementias. Samples with a predominantly young age bias may also not show an overall effect of age if they include a small number of young subjects with atypically large ventricles, the latter patients being sufficient to eliminate a statistically weak overall age effect. This is more likely to occur in samples drawn from specialist research facilities which tend to attract patients presenting unusual or intractable problems.

The present findings raise the interesting question of whether functional psychiatric patients in general and schizophrenics in particular experience the quantitative brain changes of aging earlier than do healthy normal people. No definite support for this view was forthcoming but the possibility is certainly raised. There is definitely a suggestion of an accelerated age effect in schizophrenics compared with non-schizophrenics, as Fig 3:3:6 showed. Although this difference did not reach statistical significance, analysis was conducted on a model which assumed a basically linear relationship between age and VBR. Furthermore, if the quadratic relationship is accepted as potentially valid, the present patient population appeared to develop the age effects roughly in the middle of the 5th decade - that is, approximately 10 - 15 years earlier than the literature on normal people would suggest.

The present study did not include an unequivocally normal population, and other CT scan work in this field has not included an adequate range of ages to explore this question. It is nonetheless a potentially important one, worthy of further investigation. While support for premature aging from structural studies is as yet unavailable, in the psychology literature a close qualitative parallel between cognitive test performance in younger schizophrenics and the normal elderly has been pointed out (Saccuzzo 1977).

4.2.2 LENGTH OF ILLNESS AND SEX

Neither sex nor length of illness were related to VBR. While sex differences in certain brain measures on CT have been reported in normals (Gyldensted & Kosteljanetz 1976; Haug 1977), the bulk of reports using area measures show no sex differences. The concept of length of illness however is not as refined here as in previous sections. This relates in particular to the question of how long a patient is to be considered as having been 'ill', when the illness in question is characterised by an episodic course interspersed with periods relatively free of psychological deficit. It remains unclear whether it is more appropriate in such circumstances to summate the cummulative symptomatic episodes as 'length of illness' or whether this should be dated from the time of initial presentation. The latter has been adopted here. This provided consistency with previous parts of the study and avoided the considerable element of unreliability inherent in gauging symptomatic periods over many years.

Two other areas, peripheral to the basic problem but which nonetheless produced interesting findings, are most appropriately discussed here. These concern the structural consequences of leucotomy and unsuspected intracranial pathology revealed by CT.

4.2.3 LEUCOTOMY

As was shown in Part 1, none of the deficits examined were found to be worse in those who had had leucotomy, and in Part 11 having had a leucotomy was not associated with the presence or severity of involuntary movement disorder. In the present section, the unpredictability of the lesions and the often dramatic structural damage resulting from the 'free-hand' form of the operation have been illustrated. Only 2 patients had lesions that were roughly bilaterally symmetrical, but these did not bear a constant relationship to the anterior horns. Even the single patient who had had the more standardised, bimedial procedure, did not have completely symmetrical lesions. In all cases, the variability resulted from lesions produced at the same operation by the same surgeon.

The marked variations in post-operative structural appearances following leucotomies thought to be technically similar, were demonstrated in vivo by Donovan et al (1949) using PEG, and at post-mortem by Eie (1954) and Beck et al (1950). Naeser et al (1981) who reported this phenomenon in a follow-up CT scan study, suggested that asymmetricality of lesion size may be associated with a better, long-term outcome in schizophrenia, especially when the lesions are large. Owing to the selective nature of the

leucotomised sample in the present study, no comment can be made on the efficacy of this procedure. The conclusions of Naeser et al may be based on a chance finding in a small, selected subsample.

The striking degree of brain damage, sometimes not restricted to the frontal lobes, occurring in the absence of objective clinical signs, is noteworthy, and findings such as these may force us to reconsider some of our basic concepts regarding brain function. Benson et al have stated that a complete absence of so-called frontal release signs in their sample of leucotomised schizophrenics who had gross frontal damage, calls into question the accepted view on the origins of these features (Benson et al 1981). The gross damage in the patient illustrated in Appendix VIII is an example of the amount of 'silent' abnormality the brain can harbour.

Variability and gross, coincidental damage may be things of the past - with the use of newer, standardised techniques it has been shown that a consistent, predictable pattern of lesions can be produced by the same surgeon (Banna et al 1978) - not least because of the decline in leucotomy as a treatment for schizophrenia. However, weighed against the appalling deficits of this condition in its severe form additional, sometimes extensive, structural damage to the frontal lobe would not appear to compound the disability.

4.2.4 INCIDENTAL ABNORMALITY

The organic abnormalities found in the course of the CT part of the study were of interest as they were clinically unsuspected and occurred almost exclusively in the long-stay schizophrenic

population, though it is possible that with a larger manic depressive group, more pathology would have been found in these patients.

In only one patient (congenital hemiparesis) could some cerebral damage have been anticipated, but here the degree of abnormality found was surprising based on the mildness of the clinical deficits. However, in two patients, retrospective examination of the case notes identified episodes compatible with the cause. In one of the cases of subdural haematoma, (patient 9, TABLE 3:3:19) there was a history of road traffic accident 6 weeks previously. While the nursing staff had noted the patient to be lethargic and withdrawn, this was attributed to the psychological 'shock' of the event. In patient 1 (TABLE 3:3:19), an acute episode had been recorded 3 years previously. Prior to this, the patient had been an independent woman working outside the institution though in sheltered employment. After losing her way home one day, she was noted to be suddenly much more disorganised in her behaviour and to have developed marked visual impairment. She set her hair on fire trying to light a cigarette, attributed both to her worsening psychosis and the visual impairment, thought to be due to bilateral cataracts. These were operated on 2 years prior to scanning, with some improvement, though her vision remains poor. She has no field defect on opthalmological examination. CT scanning revealed two sets of symmetrical, peripheral infarcts, one set parietal, the other at each occipital pole. In both these patients, a deterioration in mental state was attributed to psychogenic factors and accordingly both had changes made in their medication. CT scanning however, demonstrated a probable organic

cause in each.

Cystic enlargement of the pineal gland is an uncommon abnormality which is believed to produce symptoms only by compressing the aquaduct from above. However, the functional status of these lesions has not been investigated. Indeed it is only in recent years that the role of the pineal in the secretion of melatonin has been established and the properties of this hormone explored. The interest of the present case lay in the exceptionally early onset of the patient's psychosis - he was first admitted to the hospital at the age of 11 - and its distinctly cyclic nature. However, melatonin levels did not reveal any abnormality of pineal function now, though these were performed when the patient was going through an exceptionally long period of (relative) well being. Also in favour of the pineal abnormality being an authentically incidental finding is the fact that the patient's father suffered from a psychotic illness. It was more stable and 'chronic' than the son's and though atypical in its clinical features, was nonetheless thought to be schizophrenic.

Cerebral neoplasms on the other hand are not infrequently found in psychiatric populations, though whether or not they present an increased prevalence compared to non-psychiatric groups remains unclear (Lishman 1978). Among 1200 chronic schizophrenic patients having routine skull x-rays, Kraft et al (1965) found evidence of cerebral tumour in three, and there is general agreement that meningiomas contribute twice as many intracerebral neoplasms in psychiatric patients as they do in non-psychiatric patients. The association between both affective and schizophrenic type symptomatology and organic brain disorders is well known (Davison

& Bagley 1969; Lishman 1978) and raises the question as to whether the patients with tumours (the definite member of the manic-depressive group and the potential member of the schizophrenic out-patient group) actually had primarily psychiatric disorders or whether their symptomatology was secondary to their brain lesion. As neither permitted surgical intervention the point cannot be clearly established.

None of the patients with CT changes suggestive of infarction had obvious localising neurological signs. While the incidence of clinically manifest stroke appears to have declined in recent years (Garraway et al 1979), the frequency of undetected cerebral infarction remains unknown. Jacoby et al (Jacoby et al 1980; Jacoby & Levy 1980 a and b), studying a group of 41 dements, 40 affectively ill patients and 40 normal controls, all over 60, found a prevalence of unsuspected infarction of 10.8 %, over 70 % of which occurred in the dementia patients. In the present study of much younger patients, the overall prevalence was only 3.7 % in the total sample. However this rose to 5.1 % when considering the schizophrenic group as a whole, and to 6.4 % in the long-stay schizophrenic in-patients. Whether this apparently high prevalence of 'silent' infarction is comparable with the general population, or is a consequence of the illness (for example an effect of premature aging) or a result of treatment such as neuroleptic drugs, is unclear.

Thus the present study revealed a high prevalence of unsuspected organic pathology, especially in the long-stay schizophrenic group. It is however important to note that this rarely necessitated

exclusion of the subject from this part of the work and its presence did not alter the basic findings reported. In long-stay, severe schizophrenic patients, who by the nature of their illness may be frequently disturbed and possess an impaired capacity to present symptoms, and in whom mental state changes - especially if sudden - may reflect organic factors, CT is a particularly safe and efficacious investigative tool.

4.3 THE BASIC QUESTIONS

The four basic questions posed at the start of this section will each be considered separately.

4.3.1 IS SCHIZOPHRENIA ASSOCIATED WITH LATERAL VENTRICULAR ENLARGEMENT ?

The findings presented here indicate that patients with a diagnosis of schizophrenia have significantly greater group mean estimates of lateral ventricular size than patients with non-schizophrenic, functional psychiatric conditions. The difference between schizophrenics and non-schizophrenics, although definite and significant, was far from striking, and rested largely on the fact that long-stay schizophrenic in-patients had, as a group, larger ventricles than neurotics. The point of the difference lying between the group means is emphasised because the overlap in absolute values for ventricular size was considerable across the different diagnostic groups, and there were severely disabled patients in each of the schizophrenic groups who showed no enlargement. Reference to the age-adjusted group means (TABLE 3:3:5) illustrates how slight the differences were.

The relative subtlety of these findings is further illustrated by noting the verbal reports on visual assessments of the scans conducted by two radiologists highly experienced in evaluating CT scans of the brain. Only 22 (20 %) of the long-stay schizophrenic in-patients were reported as having enlarged ventricles of any degree, and in three of these the qualification was made that the appearance may have been attributable to the subject's age. Thus, only 19 cases were visually reported as having ventricular enlargement without qualification. However, in 14 of these the enlargement was stated to be "slight". On the other hand, by measurement and introduction of an age-correction, 45 (40.1 %) of the schizophrenic in-patients had VBR's greater than 1 SD above the predicted value, 27 of whom (24.5 % of chronic in-patients) were outwith 2 SD's. This emphasises both the subtlety of the change and the inadequacy of visual assessment as an investigative technique in studies of this kind.

The method of assessment adopted in the present study made it possible to measure and obtain a VBR value on all scans (the single scan that was unmeasurable belonged to the manic-depressive out-patient with a coincidental, large arteriovenous malformation who was excluded on this basis). Thus an absolute value could be obtained for even very small ventricles, thereby allowing their full participation in statistical analysis. Some schizophrenics did have ventricles in the smallest category by reference to predicted values. In the total group of schizophrenics and in the chronic institutionalised schizophrenics separately (in whom correlations were sought) this certainly did not amount to a statistical excess, and this has to be borne in mind in the subsequent discussion on

clinical correlates. The position with regard to the non-institutionalised and first episode schizophrenics considered as one group is probably not dissimilar. Although there appeared to be some excess of patients with very small ventricles as well as very large ventricles among these subjects, this only seemed to emerge in one (the second) method of distribution analysis and was not evident in analysis of skewness and kurtosis. With a genuine excess below as well as above the mean, testing for kurtosis in particular could reasonably have been expected to produce significance with a genuine finding.

It has been suggested that institutional care of itself could account for the findings in the ventricles in schizophrenics (Jellinek 1976). This clearly cannot be the case in most of the work discussed in the literature review for this section as most of these studies refer to patients who had never come to long-term care. Although the present work cannot be dogmatic on this point, it is also unlikely that this is the basis of the findings reported here. There was no difference in mean VBR's between schizophrenics and manic-depressives who had and who had not been in long-term institutional care. Thus, it does not seem probable that exposure to the environment of the institution could, of itself, account for ventricular enlargement associated with schizophrenia.

As was suggested (vide supra Chapter 1.4.2), one interpretation of the literature reviewed earlier could be that lateral ventricular enlargement in schizophrenia is associated with what are in fact parameters of severity - or 'chronicness'. The present findings are compatible with such a view. As has been

emphasised throughout this work, the institutionalised schizophrenics represent that condition in a severe form, and it was only they who significantly differed from neurotics. For reasons mentioned earlier, it is unlikely that this basic finding would have been altered by use of a 'normal' control group, though it must be admitted that surruptitious substance abuse could have tended to diminish the difference between neurotics and all other groups. It seems likely that those authors who have failed to find significant differences in their schizophrenic patients have either studied samples that are too small, or ones in which the population of 'severe' or 'chronic' patients is under-represented for schizophrenic/control differences to emerge. Nevertheless, even using the severely disabled subjects of the present work, such differences are not marked and studies reporting a difference of high magnitude undoubtedly reflect problems of selection - both of subjects and controls. It is of interest that recently, the NIMH group have reported differences of a lesser magnitude than those in their earlier work (Luchins 1982).

Thus it is concluded that the first question is answered affirmatively - schizophrenia is associated with lateral ventricular enlargement.

4.3.2 HOW SPECIFIC IS LATERAL VENTRICULAR ENLARGEMENT TO SCHIZOPHRENIA ?

The present study can give no unequivocal answer to this question, but the results make it unlikely that ventricular enlargement is diagnosis specific.

While the schizophrenic group's VBRs differed significantly from normality in their distribution, so too did those of the non-schizophrenics. This latter point is of considerable interest, but requires further comment. The deviation from normality of the non-schizophrenics arose from 4 out-patient and 2 in-patient manic depressives having ventricles greater than 2 SD's above the predicted value (18.2 % and 20 % respectively of each sample). Of the 4 out-patients, 2 had been hypothyroid in the past, presumably consequent upon long-term lithium ingestion though the exact aetiology of their hypothyroidism was not confirmed. Both however were receiving replacement therapy and were clinically and biochemically euthyroid when scanned. These two patients, both female, had the two largest VBR's in the manic-depressive out-patient group. The question is raised as to whether these 2 cases should have been excluded, on the basis that their hypothyroidism contributed to the CT scan appearances independently of psychiatric factors.

While it has long been known that hypothyroid states can be associated with significant psychopathology, including features of dementia (Lishman 1978) no evidence is available to suggest that the type resulting from lithium ingestion produces features of brain atrophy, especially of the subtle variety being described here. Furthermore, and with specific regard to the design of the present study, clinical and biochemical euthyroid status were not designated as specific inclusion criteria. Hence, these two subjects were not excluded from the calculations. It is interesting to note that had they been omitted, the distribution of the non-schizophrenics would

still have significantly differed from normal ($X^2 = 10.83$, $df = 4$, $P < 0.05$). Thus, both the schizophrenic and non-schizophrenic distributions are viewed as authentically differing from normality due to an excess, over that predicted, of subjects with very large ventricles. In the schizophrenic group it is only that this skew to the right is more marked - not that it is unique to them.

No significant differences emerged between the group of manic-depressives and either the schizophrenics or the neurotics. Other workers have claimed that increased lateral ventricular size may be present in patients with affective illness (Pearlson & Verloff 1981; Standish-Barry et al 1982), though the present study can neither confirm nor refute this. The findings reported here are however in agreement with the recent report of Weinberger et al (1982). They compared the VBR's of patients with different DSM - 111 diagnoses and found that while schizophreniform patients and chronic schizophrenics had significantly larger mean VBR's than (neurological) controls and patients with "other disorders" (mainly personality disorders), neither schizophreniforms nor chronic schizophrenics differed significantly from affective patients, who in their turn did not differ from the neurological controls or those with "other disorders".

The age-corrected group mean VBR's point to a gradation of abnormality from neurotics through those with affective disorders to schizophrenics rather than to any clear-cut distinction between schizophrenics and other psychiatric patients.

Furthermore, within the group of schizophrenics themselves

the present findings do not support the view that ventricular enlargement is a characteristic feature of the illness - that is, that this feature is reliably found in significantly high proportion of typical cases as to be of diagnostic use - or that it can be used to define a specific subgroup of schizophrenics. Even if liberally defined as > 1 SD above the predicted value, ventricular enlargement was found in only the minority of schizophrenics (44.1 %), and if more appropriately defined as > 2 SD above prediction, could be ascribed to only 24.3 %. While the present data showed a skewed distribution to ventricular size, there was no evidence of bimodality, a finding now reproduced by several groups.

These results may be interpreted as indicating that functional psychosis per se is associated with lateral ventricular enlargement and that although this may be more frequent and/or more severe in schizophrenia, it is not specific to that condition. This is compatible with PEG findings(e.g. Huber 1957; Haug 1962). In the study of Haug for example the schizophrenic group had more abnormality than the non-schizophrenic, functional patients but less than those with organic psychiatric disorders.

4.3.3 ARE PAST PHYSICAL TREATMENTS OF RELEVANCE TO LATERAL VENTRICULAR ENLARGEMENT IN SCHIZOPHRENIA ?

An obvious explanation for the basic finding reported here is that ventricular enlargement is the consequence of repeated assaults on the brain by past physical treatments, though there is evidence from PEG studies performed before the widespread use of physical treatments that this is unlikely to be the case (Donovan et al 1949).

While hypoglycaemia is known to be a potent cause of brain damage (Marks & Rose 1965), there is no evidence that when induced in controlled conditions this results in CT changes of the type described here. Although a non-significant trend existed in the present study between a past history of insulin coma and ventricular size, this as was mentioned, was felt to be insufficient evidence to assume a positive association between the two. Factors relating to the selection of those who received this treatment are likely to be important in determining its correlates. Most importantly, ventricular enlargement has regularly been demonstrated in patients never exposed to this form of treatment (this is the case in most of the studies referred to in the literature review).

Thus the above weak association is interpreted as reflecting incidental or chance factors and the present study is taken as providing no support for the view that insulin coma is of relevance to the ventricular enlargement associated with schizophrenia.

It has been suggested that ECT may damage the brain (Friedberg 1977), though there is no evidence to support the view that such presumptive damage could be detected on CT scanning. CT change has not been found following even multiple ECT shocks (Menken et al 1979). Four PEG studies which addressed the question found no difference between those treated and those not treated with ECT (Huber 1957; Haug 1962; Nagy 1963; Storey 1966). Asano (1967) stated that abnormal PEG's were more common in patients who had received more ECT's, but provides no data or analysis on this. He does point out however that it was the most deteriorated patients who received most ECT. Hence the common phenomenon connecting ventricular abnormality

and ECT was the clinical one of severity. It is likely that a similar phenomenon was acting to produce the relationship between ECT and ventricular enlargement reported in the CAT scan study of Weinberger et al (1979 a), as even those in their sample who had never received this type of treatment had significantly larger ventricles than controls. Andreasen et al (1982 c) found no relationship.

Marsden has suggested that administration of neuroleptic drugs may be associated with more widespread brain damage than has hitherto been appreciated and that this may account for the differences in ventricle size between schizophrenics and non-schizophrenics (Marsden 1976). The animal evidence to support such a view is however equivocal (APA Task Force 1979). While several studies have found no relationship between neuroleptic intake and CT scan findings (Weinberger et al 1979a;Golden et al 1981; Weinberger et al 1982), no investigations to date have been in a position to examine this question in detail.

The strategy adopted in this study of examining the scans of groups of schizophrenics matched for various factors but treated in different ways probably represents the best means now possible of evaluating the role of physical treatments in ventricle size. The results show that treatment with insulin or ECT, or neuroleptic drugs, and the degree of treatment with each, was unrelated to present ventricle size. Furthermore, the combination of physical treatments did not correlate with VBR, in that no differences in ventricle size were found between those with no history of physical treatment and matched subjects heavily treated.

Thus, it can be concluded that past physical methods of treatment (excluding leucotomy) are not the cause of ventricular enlargement associated with schizophrenia.

4.3.4 WHAT ARE THE CLINICAL CORRELATES OF LATERAL VENTRICULAR ENLARGEMENT IN SCHIZOPHRENIA ?

Few clinical correlates of lateral ventricular enlargement were identified in this study and some of those which did emerge were unusual. It must, of course, be recalled that, as only the long-stay schizophrenic in-patients significantly differed from neurotics with regard to lateral ventricular size, correlations of enlargement were sought within this group alone.

Of the Recorded Information variables only family history of schizophrenia produced significant findings and these were unexpected. In general, those with a family history of schizophrenia fell into normal ventricular size categories (i.e. were distributed around the age-corrected predicted mean), while those in both large and small ventricular size categories tended to have negative family histories. Indeed none of those in the two smallest categories of VBR (a and b) on whom information was available (25 subjects) had a positive family history of schizophrenia.

In view of the strength of the relationships this finding cannot be ignored, but the interpretation placed on it depends largely on which analysis is considered the more appropriate. Firstly, a linear relationship between increasing VBR and a positive family history could be postulated. It has for example been suggested that schizophrenics with a positive family history manifest significant psychomotor differences from normal controls or schizophrenics without

a family history (Walker & Shaye 1982). Analysis of trends, allowing as it does the collapsing of adjacent categories of data will produce significance in line with this postulate as was demonstrated (vide supra p. 302). Alternatively, reference to the distribution of the data (Fig. 3:3:12) emphasises the curvilinear form of any potential relationship. If this is accepted as the basis for analysis, significance will again be obtained (vide supra p. 303). Clearly these different modes of analysis lead to contradictory conclusions - the one that large ventricles are associated with a positive family history, the other that they are associated with a negative family history (along with small ventricles).

In the present work it is felt that the data shown in Fig. 3:3:12 cannot be ignored. The distribution of the family history variable across VBR categories is clearly curvilinear and to produce significance by collapsing the two or three largest VBR categories is statistically misleading. Furthermore, in pure statistical terms the curvilinear relationship is the stronger. This therefore is the one accepted here.

This intriguing finding invites speculation, but some major qualifications must be stated. The relationship may reflect chance factors, though as a similar type of relationship was found with other variables this seems unlikely. Most importantly are three points relating to the information on family history on which the finding rests. Although these have been noted previously (Part 1 Chapter 5.1) they will again be noted in view of their relevance to the interpretation of this CT finding.

1) This finding is based on information given by relatives at the time of the patients admission. This was usually

taken when they were young, and obviously was early in the morbid risk for other family members. It would be expected that the actual prevalence of a positive family history corrected for the age of the index subject when scanned would be higher than that on which the analysis was conducted.

2) In the absence of a definite statement of diagnosis by the relatives completing the Enquiry Form, interpretation of their statements regarding psychiatrically ill family members was conservative in this study.

3) There is evidence that the case note method of extracting information on family history underestimates the prevalence found by direct interviewing of the next of kin. (Thompson et al 1982).

For these reasons the prevalence of a positive family history of schizophrenia in the scanned group almost certainly represents an underestimate.

Despite these major qualifications, this finding raises the intriguing possibility that the illness may have a different pathological substrate in those with a positive family history as opposed to those with no such history. In a large study of 249 chronic schizophrenics, Hays (1977) found that normal EEG traces were highly significantly correlated with a positive family history of major psychoses (schizophrenia and bipolar manic-depressive psychosis), whereas traces showing one or more variants of normality were more often found in those with no family history. Campbell et al (1979) subsequently postulated that CT scan abnormalities would be more frequently found in patients with no family history of psychosis than in those with a positive

family history. The authors were unable to confirm this in a study of 35 schizophrenic outpatients, though unfortunately assessment of scans was limited to visual inspection. More recently Reveley et al have found an association between negative family history of schizophrenia and relatively large ventricles in a series of 21 schizophrenic patients (Reveley et al 1983). Although the results of the present study are less straightforward than those of Reveley and colleagues they may be seen as broadly in line with this group's work and with the hypothesis of the Canadian group.

While clinical studies have demonstrated the role of genetic factors in schizophrenia, little attention has been paid to biological variability based on family history. The results of the present investigation indicate that this may be a fruitful area for further study.

Of the five Assessed Abnormality variables initially examined (considering AIMS and RS as different ways of assessing the same variable - movement disorder), relationships with VBR categories could be established with four. Of these, the nature of the relationship was linear in two and curvilinear in two.

The absence of a straight, linear association between cognitive impairment and ventricular enlargement in this study could be understood in terms of the generally low order of the correlation between intellectual ability and brain structure in disease. Although the bulk of the literature concludes that such a relationship exists in schizophrenia (cf Part 1), this conclusion refers to a statistical correlation which, although definite, is not strong. There is considerable variation in the range of intellectual performance associated with any given structural pattern and vice versa. This is

similar to what has been found in studies correlating neuro-psychological performance and structural change in dementia (Roberts & Caird 1976; Earnest et al 1979; Jacoby and Levy 1980a). Furthermore, notwithstanding Johnstone et al's original findings (Johnstone et al 1976, 1978b) in a small selected group of schizophrenics, it may be that the Withers and Hinton, devoid as it is of any performance measures, is less sensitive in detecting such a relationship than other varieties of cognitive testing (e.g. WAIS, Luria-Nebraska, Halstead-Reitan etc). However, the finding of a relationship that is curvilinear in nature has no precedent in the literature.

The same applies to 'negative' features, though this area has not been greatly studied. While ventricular enlargement has been claimed to be associated with 'negative' type features (Andreasen et al 1982b), the quality of this evidence is poor as was noted in the introduction to this section (Chapter 1.2.2). With regard to the present study, it is perhaps not surprising that having found a curvilinear relationship between VBR and cognition the same sort of relationship emerged with 'negative' features, given that impairment on both these latter features was strongly correlated (cf Part 1).

The findings of declining behavioural performance and spontaneous involuntary movements in association with ventricular enlargement are in line with prediction.

CT techniques have been used surprisingly infrequently to investigate patients with movement disorder. Gelenberg (1976) was the first to do so, reporting no visually assessed abnormalities in the scans of 8 dyskinetic patients.

Famuyiwa et al (1979) compared the CT findings from 17 schizophrenics with "tardive dyskinesia" of mean age 49 years, with those of 33 schizophrenics without 'TD'. Scan assessments were both linear and visual. Only one difference was found - namely that "there were significantly more patients in the tardive dyskinesia group with a pathological rating on the ventricular index" than in the non-dyskinetic group. The ventricular index is a dubious way of assessing ventricular enlargement and the authors' carefully worded statement is justified. The ventricular index is "the ratio of the distance between choroid plexuses and greatest distance between anterior horns" (Meese et al 1980). It is thus a measure which is highly dependent on the angle of separation of the anterior horn, which with CT, may vary with individual anatomy and positioning during the scan in addition to any change consequent upon disease.

Jeste et al (1980) studied a number of CT parameters from 12 chronically hospitalised females (10 schizophrenics, 2 organics) with 'tardive dyskinesia' carefully defined, and compared these with findings from 12 closely matched subjects without dyskinesia. There were no differences between the groups on any parameter.

This study involved relatively small numbers and used only the global impression item of overall abnormality on the AIMS and not total scores, to evaluate movement disorder. Most surprisingly however, one patient in each group had a history of prefrontal leucotomy. In view of the wide variability in leucotomy lesions and their unpredictable effect on the ventricular system, one such subject could easily have eradicated any differences between the groups.

The lack of a relationship between VBR and 'positive' features of the mental state is in line with prediction and with other work in

the literature (Crow 1982). Only hallucinations of the individual Krawiecka items, produced a relationship with ventricular size which was statistically strong. Once again however, the nature of that relationship is open to two interpretations. With a linear model, hallucinations were less common in those with large ventricles - in line with prediction. However the curvilinear relationship was likewise significant, such that hallucinations were less common at both extremes of ventricular size. This latter interpretation is complimentary to that for cognition and 'negative' features, indicating that where these two variables predominate, hallucinations tend not to be found. Accepting that the curvilinear nature of these relationships is valid, this is compatible with prediction.

As mentioned, few workers have sought correlations of this type with ventricular size and Andreasen et al (1982b) are the only workers to do so in a standardised fashion. Owing to the different components of their "positive and negative symptoms", comparison is difficult. Only their items of hallucinations, delusions, thought disorder, and affective flattening are recognisable in terms of the Krawiecka Scale, and Andreasen and colleagues found no significant relationship between any of these and ventricular size.

Thus, in general, the search for individual mental state correlates of brain change in schizophrenia has not proved fruitful.

The rather weak overall association between behavioural deterioration (CBS totals) and ventricular size was the result of strong associations between dilatation and different components of behaviour - namely restricted social interaction, limited constructive activities and disturbed, disruptive exhibited behaviour. Antisocial

behaviour was significantly less frequently found at the extremes of ventricle size, and this was only open to a curvilinear interpretation.

4.3.5 SUMMARY

The results of this section have confirmed that schizophrenia is associated with lateral ventricular enlargement, and that this is a feature of severe forms of the illness. It is not a result of past physical treatments. While the specificity of ventricular dilatation to schizophrenia remains uncertain, the findings indicate that there is nothing characteristic or pathognomonic about these changes and that no subgroup of patients can be discretely delineated solely on the basis of radiological findings.

The correlates of ventricular enlargement were few and surprising in at least their form. The data relating to family history are of interest and suggest that this may be a valuable variable on which to base further study. By the application of CT, the major distinction to emerge in this severe long-stay population was not simply between those with and those without ventricular enlargement, but was in general between those with ventricles in roughly normal ranges of size and those at the extremes of the spectrum. These curvilinear correlates emphasise the complex relationships that exist between brain structure and clinical deficits in schizophrenia.

4.4 CONCLUDING REMARKS

Although it has been widely postulated that 'defect state' features (i.e. 'negative' mental state characteristics, intellectual impairment and behavioural deterioration) would be more likely to be found in association with structural brain change (Crow 1980; Crow et al 1982), than would the 'positive' type of clinical picture, the findings of this study of lateral ventricles offer little support for this hypothesis in its simplest form. The patients with 'negative' features and intellectual impairment did not have larger ventricles than a matched group without these features. Nor did patients with catatonic syndrome, in whom 'defect' type deficits were particularly severe (cf Part 1), have larger lateral ventricles than those in other Catego subclasses. The lack of a linear relationship between ventricular enlargement and cognitive impairment is underlined by the fact that there was no difference in VBR in the patients with higher academic attainment and either high or low Withers and Hinton scores. While the association of increased VBR with behavioural impairment and the presence of involuntary movements indicate a link with deterioration in two of its aspects, the results of this study strongly suggest that the relationship between lateral ventricular size and the so-called 'defect state' is not straightforward. Thus, behavioural deterioration was linearly associated with ventricular enlargement which also had a very strong association with abnormal involuntary movements, but apparently no linear relationship with 'negative' symptoms or intellectual impairment - despite the fact that all four clinical variables occured together in the total population from which the patients were drawn (cf Part 1). The fact is that some

subjects in the present population who were incapacitated by profound and often multiple clinical deficits, had ventricles that were either well within the normal, predicted range or even fell within the 'small' end of the spectrum of size.

Perhaps such findings partly reflect the difficulties of defining what constitutes the clinical 'defect', but it seems from the results presented here that these clinical deficits relate in different fashions to underlying brain morphology.

PART IV

GENERAL COMMENT

"The commission of medical experts consisted of three unusually solemn gentlemen whose views were such that the view of each differed gloriously from any of the views of the other two"

JAROSLAV HASEK
THE GOOD SOLDIER SVEJK

PART IV

GENERAL COMMENT

This study set out with two objectives. The first was to describe in standardised fashion, the deficits of long-standing schizophrenia, while the second was to see whether inferences regarding a cerebral basis for the disorder could be sustained from clinical and special investigative techniques.

While many subtle and varied areas of functioning could have been chosen in pursuance of the first of these objectives, those selected represent a broad range of activity of relevance to clinical psychiatric practice. The patients' disabilities were profound and often multiple. For this group at least medical intervention had acted neither to their benefit nor their detriment. Within a selected sample, particular explanations of this fact may pertain, but the implication is that the deterioration intrinsic to the disorder is largely autonomous. 'Deterioration' however, is itself a vague concept. At a purely clinical level this population, all of whom shared 'deterioration' in a general sense, nonetheless demonstrated two broad patterns of disability that were striking. Most psychiatrists would acknowledge the florid, productive picture, but many would view the 'negative' pattern as unexceptional - the "burned out" phase of the clinically more relevant florid stage. This study suggests that the term 'burned out' may refer more to the clinician's interest than to the realities of established schizophrenia. Regardless of any possible relationships they may bear to one another in the earlier history of the illness, in the established state both clinical patterns appear to have validity and to be

worthy of separate study. The essential question however is whether clinical criteria alone are sufficient to allow implications of aetiology based on primary cerebral disorder - which raises the second objective of the project.

Notwithstanding historical references, the choice of involuntary movements as the clinical neurological parameter was to some extent influenced by the unique treatment characteristics of the study population. It can certainly be claimed that the present work provides some of the strongest evidence to date in validation of the concept of 'neuroleptic - caused movement disorder'. More than this however, it has demonstrated two points - firstly, that movement disorders are to be found in high prevalence in unmodified schizophrenia, and secondly that over and above any neuroleptic factors relevant to their production, particular factors associated with the illness per se are of importance.

The first of these points must be noted with qualification. This study was not in a position to demonstrate the uniqueness of such prevalence rates to schizophrenia. The lack of a suitable control group is evident here as in so many studies of long-standing schizophrenics, especially those in institutions. Straight comparisons with published figures must be cautious because of the problems of conceptualisation and variability between examiners noted in Part II. While the present author believed himself to have operated generally conservative criteria throughout, this must not be given undue emphasis in quoting the figures published here as the 'true' ones for unmodified schizophrenia. All that is claimed is that these figures are very high - much higher than the present day literature using pooled data methods would lead one to suspect - making

involuntary movements a not uncommon feature of established, unmodified schizophrenia. This is in keeping with the impression left by the early descriptive accounts, and is a sufficient conclusion.

Of greater interest than the suggestion of such a general association, however, is that when a range of potential aetiological factors were accounted for, the study was able to demonstrate significant relationships between the presence of certain mental state/behavioural characteristics of schizophrenia and the presence of clinical neurological disorder. As long as additional potential contributing factors remain hidden and unaccounted for, such a finding cannot be held up on its own as 'proof' that schizophrenia - or schizophrenia taking a particular form - is a brain disease. It does however allow inferences of a cerebral aetiology for the 'negative' or 'defect' type of disorder to be made with an enhanced probability of accuracy. Insofar as mental state patterns predominantly 'positive' in nature do not appear to enhance such predictions, the simple 'positive'/'negative' mental state dichotomy proposed in Part I would seem to have some merit. The word 'predominantly' is again emphasised. Within the limitations of a correlational methodology, these conclusions are the most that could be expected and in general support the original hypothesis.

At the outset, Part III offered the greater likelihood of establishing a neurological bridge to schizophrenia. If interpretations are kept to the general, this part of the work did achieve its objective. The findings support a considerable body of evidence pointing to the fact that schizophrenia is associated with enlargement of the lateral ventricular system. These changes are not however characteristic nor absolute, though they could be said to

be a feature of the illness in its severe form(s). It can be stated with confidence that they are not the result of physical treatments.

Thus using both involuntary movements and structural brain change as parameters of neurological abnormality, relationships could be established between 'organicity' and features comprising so-called 'functional' illness. At this general level the study was largely successful. But to leave interpretation at this level is hardly sufficient. Such a general conclusion holds within it a caution to any simplistic theories regarding the nature of schizophrenia - particularly when such theories are founded solely on clinical evidence. As Huxley has said :

> The great tragedy of science (is) - the staying of a beautiful hypothesis by an ugly fact.

One of the difficulties in marrying the present findings to the initial hypotheses lies in the design of the study. As is often the case this sort of difficulty is highlighted in retrospect. Part II was not in a position to demonstrate that the prevalence of abnormality found was significantly higher in schizophrenia compared to other non-schizophrenic diagnostic groups, whereas Part III was designed to show just that for the abnormality it considered. This in itself may not have been of great import had the detailed pattern of clinical correlations which related to each neurological feature been uncomplicated and the same. However, the study could not unravel a consistent pattern of clinical deficits which correlated with structural change as movement disorder did. Or, to put it more accurately, it could not establish a consistent pattern which correlated in a straightforward fashion compatible

with prior prediction, as movement disorder did. The crucial decision is what interpretation is to be placed on the curvilinear relationships established in Part III. Either they are spurious and should be ignored or they are genuine and possibly tell us something hitherto undescribed regarding structural changes underlying long-standing schizophrenia.

As was shown, divergent conclusions could be reached by different applications of the statistical technique. But the illustrations of Part III demonstrated that ignoring curvilinear relationships neglected findings which were striking and occurred consistently across a number of variables. Statistical techniques must be applied to allow an accurate interpretation of data and not to support preconceptions. The curvilinear relationships have been interpreted here as genuine, established by judicious use of a robust statistical method.

If they are genuine, what then might they tell us about the nature of schizophrenia? Such unusual relationships may arise from a number of sources, of which the most obvious is probably heterogeneity within the population. Heterogeneity has remained since the time of Kraepelin and Bleuler, a favoured clinical view and is one which the present work has to some extent sought to elucidate. The family history data from Part III may, for example, be interpreted as showing a genetic and a non-genetic form of the condition, the latter associated with two strikingly different structural pictures. The one (enlargement of lateral ventricles) was clearly found in statistical excess and can be readily accepted as abnormality. The other (small ventricles) was not represented excessively overall in statistical terms. Within a homogeneous group these subjects at

the left hand end of the distribution should be considered as normal variants. It nonetheless remains theoretically possible that in a hetereogeneous grouping these subjects may represent abnormality occurring within the distribution of a sub-type of small ventricle patients who are less commonly found than those with normal or large sizes. For the reasons discussed however such detailed extrapolations of family history data, especially those from retrospective studies over a time span of decades, are risky. Nevertheless, family history data can be used to illustrate the possible influence of hetereogeneity. Family history data did not however correlate similarly with both neurological parameters or with any other examination variables.

Here an inherent danger emerges. It is that of confusing clinical heterogeneity with pathological - and hence presumably aetiological - heterogeneity. Two basic assumptions can in retrospect be seen running through the present work. The first is that clinical features and 'syndromes' derived from them, would relate to structural change in a uniform and predictable fashion, The second is that clinical skills are sufficiently refined to identify these features and distinguish them with confidence from other similar but not identical phenomena. On reflection such assumptions are clearly fallacious, and force artificially restrictive interpretations on results. General medicine offers many examples to dispose the former, and were the latter true dissentions of the sort discussed in Part I (pp 105-107) would not exist. Negative features may arise from divergent pathological changes at different brain sites; or what we rate as, say, flattening of affect may cover a number of varied clinical phenomena as yet

undistinguishable.

In a large scale correlational study such factors may account for a degree of inconsistency, but it is unlikely that they represent the total explanation. If they did it is improbable that movement disorder would have related linearly to both ventricular enlargement and the examination variables of 'negative' features and cognitive impairment.

Alternatively even simpler explanations of genuine curvilinear relationships may pertain. It may be said, for example, that those variables which failed to demonstrate straightforward relationships across both neurological parameters were the two for which it is most difficult to be confident of objectivity in assessment. The problem with 'negative' features in this regard has been noted throughout the present work, and in Part I the uncertainties surrounding the evaluation of cognitive performance in a setting of poverty of speech was discussed.

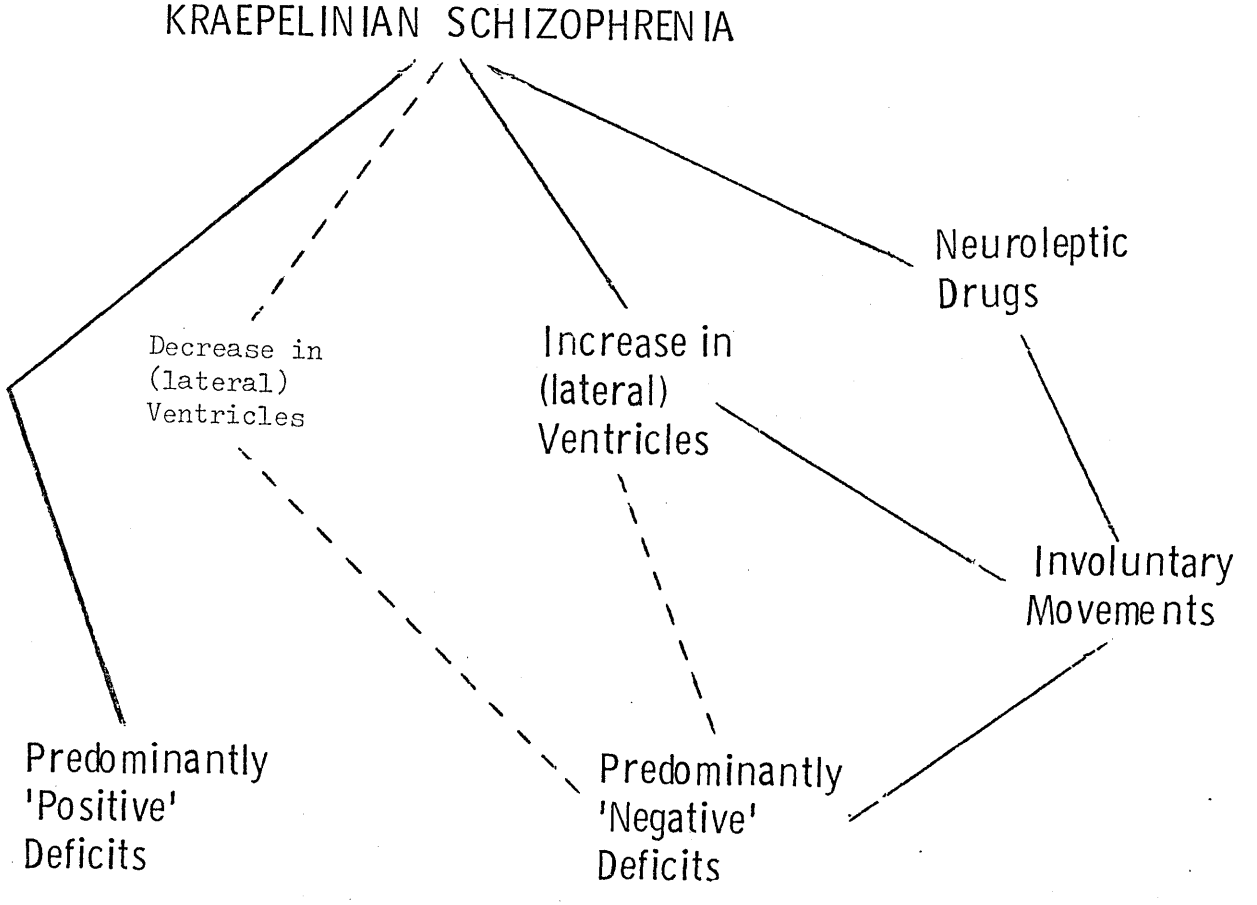
At the end of the day, however, such inconsistencies as the study did reveal may be irrelevant in the context of its objectives, and attempted explanations of them an unprofitable exercise. It is perhaps more appropriate that the evidence in support of the basic hypothesis should be emphasised, with unexpected findings merely noted to await future elucidation. This is the favoured view, especially since such surprises as did emerge were outweighed by data which were consistent. If the analogy of dementia is taken, the results of the present study are in fact reassuring. The symptomatology, including the neurological signs, associated with dementia is varied, even when specific subtypes of dementia such as Alzheimer's Disease are studied, and the correlations between

clinical features and structural change are not of a high order. Seen in this light, the data reported here are encouraging.

Reduced to their essence, the results of this study may be summarised as follows:

- Kraepelinian schizophrenia is associated with lateral ventricular enlargement.
- Lateral ventricular enlargement is associated with the presence of involuntary movement disorder.
- Involuntary movement disorder is associated with a particular pattern of established ('negative' type) schizophrenic deficit (though it is suggested that Kraepelinian schizophrenia in general may be associated with movement disorder). Movement disorder is furthermore associated with neuroleptic exposure.

These may be illustrated thus:



Furthermore:

- 'Negative' type deficits relate to lateral ventricular change in an unpredictable fashion (? usually but not always enlargement).

Although in practice important, the role of neuroleptic drugs in promoting clinical disorder is, in this schema, aetiologically peripheral.

Taken at this general level of interpretation the initial hypotheses were supported. This study lends weight to a growing body of evidence which indicates that the old functional/organic dichotomy of psychoses is no longer adequate for the understanding of schizophrenia. In its detail however, the project also left one impressed by the obvious complexity of the relationships between some of the psychopathological features of established schizophrenia and the disorganisation of brain structure which underlies them. Notwithstanding the authenticity of the relationships reported within the population as a whole, some patients with profoundly incapacitating deficits showed neither ventricular change nor movement disorder.

This point is worth re-iterating, not only because it illustrates the complexity of cerebral function and structure in psychiatric disease, but also because it highlights the fundamental disappointment of schizophrenia research up to the present time. No matter the impressiveness and uniformity of association of variables within and between groups, biological research is not yet in a position to offer the clinician hard facts of diagnostic and/or prognostic value to the individual case at the time they are most needed - i.e. at first presentation. That objectivity so much envied of general medicine remains elusive.

For the future, there is an urgent need for further study of

the deficits of established schizophrenia. For this to remain 'the poor relation' of psychiatric research is clinically, economically and scientifically indefensible.

Firstly, the nature of 'chronic' schizophrenic deficits must be agreed. The present contradictory jungle of proposals does psychiatry no credit, and obfuscates further a naturally complex situation. Increasingly detailed speculations based on 'theorising' must give way to proposals developed out of clinical study. The simple suggestions produced here are certainly not definitive, but the method must progress from observation $\longrightarrow$ proposal, and not the other way.

Secondly, those deficits on which agreement exists must be studied objectively where this is possible. It is fortunate that a number of these deficits, such as poverty of speech, loss of affective resonance and neurological dysfunction, share the inherent potential for objective evaluation. The techniques to make a start - especially computer technology - already exist.

The combination of objective clinical observation with radiological imaging offers one of the most exciting avenues for future research, though the present work, and that preceding it, makes it clear that imaging techniques are not in themselves the sources of all knowledge about schizophrenia. By their very nature they demand more - not less - attention to research methodology and subject selection. At the end of the day such technologies are only as useful as the expertise applied to the clinical material. Without that expertise they are little more than expensive toys for locating a pathological needle in the cerebral haystack.

In deciding future priorities, it may well be that the 'negative'

clinical picture, so long the subject of resignation and neglect in fact holds within it great potential for understanding the basis of at least some of the disabilities of this fell and enigmatic disorder.

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APPENDICES

KRAWIECKA SCALE

PATIENT'S NAME ..... DATE ..... INTERVIEWER'S INITIALS .....

Key symptoms in the past:

(Questions about past week should include: whether depressed (? severe ? frequent); whether anxious (? severe, ? frequent); how getting on with other people; whether anyone seems against him; whether he can think clearly; any interference with thoughts; thoughts read; reference to him on television or newspapers; hearing voices or seeing visions)

RATING	REASON FOR MORBID RATING	RATING
Rating made by replies to questions:		
DEPRESSED		0 1 2 3 4
ANXIOUS		0 1 2 3 4
COHERENTLY EXPRESSED DELUSIONS		0 1 2 3 4
HALLUCINATIONS		0 1 2 3 4
Rating made by observations:		
INCOHERENCE AND IRRELEVANCE OF SPEECH		0 1 2 3 4
POVERTY OF SPEECH MUTE		0 1 2 3 4
FLATTENED		0 1 2 3 4
INCONGRUOUS		0 1 2 3 4
PSYCHOMOTOR RETARDATION		0 1 2 3 4

APPENDIX I(a)

KRAWIECKA SCALE ITEMS - DIVISIONS USED IN THE PRESENT WORK

'POSITIVE' FEATURES	'NEGATIVE' FEATURES	'NON SPECIFIC' FEATURES
HALLUCINATIONS	FLATTENING OF AFFECT	DEPRESSION
DELUSIONS	POVERTY OF SPEECH/MUTENESS	ANXIETY
INCOHERENCE OF SPEECH		RETARDATION
INCONGRUITY OF AFFECT		

TESTS OF THE SENSORIUM - FORM A

WITHERS & HINTON (W & H)

N.B.

1. Unless instructed otherwise, record subject's answers verbatim.
2. Record any comments (e.g. on subject's behaviour) on the test record.
3. Fill in date and time after 'Orientation' has been administered.
4. Score during or immediately after the session. Maximum possible scores are shown in brackets in the scoring column.

Patient's Name .....

Date .....

Tester .....

INTRODUCTION	Test material	Score

Say:

I am going to give you a few short tests which we give routinely to all patients. The tests are varied - some you may find easier than others - but we should like you to do your best in all of them.

ORIENTATION

Say:

We start with some questions:

1. Please will you give me your full name?	1. (1 for surname and (1 for Christian name	(2)
2. What is the name of this place?	2. (1 for name of hospital	(1)
3. What is the address?	3. (1 for London, W1, etc.	(1)
4. Can you give me to-day's date in full? (If necessary specify day of the week, date month and year)	4. (1 for each item	(4)
5. Can you, without looking, tell me what time it is?	5. Allow 1/2 hr. deviation	(1)

ATTENTION AND CONCENTRATION

6. Please say the days of the week backwards, starting from Tuesday.	6. Subtract the number of errors from 7	(7)
7. Take 7 from 100 and keep on taking 7 away. Ready?	7. Subtract the number of errors from 14	(14)

Start timing. Record total time for Serial 7's.

MEMORY

Say:

I am going to give you an address and a telephone number. I shall read each of them once. You are to repeat them immediately and after 2 minutes. Ready?

8. Mr. Percy White, 14 East Drive, Bath. Will you repeat that?	8. 1 for each correct word.	(7)
9. And the telephone number is Birmingham 4891.	9. 1 for town and 1 for number	(2)

(Instructions for a test of copying digits inserted here; until:)

At the end of the 2 minute period say:

10.	Can you remember the address?	10. 1. for each word (7)
11.	And the telephone number?	11. 1 for town and 1 for number (2)

Here is a sentence which I should like you to repeat, word for word, after I have finished:

12.	One thing a nation must have to become rich and great is a large, secure supply of wood.	12. Subtract number of attempts from 9 (8)

If subject makes a mistake, ask him to listen again.
Repeat the sentence, if necessary, 8 times.

Say:

I am going to read you a short passage. Afterwards you are to repeat as much of it as you can. I shall ask you twice. Ready?

13.	A fire/last night/burnt/several houses/ near the centre/of the city/It took some time/to put it out/The loss/was five thousand/ pounds/and seventeen/families/lost their homes/ In saving/a girl/who was asleep/in bed,/a fireman/ was burnt/on the hands./	13. 1 for each idea

All right. Now tell me all you can remember.

Start timing 5 mins. (when subject will be retested). Fill in the period by asking as many of the following questions as is convenient.

GENERAL INFORMATION

Say:

Here are some general questions:

14. Who is on the throne at the moment? (If subject answers 'Elizabeth' Say: Elizabeth the.....?)	14. In 'General Information' score 1 for all questions except 22.

15.	Who was before her?	15.	(1)
16.	And before that?	16.	(1)
17.	What is the capital of the United States?	17.	(1)
18.	And what is the capital of France?	18.	(1)
19.	And the capital of Scotland?	19.	(1)
20.	And the capital of Belgium?	20.	(1)
21.	And what is the capital of Yugoslavia?	21.	(1)
22.	Name five large English towns.	22.	(5)
23.	How many pence are there in two shillings and threepence?	23.	(1)
24.	How many fourpence are there in two shillings?	24.	(1)
25.	How many pence are there in thirteen shillings?	25.	(1)

I am going to name some famous people. You are to tell me for what they are known. Ready? They are:

26. Beethoven.	26.	(1)
27. Keats.	27.	(1)
28. Constable.	28.	(1)

(Instructions giving additional names and tests for meanings of proverbs; until:)

MEMORY

5 mins after reading the short passage (13) say:

29. Will you once more repeat the short passage about the fire which you told me before?	29.	(21)

Say:

I am going to say some numbers. Listen carefully because, when I have finished, you are to say them after me. Ready?

Read digits evenly, 1 per second. If subject fails any series, give the second of the pair. Discontinue when he fails both series in any pair. Record the number of the longest series at which he succeeds.

30.	8 6	3 1	(2)
	1 4 2	5 8 3	(3)
	7 5 3 6	9 7 2 5	(4)
	4 9 1 3 8	2 4 7 5 9	(5)
	6 2 7 1 8 4	9 4 8 5 7 1	(6)
	3 6 5 8 7 4 2	8 2 5 9 4 1 7	(7)
	5 1 4 6 2 7 9 3	1 8 5 9 2 7 3 6	(8)
	9 4 8 3 6 2 7 5 1	6 3 1 7 5 9 2 8 4	(9)
	2 5 1 6 9 3 8 1 4 7	4 2 7 9 6 1 4 3 5 8	(10)

30. Number of digits in longest correct series (10)

Say:

I am going to say some more numbers but, this time when I stop, you are to say them backwards. For example, if I said 674 you would say 476. Ready?

31.	6 7	9 1	(2)
	2 6 9	6 3 8	(3)
	4 2 5 8	2 7 4 9	(4)
	1 7 3 9 4	8 4 1 5 2	(5)
	7 4 8 6 1 3	1 5 9 6 4 7	(6)
	5 8 3 7 2 1 6	3 6 8 4 2 9 5	(7)
	8 2 4 7 9 5 3 1	4 1 2 9 3 5 9 6	(8)
	3 6 9 5 7 1 8 4 2	8 1 4 6 5 2 9 7 3	(9)
	9 4 2 1 7 3 6 8 3 5	7 2 6 9 3 6 8 5 7 4	(10)

31. Number of digits in longest correct series (10)

Age:

Date of birth:

Year of admission:

Now I am going to read a short story. Afterwards I shall ask you to tell it in your own words. Ready?

32. A cowboy went to San Francisco with his dog, which he left at a friend's while he went to buy a new suit of clothes. Dressed in his grand new suit, he came back to the dog, whistled to it, called it by name and patted it. But the dog would have nothing to do with him and his new hat and coat and gave a mournful howl. Coaxing was of no avail, so the cowboy went away and put on his old suit, and then the dog immediately showed its wild joy on seeing its master as it thought he ought to be.

32. 1 each for following ideas (8)
Cowboy;
went to buy new clothes;
left dog behind;
he came back wearing new clothes, unrecognized by dog;
He changed into old clothes;
dog greeted master;
pleased to see him as it thought he ought to be.

33. What do you consider was the point of the story? 33. Rate 0 - 5.

CRC DIVISION OF PSYCHIATRY

SCHEME FOR BRIEF NEUROLOGICAL ASSESSMENT

IDENTIFICATION

Survey number 1-3 [ ][ ][ ]

Date of examination 4-9 [ ][ ][ ][ ][ ][ ]

FACE (Cranial nerves - modified) 10 [2]

PUPILS

Equal YES/NO 1/2

if no, specify.....

Reaction to light:

Left YES/NO 1/2 16 [ ]

Right YES/NO 1/2 17 [ ]

Reaction to accommodation:

Left YES/NO/D.K. 1/2/3 18 [ ]

Right YES/NO/D.K. 1/2/3 19 [ ]

EYE MOVEMENTS Normal/Abnormal 1/2 20 [ ]

if abnormal, specify.....

NYSTAGMUS YES/NO 1/2 21 [ ]

MOUTH MOVEMENTS Normal/Abnormal 1/2 22 [ ]

if abnormal, specify.....
and proceed to:

ORBICULARIS OCULI

Left Normal/Weakness 1/2 23 [ ]

Right Normal/Weakness 1/2 24 [ ]

VISUAL FIELDS Normal/Abnormal/Untestable 1/2/3 25 [ ]

if abnormal, specify.....

FUNDOSCOPY

Left disc Normal/Abnormal 1/2 26 [ ]

if abnormal, specify.....

Right disc Normal/Abnormal 1/2 27 [ ]

if abnormal, specify.....

LIMBS

TONE

Upper limbs : Left Increased/Normal/Decreased 1/2/3 28 [ ]

Right Increased/Normal/Decreased 1/2/3 29 [ ]

Lower limbs : Left Increased/Normal/Decreased 1/2/3 30 [ ]

Right Increased/Normal/Decreased 1/2/3 31 [ ]

POWER for WEAKNESS

Upper limbs : Left	Absent/Present	1/2	32	
if present,	LT/ST	1/2	33	
Right	Absent/Present	1/2	34	
if present,	LT/ST	1/2	35	
Lower limbs : Left	Absent/Present	1/2	36	
if present,	LT/ST	1/2	37	
Right	Absent/Present	1/2	38	
if present,	LT/ST	1/2	39	

CO-ORDINATION

Upper limbs :

Finger-nose test Left	Normal/Equivocal/ Definitely abnormal	1/2/3	40	
Right	Normal/Equivocal/ Definitely abnormal	1/2/3	41	

Hand-tapping test

Left	Normal/Equivocal/ Definitely abnormal	1/2/3	42	
Right	Normal/Equivocal/ Definitely equivocal	1/2/3	43	

Lower limbs

Heel-shin test

Left	Normal/Equivocal/ Definitely abnormal	1/2/3	44	
Right	Normal/Equivocal Definitely abnormal	1/2/3	45	

TENDON JERKS

Upper limb :

Biceps				
Left	Reduced/Normal/Increased	1/2/3	46	
Right	Reduced/Normal/Increased	1/2/3	47	
Supinator				
Left	Reduced/Normal/Increased	1/2/3	48	
Right	Reduced/Normal/Increased	1/2/3	49	
Triceps				
Left	Reduced/Normal/Increased	1/2/3	50	
Right	Reduced/Normal/Increased	1/2/3	51	

Lower limbs :

Knee				
Left	Reduced/Normal/Increased	1/2/3	52	
Right	Reduced/Normal/Increased	1/2/3	53	
Ankle				
Left	Reduced/Normal/Increased	1/2/3	54	
Right	Reduced/Normal/Increased	1/2/3	55	

PLANTAR RESPONSE

Left	Flexor/Extensor/Equivocal	1/2/3		56	
Right	Flexor/Extensor/Equivocal	1/2/3		57	

MOVEMENT DISORDERS

Face				
Spontaneous involuntary movements	Present/Absent	1/2	58	
Trunk				
Spontaneous involuntary movements	Present/Absent	1/2	59	

UPPER LIMBS

Left				
Spontaneous involuntary movements	Present/Absent	1/2	60	
Right				
Spontaneous involuntary movements	Present/Absent	1/2	61	

LOWER LIMBS

Left				
Spontaneous involuntary movements	Present/Absent	1/2	62	
Right				
Spontaneous involuntary movements	Present/Absent	1/2	63	

GAIT

Normal/Equivocal/Definitely abnormal		1/2/3	64	

CURRENT BEHAVIOUR SCHEDULE

To be based on information given by ward staff

Identification: Survey number 1-3 [ ][ ][ ]

Date of inquiry 4-9 [ ][ ][ ][ ][ ][ ]

10 [3]

Name of patient.....

Name of informant.....

How long has informant known patient:

years(2), months(1), weeks(0) 11 [ ]

Status of informant.....

A: SOCIAL BEHAVIOUR

Spontaneous contacts;

patient initiates full sensible conversations (2) 12 [ ]

patient initiates brief sensible verbal exchanges (1)

(greetings, factual exchanges, etc.)

no sensible spontaneous contacts (0)

Response to approaches;

patient will engage in full sensible conversations (2) 13 [ ]

patient makes appropriate, but limited

verbal responses (1)

patient does not respond appropriately

or patient does not respond at all (0)

Ability to carry out instructions;

carries out complex instructions (2) 14 [ ]

carries out simple instructions (1)

does not carry out instructions (0)

General social behaviour;

feeding; acceptable (2), poor (1), very degraded (0) 15 [ ]

dressing; acceptable (2), poor (1), very degraded (0) 16 [ ]

cleanliness; acceptable (2), poor (1),

very degraded (0) 17 [ ]

verbal hostility, non-verbal hostility, stealing,
destruction, self mutilation etc.) 18 ☐
Specify.....
None (3), occasional (2), frequent, but mild (1),
frequent and severe (0)

Appearance (dress, etc.); normal (2), slightly odd (1),
bizarre (0) 19 ☐
Specify.....

Social withdrawal; mixes normally (2) 20 ☐
usually solitary, but will mix (1)
never mixes (0)

B: ACTIVITIES

Employment: open employment outside hospital (4) 21 ☐
sheltered employment outside (3)
work outside ward (2)
work on ward (1)
no work (0)
Specify.....

Leisure activities; major activities (clubhouse,
arts & crafts, outings, etc.) (2) 22 ☐
minor activities (television, newspaper,
solitary walks) (1)
no activities (0)
Specify.....

General level of activity;
patient grossly overactive (3) 23 ☐
keeps active without encouragement (2)
some underactivity (e.g. stays in bed) (1)
gross underactivity (0)

Nature of activity: activity mostly useful (2)
some purposeless activity (1) 24 ☐
all activity purposeless (0)

C: EXHIBITED BEHAVIOUR

Does the patient laugh and talk to himself;
never (2) 25 ☐
sometimes (1)
often (0)

no evidence (2)
indirect evidence (1)
direct evidence from patient (0) 26 ☐
Specify.....

Delusions:
no evidence (2) 27 ☐
indirect evidence (1)
direct evidence from patient (0)
Specify.....

Posturing and mannerisms (e.g. odd, stylised movements or acts, maintaining strange postures, etc.) 28 ☐
never, (2), sometimes, (1), often, (0)
Specify.....

Obsessional activities (e.g. repetitive and purposeless behaviours)
never (2), sometimes (1), often (0) 29 ☐
Specify.....

Does the patient talk nonsense;
never (2), sometimes (1), often (0) 30 ☐

Uncontrolled, aggressive outbursts;
never (2), sometimes (1), often (0) 31 ☐

Incontinence; never (3)
occasional urinary (at least once a month), (2)
frequent urinary (at least twice a week) (1)
urinary and faecal incontinence (0) 32 ☐

Stability of behaviour;
very stable (2), some variation (1), much variation (0) 33 ☐

D: MEDICATION

Does the patient take medication;
without difficulty (2)
with some difficulty (1)
with great difficulty (0) 34 ☐
What is the current medication.....

ANY OTHER COMMENTS:

IDENTIFICATION

Survey number

Date of form

DATE OF BIRTH - Day/Month/Year

SEX - M/F 1/2

DATE OF 1st ADMISSION - YEAR

DATE OF CURRENT ADMISSION - YEAR

NUMBER OF PSYCHIATRIC ADMISSIONS
(Transfer does not equal admission)

EARLY HISTORY

Informant - mother/relative/other 1/2/3
Specify.....

Any relatives with schizophrenia? - DK/YES/NO 0/1/2

How many?

Any relatives with other psych. illness? - DK/YES/NO 0/1/2
How many?

Birth trauma? - DK/YES/NO 0/1/2

Normal infant development? - DK/YES/NO 0/1/2

Any febrile illnesses? - DK/YES/NO 0/1/2
Specify.....

Any head injuries? - DK/YES/NO 0/1/2
Specify.....

Any fits? - DK/YES/NO 0/1/2
Specify.....

School record - DK/ESN/NORMAL/HIGHER 0/1/2/3
Specify.....

Job record - DK/UNEMPLOYED/MANY JOBS/STEADY 0/1/2/3
Specify.....

Social adjustment (friends, hobbies, etc.)
-DK/POOR/GOOD 0/1/2 ☐

History of alcoholism - DK/YES/NO 0/1/2 ☐

Any other comments.....
.....

TREATMENT

Leucotomy - DK/YES/NO 0/1/2 ☐

Insulin - DK/YES/NO 0/1/2 ☐

How many? ☐☐☐

ECT - DK/YES/No 0/1/2 ☐

How many? ☐☐☐

Phenothiazenes - DK/YES/NO 0/1/2 ☐

Specify.....

Barbiturates - DK/YES/NO 0/1/2 ☐

Specify.....

Paraldehyde - DK/YES/NO 0/1/2 ☐

Specify.....

Chemical convulsants - DK/YES/NO 0/1/2 ☐

Specify.....

Serious illnesses while in hospital YES/No 1/2 ☐

- DK/DETERIORATING/FLUCTUATING/NO CHANGE/IMPROVEMENT 0/1/2/3/4 ☐

ANY OTHER COMMENTS :

ABNORMAL INVOLUNTARY MOVEMENT SCALE (AIMS)

PATIENT'S NAME

APPENDIX VI

RATER

DATE

INSTRUCTIONS: Complete Examination Procedure (reverse side) before making ratings.
MOVEMENT RATINGS: Rate highest severity observed. Rate movements that occur upon activation one *less* than those observed spontaneously.

Code: 0 = None
1 = Minimal, may be extrem
2 = Mild
3 = Moderate
4 = Severe

		(Circle One)
FACIAL AND ORAL MOVEMENTS:	1. Muscles of Facial Expression e.g., movements of forehead, eyebrows, periorbital area, cheeks; include frowning, blinking, smiling, grimacing	0 1 2 3 4
	2. Lips and Perioral Area e.g., puckering, pouting, smacking	0 1 2 3 4
	3. Jaw e.g., biting, clenching, chewing, mouth opening, lateral movement	0 1 2 3 4
	4. Tongue Rate only increase in movement both in and out of mouth, NOT inability to sustain movement	0 1 2 3 4
EXTREMITY MOVEMENTS:	5. Upper *(arms, wrists, hands, fingers)* Include choreic movements, (i.e., rapid, objectively purposeless, irregular, spontaneous), athetoid movements (i.e., slow, irregular, complex, serpentine). Do NOT include tremor (i.e., repetitive, regular, rhythmic)	0 1 2 3 4
	6. Lower *(legs, knees, ankles, toes)* e.g., lateral knee movement, foot tapping, heel dropping, foot squirming, inversion and eversion of foot	0 1 2 3 4
TRUNK MOVEMENTS:	7. Neck, shoulders, hips e.g., rocking, twisting, squirming, pelvic gyrations	0 1 2 3 4

GLOBAL JUDGMENTS:	8. Severity of abnormal movements	None, normal	0
		Minimal	1
		Mild	2
		Moderate	3
		Severe	4
	9. Incapacitation due to abnormal movements	None, normal	0
		Minimal	1
		Mild	2
		Moderate	3
		Severe	4
	10. Patient's awareness of abnormal movements Rate only patient's report	No awareness	0
		Aware, no distress	1
		Aware, mild distress	2
		Aware, moderate distress	3
		Aware, severe distress	4
DENTAL STATUS:	11. Current problems with teeth and/or dentures	No	0
		Yes	1
	12. Does patient usually wear dentures?	No	0
		Yes	1

Either before or after completing the Examination Procedure observe the patient unobtrusively, at rest (e.g., in waiting room).

The chair to be used in this examination should be a hard, firm one without arms.

---

1. Ask patient whether there is anything in his/her mouth (i.e., gum, candy, etc.) and if there is, to remove it.

2. Ask patient about the current condition of his/her teeth. Ask patient if he/she wears dentures. Do teeth or dentures bother patient now?

3. Ask patient whether he/she notices any movements in mouth, face, hands, or feet. If yes, ask to describe and to what extent they currently bother patient or interfere with his/her activities.

4. Have patient sit in chair with hands on knees, legs slightly apart, and feet flat on floor. (Look at entire body for movements while in this position).

5. Ask patient to sit with hands hanging unsupported. If male, between legs, if female and wearing a dress, hanging over knees. (Observe hands and other body areas.)

6. Ask patient to open mouth. (Observe tongue at rest within mouth.) Do this twice.

7. Ask patient to protrude tongue. (Observe abnormalities of tongue movement.) Do this twice.

8. Ask patient to tap thumb, with each finger, as rapidly as possible for 10--15 seconds; separately with right hand, then with left hand. (Observe facial and leg movements.)

9. Flex and extend patient's left and right arms (one at a time.) (Note any rigidity and rate on DOTES.)

10. Ask patient to stand up. (Observe in profile. Observe all body areas again, hips included.)

11. Ask patient to extend both arms outstretched in front with palms down. (Observe trunk, legs, and mouth.)

12. Have patient walk a few paces, turn, and walk back to chair. (Observe hands and gait.) Do this twice.

Activated movements

ROCKLAND RESEARCH INSTITUTE
TARDIVE DYSKINESIA RATING SCALE

Patient _____ _____ a.m.

Date _____ Time _____ p.m.

Setting _____ Rater _____

	Absent	?	Mild	Moderate	Moderately severe	Very severe
FACE						
1. Blinking of eyes	0	1	2	3	4	5
2. Tremor of eyelids	0	1	2	3	4	5
3. Tremor of upper lip (Rabbit Syndrome)	0	1	2	3	4	5
4. Pouting of the (lower) lip	0	1	2	3	4	5
5. Puckering of lips	0	1	2	3	4	5
6. Sucking movements	0	1	2	3	4	5
7. Chewing movements	0	1	2	3	4	5
8. Smacking of lips	0	1	2	3	4	5
9. Bon Bon sign	0	1	2	3	4	5
10. Tongue protursion	0	1	2	3	4	5
11. Tongue tremor	0	1	2	3	4	5
12. Choreoathetoid movements of the tongue	0	1	2	3	4	5
13. Facial Tics	0	1	2	3	4	5
14. Grimacing	0	1	2	3	4	5
15. Other movements (when periorbital in situation)	0	1	2	3	4	5
16. Other movements (when perioral in situation)	0	1	2	3	4	5
NECK AND TRUNK						
17. Head nodding	0	1	2	3	4	5
18. Retrocollis	0	1	2	3	4	5
19. Spasmodic Torticollis	0	1	2	3	4	5
20. Torsion movements (trunk)	0	1	2	3	4	5
21. Axial Hyperkinesia	0	1	2	3	4	5

		Absent	?	Mild	Moderate	Moderately severe	Very severe
22.	Rocking movement	0	1	2	3	4	5
23.	Other movements (when involving upper limb girdle)	0	1	2	3	4	5
24.	Other movements (when involving axial musculature)	0	1	2	3	4	5
EXTREMITIES							
(Upper)							
25.	Ballistic movements	0	1	2	3	4	5
26.	Choreoathetoid movements - fingers	0	1	2	3	4	5
27.	Choreoathetoid movements - wrists	0	1	2	3	4	5
28.	Pill-rolling movements	0	1	2	3	4	5
29.	Carressing or rubbing face and hair	0	1	2	3	4	5
30.	Rubbing of thighs	0	1	2	3	4	5
31.	Other (fine regular tremor of upper limbs)	0	1	2	3	4	5
32.	Other (additional involuntary movements involving upper limbs)	0	1	2	3	4	5
(Lower)							
33.	Rotation and/or flexion of ankles	0	1	2	3	4	5
34.	Toe movements	0	1	2	3	4	5
35.	Stamping movements - standing	0	1	2	3	4	5
36.	Stamping movements - sitting	0	1	2	3	4	5
37.	Restless legs	0	1	2	3	4	5
38.	Crossing/uncrossing legs - sitting	0	1	2	3	4	5
39.	Other (fine regular tremor of lower limbs)	0	1	2	3	4	5
40.	Other (additional involuntary movements involving lower limbs)	0	1	2	3	4	5

ENTIRE BODY	Absent	?	Mild	Moderate	Moderately severe	Very severe
41. Holokinetic movements	0	1	2	3	4	5
42. Akathisia	0	1	2	3	4	5
43. Other (whole-body) movements	0	1	2	3	4	5

COMMENTS

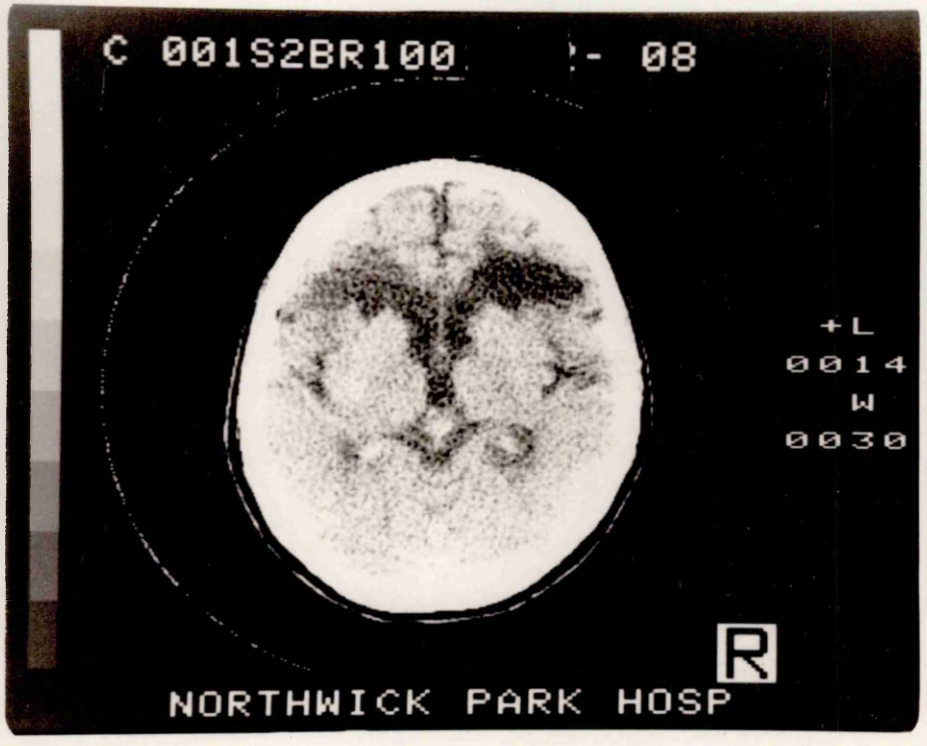
_____

_____

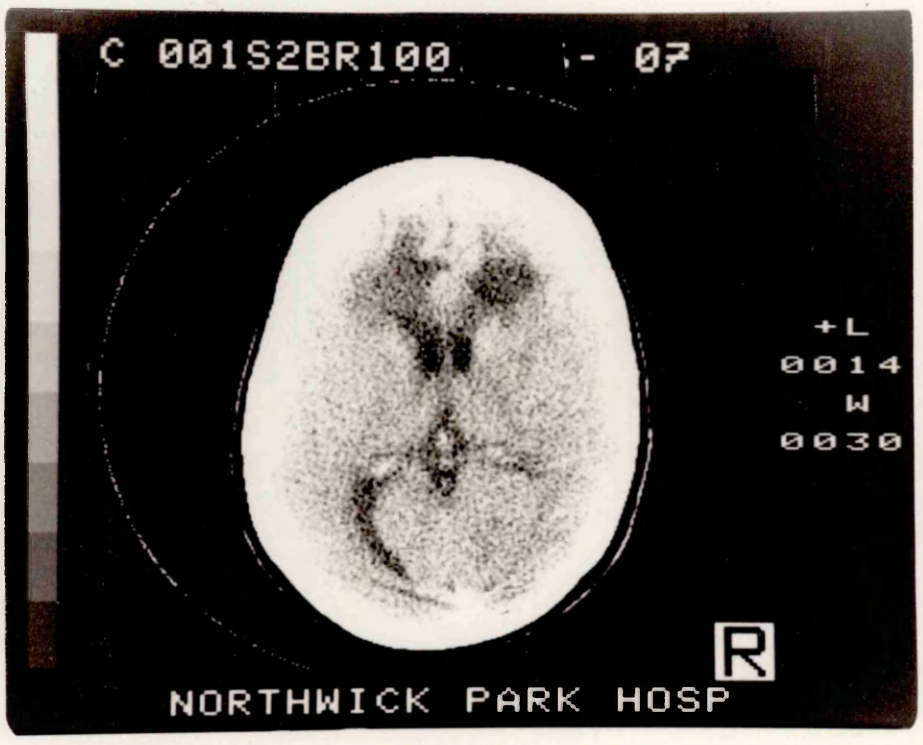
APPENDIX VIII — CT SCANS

POST - LEUCOTOMY

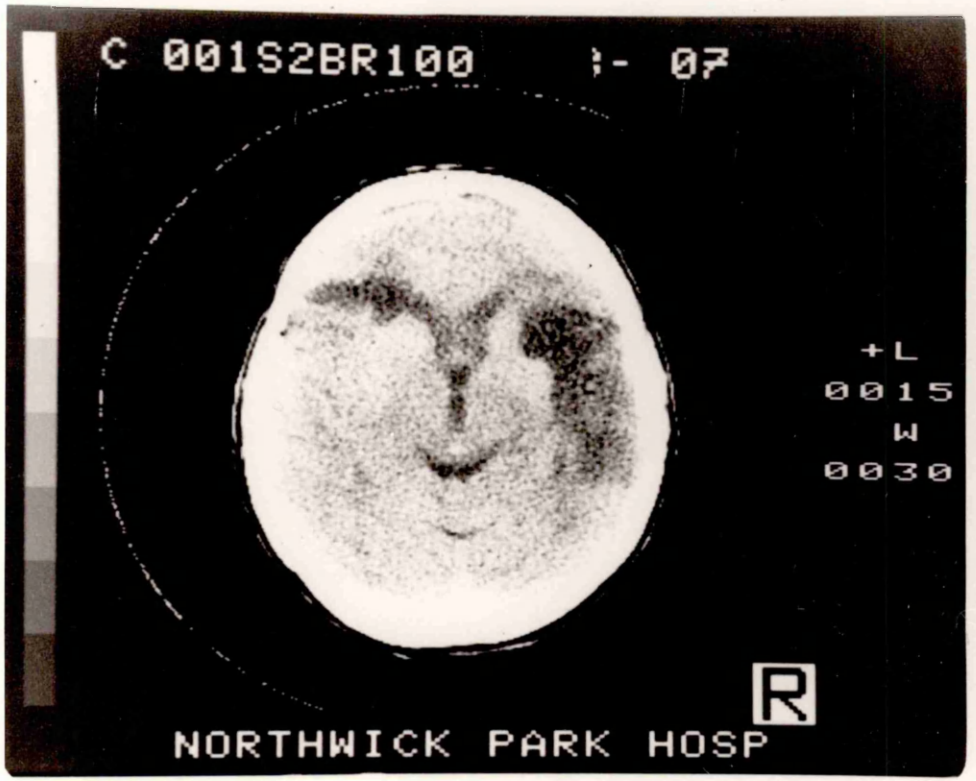
PREFRONTAL

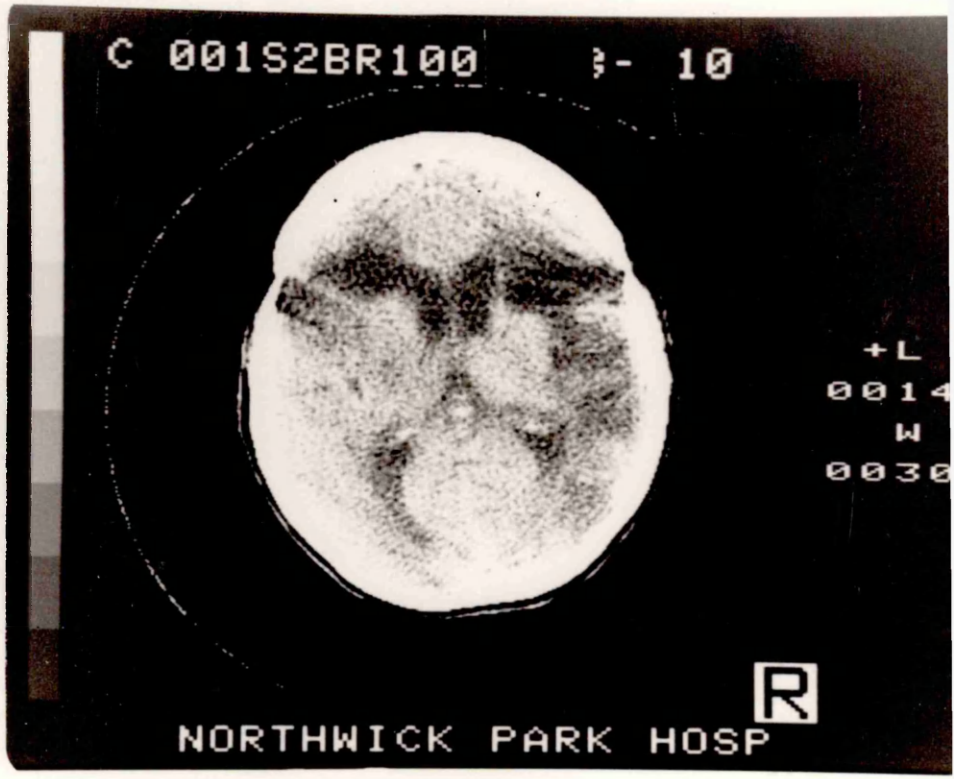


BIMEDIAL



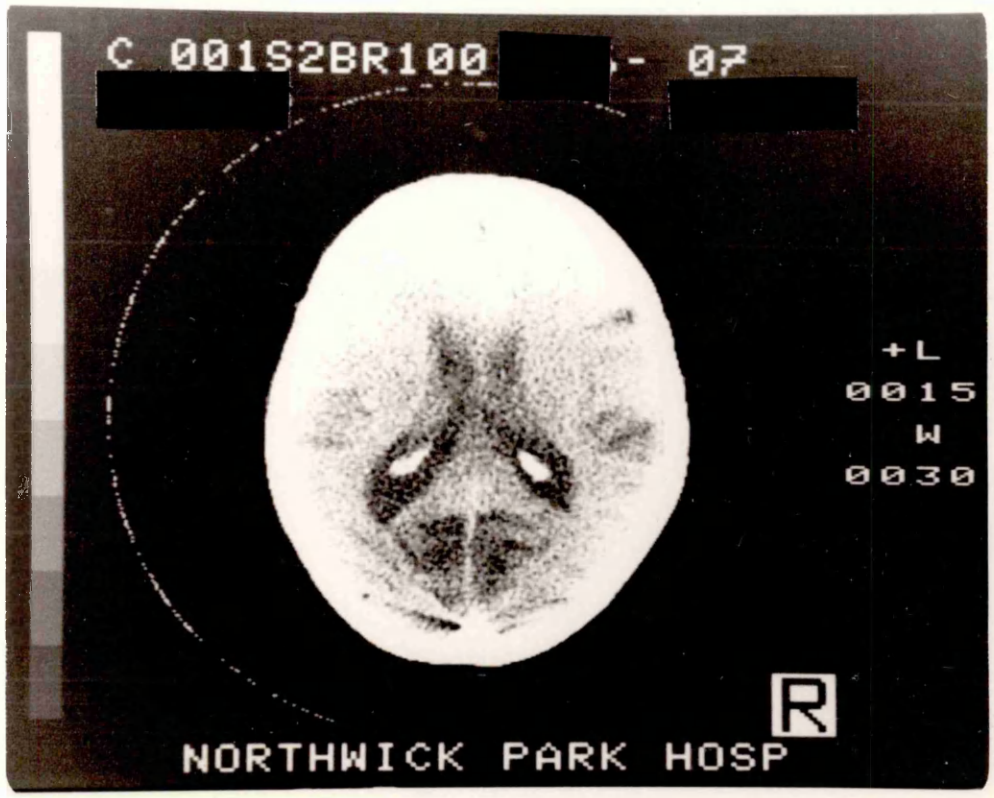
LEUCOTOMY COMPLICATED BY EXTENSIVE R SIDED INFARCTION



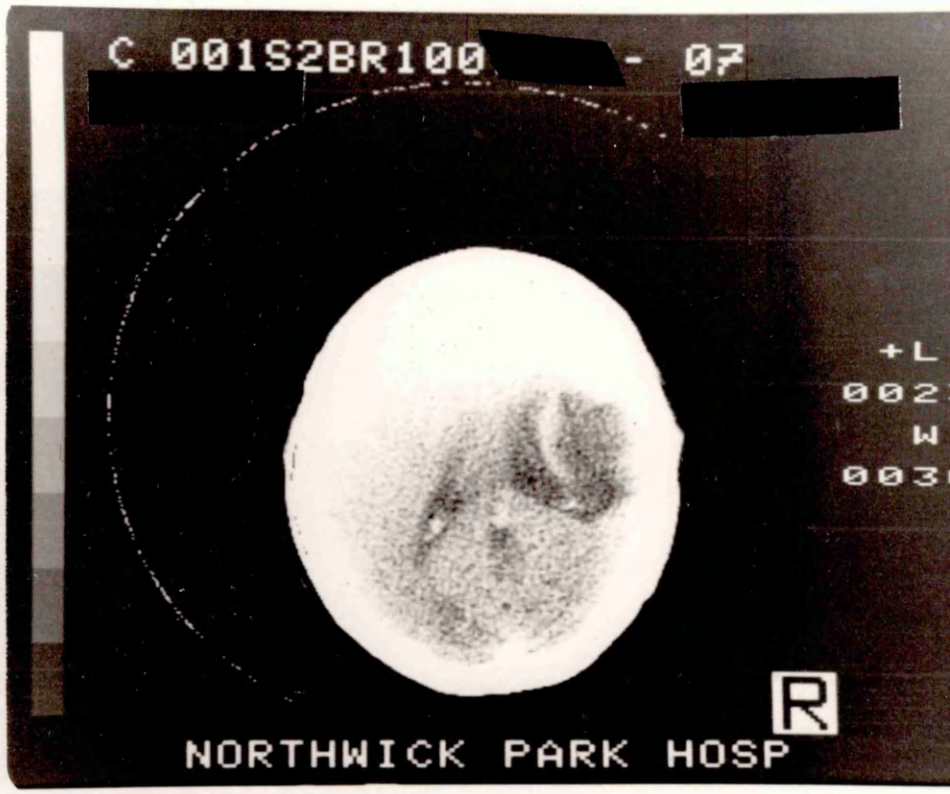


INCIDENTAL PATHOLOGY

MULTIPLE INFARCTS

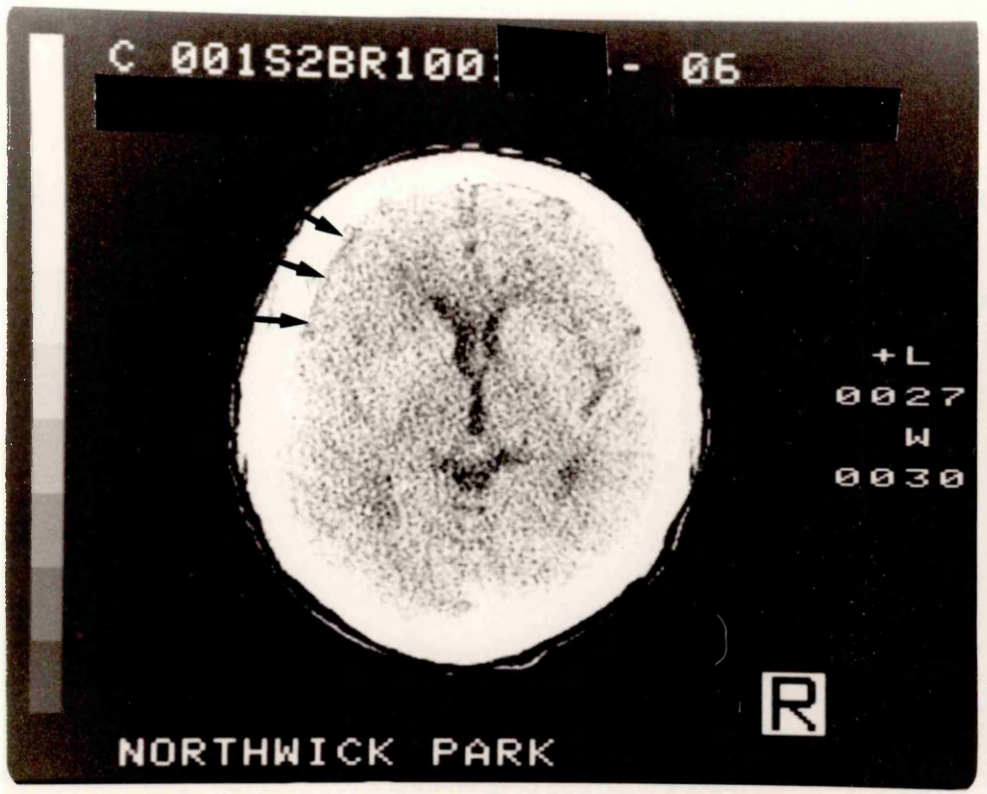


CONGENITAL HEMIPLEGIA



INCIDENTAL PATHOLOGY

SMALL (L) SUBDURAL HAEMATOMA



CYSTIC ENLARGEMENT OF THE PINEAL