NEUROANATOMICAL ASPECTS OF SCHIZOPHRENIA

by

ROBERT GORDON BANKIER

M.B.,Ch.B.,D.Psych.,M.Sc.,M.R.C.Psych.,F.R.C.P.(C).

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Dedicated to

the late John Baskerville Hyde, Ph.D.

who encouraged me to become

a graduate student

and to my wife

Margaret Isabel

who patiently endured the consequences

Babylon in all its desolation is a sight not so awful as that of the human mind in ruins.

Scrope Berdmore Davies (1783-1852).

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ABSTRACT

For the last few years there have been reports in the literature claiming that the dementia which is often seen in chronic schizophrenia is associated with enlargement of cerebral ventricles and in particular the third ventricle. It has been proposed that an atrophic process affecting mainly the periventricular grey matter results in an enlargement of the third ventricle and is causally related to the lack of drive, emotional blunting, cognitive disturbances and social rehabilitation problems characteristic of chronic schizophrenia.

The objectives of this study were to determine the size of the third ventricle in schizophrenics and whether there is any relationship between third ventricle size and the organic brain impairment which is a characteristic of chronic schizophrenia.

Three groups of subjects were studied:

Group 1. Fifty healthy subjects from hospital staff who had no personal or family history of mental illness and no history of epilepsy, head injury or intracranial disease.

Group 2. Forty-three hospitalized chronic schizophrenic patients were selected from a total of 142 patients surveyed. Epileptics, chronic alcoholics and those with a history of head injury and intracranial disease were rejected. Also excluded were patients recently treated with electroconvulsive therapy.

Group 3. Forty-five acutely ill schizophrenics recently admitted to hospital and also screened to exclude physical illness of a

neurological type.

The third ventricle width was established by using an ultrasonic transducer which produced echoes on the calibrated display of a cathode ray oscilloscope. Brain function was tested by means of a broad battery of neuropsychological tests giving a total of 52 variables measured. All data were submitted to statistical analysis. Results of the study showed that:

1. While the mean width of the third ventricle in the chronic schizophrenic group was significantly ($p<0.01$) greater than that of the other two groups, only six of the 43 subjects (14%) had enlarged ventricles according to the generally accepted normal maximum width.

2. Both patient groups showed evidence of impaired brain function on the neuropsychological tests but the chronic group was significantly impaired.

3. Discriminant analysis of the data revealed 20 neuropsychological tests which were the best discriminators of the groups. These were found to be tests which could be related to temporal and parietal lobe function and also to left frontal lobe function. However one must interpret these findings with caution.

4. Comparison of the 10 chronic patients with the largest ventricles versus those with ventricles of less than 8 mm revealed only a few (10 out of 52) variables which showed a significant difference between the two subgroups.

In conclusion, it may be stated that only a small percentage of schizophrenic patients developed an enlarged third ventricle; the disturbance of brain function is global in nature although there are

suggestions that the temporo- parietal and left frontal cortex are most affected in chronic schizophrenia; the degree of impaired brain function is not related to ventricle size.

Anatomical relations between the periventricular grey matter of the diencephalon and the temporo-parietal cortex are discussed and avenues for future research are proposed.

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LIST OF ABBREVIATIONS

ANOVA	: analysis of variance
cAMP	: 3,5 cyclic adenosine monophosphatase
CEEG	: computerised electroencephalogram
CSF	: cerebrospinal fluid
CT	: computerised tomography
DA	: dopamine
DEγE	: des-enkephalin-γ-endorphin
3,4 DMPEA	: 3,4 dimethoxy-phenylethanolamine
DTγE	: des-tryosine-γ-endorphin
ECT	: electro-convulsive therapy
EEG	: electroencephalogram
GABA	: γ-aminobutyric acid
GH	: growth hormone
HLA	: human lymphocyte antigen
HRNB	: Halstead-Reitan neuropsychological battery
5-HT	: 5-hydroxy-tryptamine
ICT	: insulin coma therapy
L-DOPA	: L-dihydroxyphenylalanine
MHPG	: 3 methoxy-4-hydroxy-phenylglycerol
NGF	: nerve growth factor
NREM	: non-rapid eye movement (sleep)
PEG	: pneumoencephalogram
RAS	: reticular activating system
REM	: rapid eye movement (sleep)
WAIS	: Weschler Adult Intelligence Scale

PREFACE

The discovery in 1905 of the spirochaeta pallida by Schaudinn and Hoffman (cited in Haggard: Devils, Drugs and Doctors) generated a wave of excitement and enthusiasm throughout the medical world. Here at last was the culprit responsible for the crippling, disfiguring and dementing diseases that filled so many mental hospital beds. The treatment of syphilis was revolutionized and soon antiluetic agents were introduced.

Noguchi in 1913 (cited in Haggard: Devils, Drugs and Doctors) demonstrated the spirochaete in the brains of patients suffering from general paresis of the insane. He was later able to transmit infection from human brain tissue to rabbits. These findings brought hope to psychiatrists who were coping with great numbers of demented, psychotic and retarded patients in badly overcrowded mental hospitals. Now that the cause of one mental disease was known, it seemed reasonable to assume that all mental diseases were caused by micro organisms and so the search was on.

Apart from general paresis and mental retardation, the next biggest problem in mental hospitals was dementia praecox, to be renamed schizophrenia by Eugen Bleuler in 1911. While the search for an organism and structural pathology was intense, all efforts proved to be fruitless and enthusiasm gradually waned. There are probably two main reasons for this: first, the unsophisticated (by today's standards) laboratory techniques and equipment that were then available and secondly, the advent of Sigmund Freud and his psychoanalytic theory. Here was a panacea for the weary physician. An explanation of mental illness that did not depend on organisms or pathology, but laid the blame on psychological mechanisms and developmental experiences. Although accepted timidly and cautiously at

first, the new gospel gradually gained strength and in the face of unproductive biological research, was eventually established as psychiatric doctrine.

Ironically, Freud was a neurologist and reputedly a skilled neuropathologist and neuroanatomist who apparently never lost his interest in basic sciences. Nevertheless, the neurobiology of mental disease was shelved to await the birth of the neurochemist, the electro-encephalograph, ultrasonography and in recent years, computerized axial tomography.

The research presented in this thesis serves to demonstrate both structural pathology in the brains of some schizophrenic patients and functional disturbances of perception and cognition which are compatible with cerebral pathology, but not necessarily related to the structural changes. Possible avenues for future research are discussed and some speculative suggestions concerning the neuroanatomical basis of schizophrenia are advanced.

INTRODUCTION AND REVIEW OF LITERATURE

The last decade has seen a renewed interest in the search for a biological lesion in schizophrenia. This is largely due to the diverse applications of computer science and the refinements of microchemistry and microscopy. Major contributions from the field of neuroscience are relevant to this research and will be reviewed.

Neurophysiology

The first recording of a human electroencephalogram (EEG) by Hans Berger (15) in 1929 set the stage for an objective scientific and non-intrusive study of brain function in both health and disease. Mental hospital patients were readily available and it was not long before EEG studies of schizophrenics began to appear in the literature. Lemere (129) as early as 1936 said "the apathy and affective deficiency of the schizophrenic is the feature of the illness most clearly related to an absent or 'poor' alpha rhythm". This was supported by Gibbs (57) who also studied frequency spectra of the EEG and noted that in addition to less alpha activity, schizophrenics have more fast activity than normal subjects. Davis (37) reported that 61% of schizophrenics have low amplitude disorganized fast tracings and coined the descriptive term "choppy rhythm" as a diagnostic feature.

The first description of the brain stem reticular formation by Moruzzi and Magoun (156) in 1949 was followed by the observation that stimulation of the reticular formation produces desynchronized fast activity in the EEG. Hill (91) was quick to conclude that the low voltage fast beta activity emanated from subcortical mechanisms. The

FIG. 1. Electroencephalograph (bipolar montage) from an acutely ill young adult male schizophrenic.

Locations of scalp electrodes

A1 - Left ear

A2 - Right ear

Fp1 - Left pre-frontal

Fp2 - Right pre-frontal

F3 - Left frontal

F4 - Right frontal

F7 - Left anterior temporal

F8 - Right anterior temporal

T3 - Left mid-temporal

T4 - Right mid-temporal

T5 - Left posterior temporal

T6 - Right posterior temporal

C3 - Left central

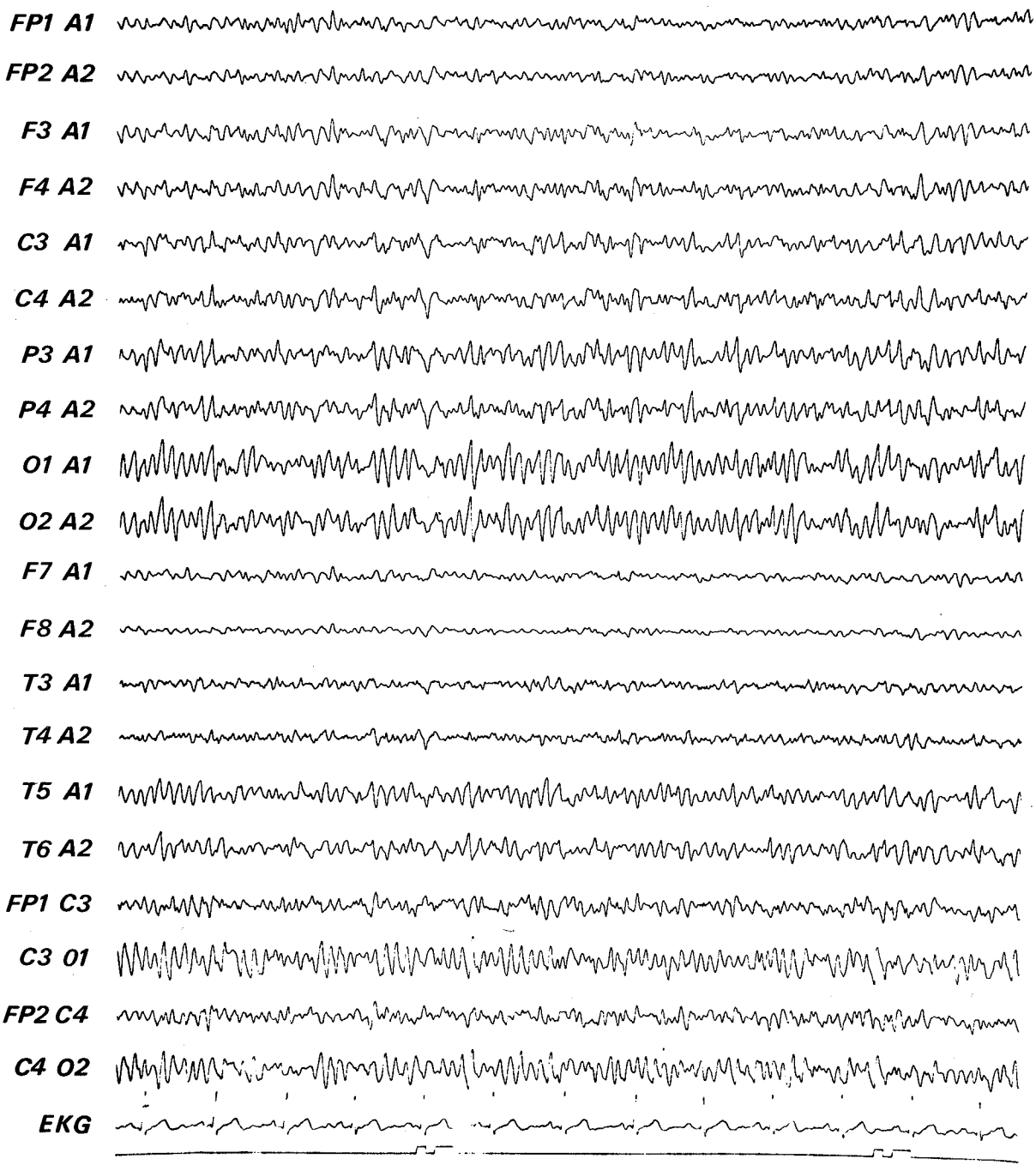
C4 - Right central

P3 - Left parietal

P4 - Right parietal

O1 - Left occipital

O2 - Right occipital


FP1 A1
FP2 A2
F3 A1
F4 A2
C3 A1
C4 A2
P3 A1
P4 A2
O1 A1
O2 A2
F7 A1
F8 A2
T3 A1
T4 A2
T5 A1
T6 A2
FP1 C3
C3 01
FP2 C4
C4 O2
EKG

introduction of hallucinogens, both illicit and for authorized experimental use, led to comparisons with schizophrenic psychosis and speculation about a common pathological basis. Fink (47) showed that hallucinogens of both anticholinergic and indole types produced an increased amount of fast beta activity and a diminished amount of alpha activity similar to that reported in schizophrenics.

At this stage EEG research into schizophrenia reached an impasse and enthusiasm waned. This was largely due to the limitations of technical equipment and to crude interpretative and analytical methods which were dependent on visuomanual techniques. The last decade has seen the application of computer analysis to EEG components especially frequency and power spectra, and studies of evoked potentials, with a resultant re-awakening of interest.

Studies of the computer-analysed electroencephalogram (CEEG) by Itil (101,104,105) and Itil and colleagues (100, 102,103) have demonstrated characteristic features of schizophrenia. These included: 1) high frequency beta (50-70 Hz) activity, 2) a diminished amount of alpha (8-13 Hz) activity, 3) an increased amount of low voltage delta (0.5-3.5 Hz) activity, 4) a shorter latency period in auditory evoked potentials. Itil (105) suggested that low voltage very fast activity is a correlate of schizophrenia and in his follow-up of 100 patients noted that those patients with typical CEEG findings showed a better response to neuroleptic drug treatment. Furthermore, as the clinical condition improved the CEEG showed a return to normal pattern. It is interesting that in a comparison of high risk children (children of schizophrenic parents) with normal children, the former showed to a significant degree ($p<0.01$)

the CEEG pattern of schizophrenia (102). One could assume that in schizophrenia there is a state of fluctuating vigilance characterized by over-activity of the reticular activating system (RAS) producing hyper-arousal and at other times slow low voltage delta activity.

Results from evoked potential studies have been variable and inconclusive. Itil (102) and Shagass and Schwartz (192) noted a faster latency period with visual evoked responses and in other studies (192-196) increased amplitude of somato-sensory response to stimuli of varying intensity. A more consistent finding has been a lower than normal amplitude of the auditory evoked response in schizophrenics (113,187). The significance of these observations is far from clear.

The discovery of rapid eye movement (REM) sleep by Aserinsky and Kleitman (9) in 1953 opened up research into sleep patterns in health and disease. These workers believed non-REM (NREM) sleep to be primarily a cortical phenomenon resulting from inhibition of the RAS (telencephalic sleep) and REM sleep to be the activity induced and maintained by pontine mechanisms (rhombencephalic sleep). Jouvet (114) studying the histochemistry of the sleep-waking cycle concluded that NREM sleep is controlled by the release of serotonin from neurons in the anterior raphe system while activity in other more posterior neurons "primes" the REM sleep mechanisms by interaction with catecholamine-containing and acetylcholine-containing neurons of the locus coeruleus.

Studying the sleep patterns of schizophrenics, Caldwell and Domino (23) and Feinberg et al. (45) reported that these patients typically exhibit less stage 4 (deep) sleep than normal subjects. Itil et al. (100) confirmed this finding and in addition observed very fast activity and less delta activity during the REM phases. Schizophrenics also have more

awakening periods. Other studies by Luby and Caldwell (135), Zarcone et al. (231) and Karacan et al. (116) showed that schizophrenics do not respond to sleep deprivation by compensatory increases in REM and stage 4 sleep during recovery nights. Zarcone et al. (231) suggested that the REM sleep mechanism is affected by the schizophrenic process and Karacan et al. (116) were able to reduce the amount of REM sleep by using para-chlorophenylalanine to block the synthesis of serotonin. They also claimed that an increase in catecholamine levels or a decrease in acetylcholine levels will also reduce the amount of REM sleep.

An intriguing and rewarding area of research has been explored by Heath and his colleagues (75-79) at Tulane University in an attempt to identify the neuroanatomical substrate of human emotions. Surface and chronically implanted depth electrodes have been used in both animal and human subjects employing electro-stimulant and destructive (in animals) techniques. Heath (75) and Heath and Mickle (76) in their early work with depth electrodes noted that destruction of the septal region (Fig. 5) of animals' brains resulted in emotional flattening and diminished awareness while stimulation produced pleasure and heightened awareness. Subsequent human studies (77,80,83,85) confirmed that areas of the brain which generated pleasure on stimulation included the septal region, the medial forebrain bundle and interpeduncular nuclei in the mesencephalon. Given an opportunity for self-stimulation, subjects invariably and frequently stimulated these areas (77). A similar pleasure response was obtained when acetylcholine was injected into the pleasure sites (79). During pleasure states, high amplitude slow wave activity was recorded from the septal region and during intense pleasure such as sexual orgasm, high amplitude spike activity appeared (78,79,85).

By contrast, Heath and his co-workers (77,79,83) showed that stimulation of the hippocampus, the amygdala, periaqueductal sites in the mesencephalon and the medial hypothalamus near the third ventricle produced an adverse reaction with fear and rage. Patients abstained from self-stimulation of these sites. Certain epileptic patients who experienced an aura of fear prior to a seizure produced epileptiform activity from the hippocampus and amygdala (83). Heath (86) pointed out that the clinical features of schizophrenia are characterized by impairment of feelings and emotional expression, fluctuating levels of awareness, disturbances of sensory perception and hallucinations. An inability to integrate pleasurable feelings and outbursts of anger and/or fear are commonly seen. Heath postulated that in schizophrenia there exists a deficiency in the pleasure-pain systems which is intimately connected to the sensory perceptive system. This is supported by studies with depth electrodes in monkeys. Electrodes were placed in the lateral posterior ventral nucleus of the thalamus (somato-sensory), the fastigial nuclei of the cerebellum (proprioceptive), the medial geniculate bodies (audition) and the lateral geniculate bodies (vision) as well as the pleasure and aversion areas described. He was able to demonstrate direct monosynaptic connections between the sensory nuclei and the sites of emotional expression. The pathways have subsequently been verified by anatomical techniques (72). In human subjects it has been noted that the ability to experience pleasure is reduced if the function of the septal region is impaired; for example, in acute psychotic episodes when spikes and slow wave activity are recorded (86), under the influence of hallucinogenic drugs (80), or if spiking is induced in the septal region by electrical stimulation (77). Figures 2, 3 and 4 show location and connections of the septal area.

FIG. 2. View of the base of the brain showing anatomical relationships of major components.

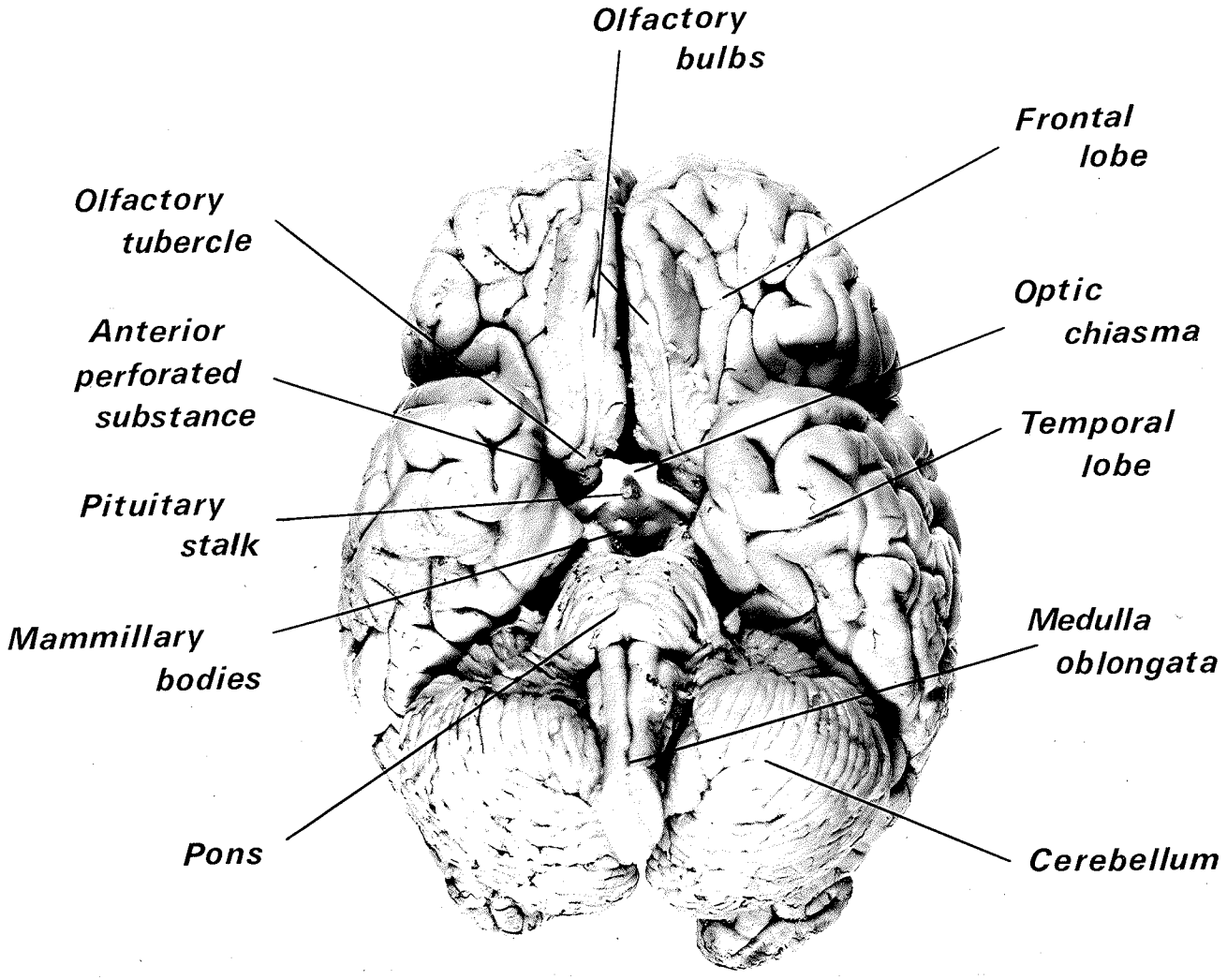

Olfactory bulbs
Frontal lobe
Olfactory tubercle
Optic chiasma
Anterior perforated substance
Temporal lobe
Pituitary stalk
Mammillary bodies
Medulla oblongata
Pons
Cerebellum

FIG. 3. Enlarged view of the base of the brain showing ventral aspect of the septal cortex (sub-callosal area).

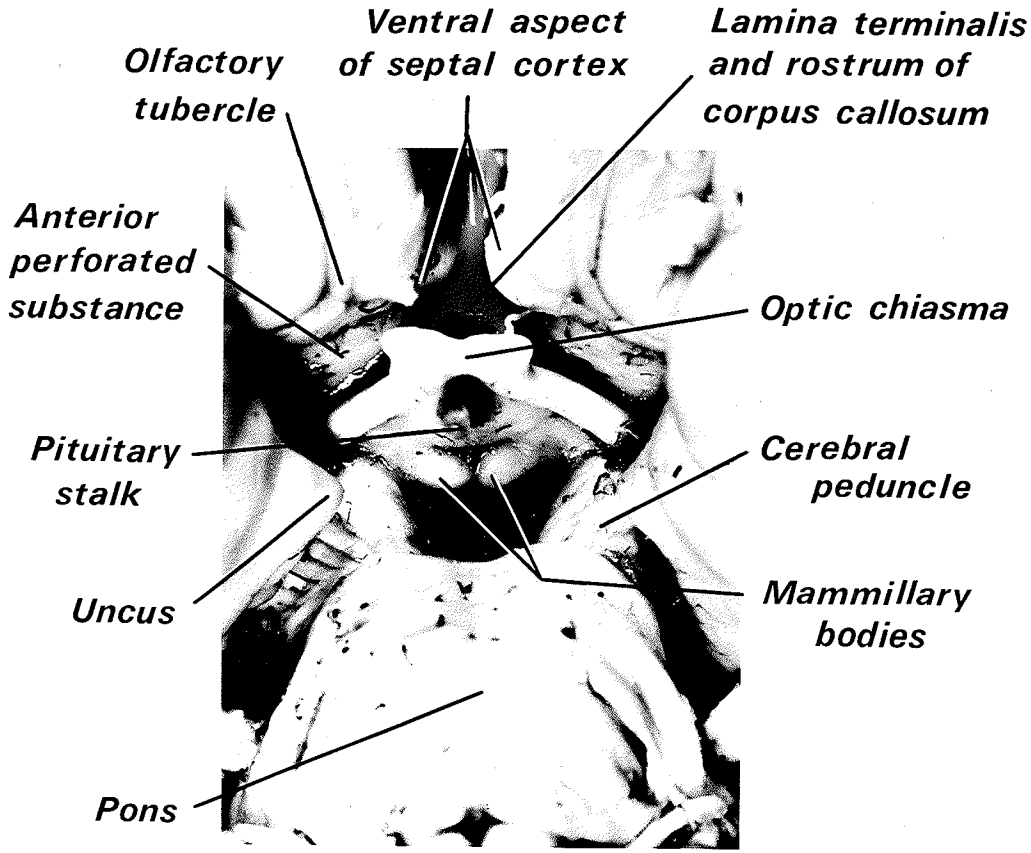

Olfactory tubercle
Ventral aspect of septal cortex
Lamina terminalis and rostrum of corpus callosum
Anterior perforated substance
Optic chiasma
Pituitary stalk
Cerebral peduncle
Uncus
Mammillary bodies
Pons

FIG. 4. CONNECTIONS OF THE SEPTAL NUCLEI

(a) Efferent (mainly from medial septal nucleus).

.to the midbrain tegmentum and the hypothalamus via the medial forebrain bundle.

.to the habenular nucleus via the stria medullaris then on to the tegmentum via the fasciculus retroflexus.

.to the amydgala via the stria terminalis and also by way of the diagonal band.

.to the hippocampus via the fornix.

.to the anterior and medial thalamus.

(b) Afferent (mainly to lateral septal nucleus).

.from the amygdala via the diagonal band and via the cingulate gyrus.

.from the hippocampus via the fornix.

.from the midbrain tegmentum via the mammillary peduncle.

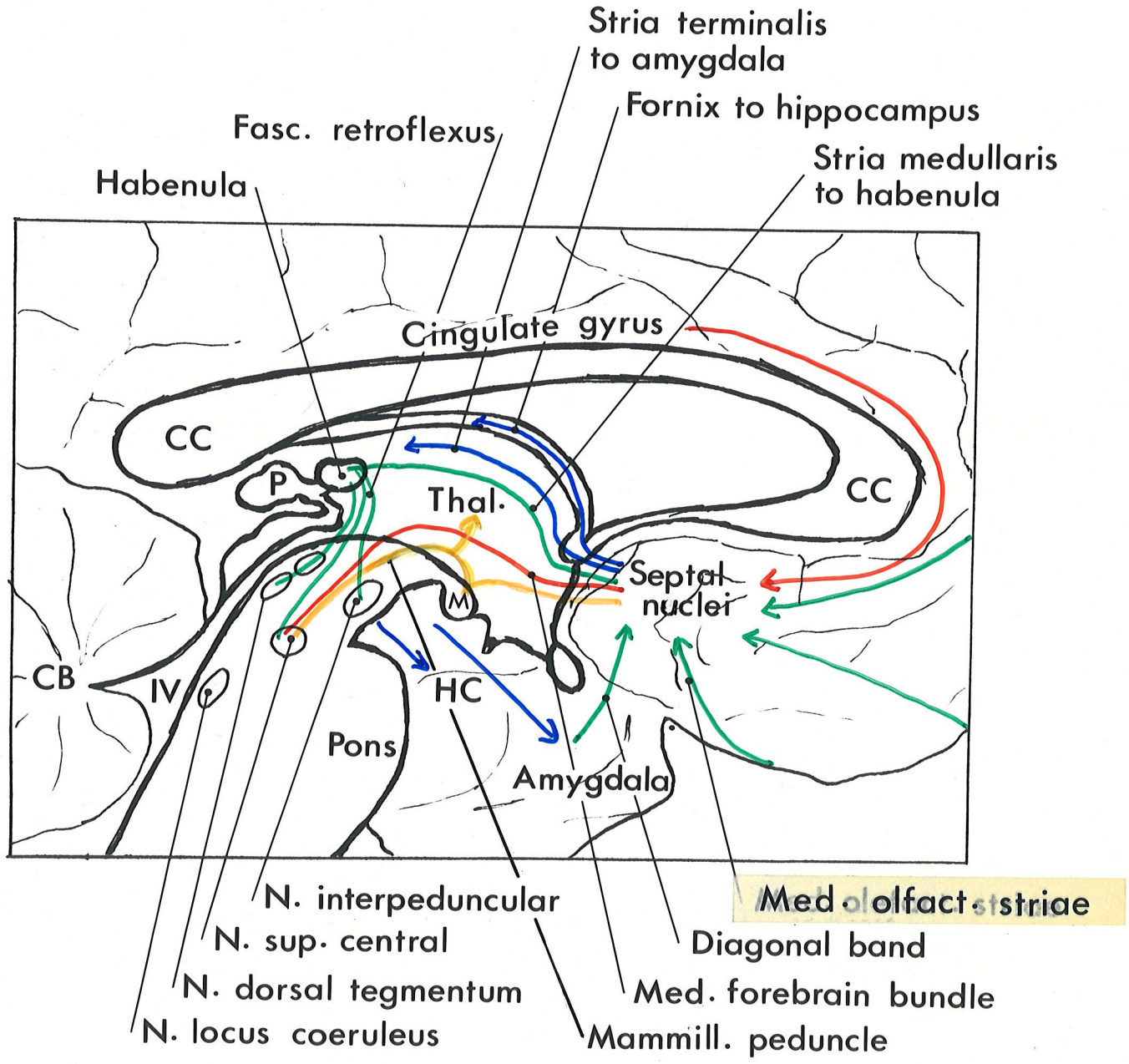
.from the midbrain reticular formation, the locus coeruleus and raphe nuclei via the mammillary peduncle and the medial forebrain bundle.

.from the olfactory tubercle via the medial olfactory striae.

.from areas 9 and 11 (Brodmann) of the pre-frontal cortex.

CB: Cerebellum; CC: Corpus Callosum; HC Hippocampus; M: Mammillary Body; P: Pineal; THAL: Thalamus; IV: Fourth Ventricle.

The med-forebrain bundle, fornix, diagonal band and mammillary peduncle contain afferent and efferent fibers.


Stria terminalis
to amygdala
Fornix to hippocampus
Fasc. retroflexus
Stria medullaris
to habenula
Habenula
Cingulate gyrus
CC
CC
P
Thal.
Septal
nuclei
M
CB
IV
HC
Pons
Amygdala
N. interpeduncular
N. sup. central
N. dorsal tegmentum
N. locus coeruleus
Med. olfact. striae
Diagonal band
Med. forebrain bundle
Mammill. peduncle

Neuropathology

Since schizophrenic patients are usually normal on neurological examination, one would not expect to find any gross neuropathology on examining the brain. Nevertheless there have been reports during the last four decades claiming specific histological changes in the schizophrenic brain. The surgical operation of frontal lobotomy became popular and this afforded access to living tissue for microscopic study. The claims were many and varied. Papez and Bateman (163) noted deformed nuclei, inclusion bodies, vesicular nuclei and increase of microglia and astrocytes. Winkelman and Book (227) found a decreased number of cells, loss of polarity, vacuolation of cytoplasm and fatty infiltration. Unfortunately all of the studies at this time were restricted to frontal cortical tissue although Bateman and Papez (12) studying post-mortem brains also implicated the thalamus. In an exhaustive study by Wolf and Cowan (228) these authors concluded "in the majority of subjects in whom the diagnosis of dementia praecox is made, no obvious morphologic changes in the brain have been encountered.", and Weinstein (224) after reviewing all of the literature concluded that there is no characteristic change in the brains of schizophrenics. However, a recent study by Averback (10) using conventional histological techniques on post-mortem specimens compared 13 schizophrenic brains with an equal number of age and sex matched controls. Sections were examined from the areas of the septal nuclei and the nuclei ansae peduncularis and the author reported a constant finding of swollen neurons, fragmentation of cells, peripherally placed nuclei, bizarre shapes due to vacuolar distortion, lipid distention and abundant pigment in the schizophrenic group but not in the

control group. Since the mean age of the groups was 38 years an aging process was discounted. Similar degenerative changes have been noted in Huntington's and Alzheimer's diseases, but the pigment and lipid laden neurons were a constant feature of the schizophrenic brains which is suggestive of lipid storage diseases. A similar study by Stevens (201) compared brain tissue from 25 schizophrenic patients with a group of 28 age matched non-schizophrenic patients and 20 age matched non-psychiatric patients all of whom had died in hospital during the same time period. Using Holzer's stain for glial fibrils, Stevens was able to demonstrate a marked increase of fibrillary gliosis in the periventricular structures of the diencephalon, the periaqueductal region of the mesencephalon, and in the basal forebrain (septal) region in three-quarters of the schizophrenic group which was not present in the other groups. The structures most affected were the hypothalamus, the midbrain tegmentum and the substantia innominata. Stevens suggested that the appearance was compatible with a low grade inflammatory process. Hopefully recent development of the computer microscope will afford more precise examination of neural structures (148).

Although gross neuropathology has not been evident in schizophrenia, an association between pathology of the basal ganglia and schizophrenia-like illness is well recorded (121). Kalamboukis and Molling (115) and Francis (50) reported schizophreniform psychosis associated with calcification of the basal ganglia and Beard (14) described a relationship to hepatolenticular degeneration. Rosenthal and Bigelow (183) measured the corpora callosa of 10 post-mortem schizophrenic brains and claimed that the structure is wider in schizophrenics compared to controls. More

sophisticated and accurate measurement using computerized tomography (CT) scans has brought to light other interesting differences. LeMay (127) and LeMay and Kido (128) showed that normal right-handed subjects have wider right frontal and left occipital lobes on CT scans. With a similar study of 57 right-handed schizophrenics, Luchins et al. (136) demonstrated a significant reversal of the normal findings. Golden et al. (62) were able to show a lower density in the left anterior area of the brain on CT scans. Other CT scan findings (217) suggested an atrophy of the cerebellar vermis in chronic schizophrenics, although there was no clinical evidence of cerebellar disturbance in the subjects.

Multiregional cerebral blood flow studies using the ^{133}Xenon clearance technique have demonstrated further regional differences in the brains of schizophrenics. Ingvar and his colleagues (51,97,98,99) have demonstrated that while the total cerebral blood flow is normal in chronic schizophrenics, the regional flows are different. They pointed out that increased neuronal activity creates increased metabolic changes with consequent dilatation of cerebral blood vessels. In normal subjects at rest, the cerebral blood flow rate was higher in the frontal regions than it was posterior to the central fissure. In schizophrenics the resting blood flow rate was found to be the reverse. While a painful stimulus resulted in an increased frontal blood flow in normal subjects, a similar stimulus had little effect on the schizophrenic patients (52). The authors suggested that the increased cerebral activity in the post central regions may be related to the perceptual disturbances characteristic of schizophrenia. Mathew et al. (145) also using the ^{133}Xenon inhalation technique compared 23 schizophrenic patients with 18 age and

sex matched controls and showed that the mean cerebral blood flow was less for the patient group but they were unable to demonstrate any differences between hemispheres, medicated or non-medicated patients, paranoid or non-paranoid patients or any relationship to chronicity of the disease. They did, however, find that reduced blood flow in the post-central regions was associated with the clinical symptoms of hallucinations.

Neurochemistry

Although several writers had proposed a biochemical basis of mental illness as early as the nineteenth century, the first major hypothesis was not proposed until 1952 by Osmond and Smythies (158). They proposed an abnormal methylation of norepinephrine in the body with the resultant production of 3, 4-dimethoxy phenylethanolamine (3, 4 DMPEA) which bears some chemical similarities to mescaline, a known psychotogenic substance. It was suggested that this abnormal pathway may be operative in response to stress when the production of catecholamines reaches high levels. The hypothesis gained some support from the observation that methionine loading (250 mgm/Kg body weight) caused a clinical deterioration of schizophrenic patients (7), although cysteine, which is not a methyl-donor has a similar effect (199). The credibility of this hypothesis suffered somewhat when 3, 4 DMPEA was found in the urine of normal subjects and patients with other psychiatric illnesses as well as schizophrenia. Nevertheless, these studies laid the groundwork for further research into the metabolism of catecholamines and their possible relationship to schizophrenia.

The subsequent search for a biochemical 'marker' in schizophrenia has been motivated by two main areas of observation. First, reports

that certain groups of drugs, notably amphetamines (4,13,27) and hallucinogens (93) can produce a clinical illness which closely mimics schizophrenia although Hollister (93) pointed out some important differences in the psychosis due to hallucinogens. On the other hand amphetamine psychosis can be easily mistaken for paranoid schizophrenia and may produce its toxic effect by interacting with central neurotransmitter systems, either dopamine or norepinephrine. Both the d- and l- forms of amphetamine inhibit the dopamine uptake systems of neurons (5,93) but the d- form is a much more potent inhibitor of the norepinephrine system (93). The second area of observation concerns the mode of action of 'neuroleptic drugs', a term introduced to describe drugs having antipsychotic properties. It soon became apparent that central dopamine and norepinephrine systems were affected by neuroleptic drugs. Matthysse and Kety (147) proposed that schizophrenia was caused by an excess of monoaminergic activity in the brain and Angrist et al. (6) noted the deleterious effects of L-DOPA on the behaviour of schizophrenic patients.

Out of these studies emerged the dopamine hypothesis of schizophrenia which essentially states that dopamine is responsible for the activation of adenyl cyclase on the neuron which in turn promotes the formation of the 3', 5' cyclic adenosine monophosphatase (cAMP) essential for the phosphorylation of membrane proteins. In other words, schizophrenia results from a breakdown in the second messenger systems of the cell membrane. Creese et al. (28) have shown that the efficacy and pharmacological potency of anti-schizophrenic drugs are related to their ability to bind with dopamine receptors. Furthermore dopamine and apomorphine, a dopamine agonist, block the synthesis of dopamine and the

firing of dopaminergic neurons, both of which actions can be inhibited by neuroleptic drugs. Topographical plotting of biogenic amine concentrations in various parts of the brain revealed that the striatum, particularly the caudate nucleus, the putamen and the nucleus accumbens, are rich in dopamine and the concentrations are higher in schizophrenics as measured by post-mortem studies (16,31,106,125,160,190) and isotope binding techniques (30,124,189). Binding of 3H-Haliperidol and 3H-Spiperone has been reported 50%-60% higher in schizophrenic brains which led Seeman et al. (190) to suggest that schizophrenia is associated with overactivity of post-synaptic dopamine receptors. Other workers (16,24,44) have focused attention on increased concentrations of norepinephrine in various regions of schizophrenic brains, mainly the mesencephalon and nucleus accumbens while Karoum and colleagues (117,118) with a small study of eight schizophrenic brains reported an 83% increase of 3-methoxy-4-hydroxy-phenylglycerol (MHPG) in the hypothalamus. They suggested the possibility of deficient conjugation but admitted to the possible effects of long term neuroleptic therapy and the long (27 hours average) post-mortem interval before freezing the specimens. More recently, Phillipson and Pycock (168) using microdissection and microradiochemical assay in rats have demonstrated a dopamine pathway projecting from neurons in the ventral tegmental area of the midbrain to the medial habenular nucleus. These nuclei are rich in dopamine and the authors believed that other dopamine rich areas such as the frontal cortex, cingulate gyrus and nucleus accumbens were similarly innervated from the ventral tegmental area and in turn projected to the lateral habenular nucleus. Their biochemical evidence indicated that the habenula is a site which controls the activity

of dopaminergic neurons projecting to the frontal cortex since lesions of the habenula resulted in an increase of dopaminergic neuron activity in mesocortical areas.

In an effort to locate more accurately the cellular origin of the dopamine receptors, Henn and his co-workers (88,89,90) used fractionation techniques with bovine caudate nucleus and were able to separate astroglial, neuronal and synaptosomal fractions. It is interesting that they found the astroglial fraction to be the richest in dopamine receptors and to contain adenyl cyclase which was sensitive to dopamine but not to adrenergic stimulation. This sensitivity could be inhibited by neuroleptics. They also found phosphokinase activity to be higher in the glial fraction. Henn (90) suggested that dopamine in the astrogial cells may play a modulator role and govern the rate of firing of neurons. In all studies reviewed, none of the authors found any significant differences in the levels of dopamine between schizophrenic patients who had longer term neuroleptic therapy and those who had not received drugs. Following up on the idea of a defective cell membrane, Stevens (200) using red blood cells from schizophrenic patients compared four phospholipid fractions and has found consistent differences in the percentage distributions among the fractions compared to normal controls. No differences were found between treated and untreated patients and Stevens suggested that his findings may indicate a biological marker to diagnose schizophrenia. Phosphatidylserine and sphingomyelin form a higher than normal percentage of the total phospholipids while phosphatidylcholine and phosphatidylethanolamine tend to be low. Along the same line of investigation, the uptake properties of blood platelets have been studied for serotonin (5-HT) and other monoamines such as dopamine and norepinephrine. Sneddon (198) and others (184,206) have noted similarities between platelets and

synaptosomes with regard to 5-HT uptake, uptake of inhibitors and the metabolism of monoamine oxidase. So far however, no significant differences have been noted between schizophrenics and control subjects.

The disturbance of γ-aminobutric acid (GABA) function in the striatal areas of patients with Parkinson's disease and Huntington's Chorea led to the implication of GABA in the aetiology of schizophrenia (181) but subsequent studies have failed to demonstrate any dysfunction of GABA neurons in the brain. Furthermore GABA agonists such as mucimol have no apparent effect on schizophrenic patients (26). In both Parkinson's disease and Huntington's Chorea, pathological changes have been identified in the corpus striatum and yet psychosis is not a clinical feature of either illness. In spite of this, several workers (18,152) have attempted to explain the psychopathology of schizophrenia on the basis of disturbed striatal function.

Neuroendocrinology

The German psychiatrist, Kraepelin first suggested in 1881 a possible relationship between endocrine dysfunction and schizophrenia. This has been supported by the clinical observation that the onset of illness often begins at or shortly after puberty and by the frequent association in males with the so-called "immaturity syndrome", i.e., males with little chest hair or beard growth and a female pubic hair distribution. Post-partum psychosis, although not common, is often schizophreniform in type. For years insulin coma therapy (ICT) was a popular treatment for schizophrenia and many enthusiastic claims were made for its benefits. In the first half of this century many studies showed evidence of a variety of degenerative changes related to endocrine function but laboratory techniques were crude

and controls were not used (169). Investigations into the mode of action of neuroleptic drugs have shown that they produce an increase in serum prolactin levels as a result of the inhibition of dopaminergic activity. On the other hand, drugs which enhance dopaminergic activity such as dopamine (DA), L-Dopa, apomorphine and bromocriptine all produce a drop in prolactin levels (141,148). It is known that the secretion of prolactin from the anterior pituitary is controlled by dopamine receptors in the tuberoinfundibular region of the hypothalamus. It was therefore assumed that the increase of serum prolactin was a direct result of neuroleptic action as on these DA receptors and this has been an area of intense research. However, well controlled studies (19, 67,111,151) have failed to show any significant differences in the levels of serum prolactin between schizophrenic and normal control groups. Furthermore, the intramuscular injection of chlorpromazine showed no significant difference between the resultant increases of serum prolactin of unmedicated schizophrenics and normal subjects. It therefore appears that the pathophysiology of schizophrenia does not lie in the tuberoinfundibular DA receptors but possibly in other DA receptors located in medial cortical or medial limbic structures.

Study of growth hormone (G.H.) has also failed to show any difference between schizophrenics and normal subjects (67) except during sleep (215) when schizophrenics did not produce the normal increase of G.H. in the serum. At the present time the mechanism of production of G.H. is far from clear since several neurotransmitters including DA and serotonin can stimulate the production of hormone. The possible role of serotonin in sleep (114), the disturbed sleep pattern in schizophrenics (23,45,100,116, 135,231) and the effect of serotonin in G.H. production entice one to re-examine the serotonin hypothesis of schizophrenia first proposed by

Gaddum (54) and Woolley and Shaw (229). These workers found increased amounts of serotonin in the putamen of post-mortem schizophrenic brains.

A report by Hendry (87) that nerve growth factor (NGF) is essential for the *in vitro* production of neurites during innervation by adrenergic neurons of the peripheral nervous system resulted in an investigation of the possible role of NGF in schizophrenia. NGF is a large molecular weight protein which has been isolated from all vertebrate animals so far investigated and has also been identified in human serum and placenta (65). An organ culture of mammalian sympathetic ganglia responded to the addition of NGF by producing a rapid growth of neurites (131) while absence of NGF resulted in a rapid drop in enzymes tyrosine hydroxylase, dopamine beta hydroxylase, loss of action potential and final degeneration (205). It would appear that NGF is perhaps a maintenance factor necessary for proper function of cholinergic systems which have been implicated in the pathophysiology of schizophrenia. Perez-Polo and his co-workers (166) measured NGF protein and NGF activity in the serum of unmedicated schizophrenics and found a significant depression of both compared to matched controls. The significance of this finding is not clear since the origin, synthesis and role of NGF in humans is not known at this time.

Clinicians have realised for a long time that schizophrenics are less sensitive to pain. Bleuler (17) pointed out that they were undistracted by the discomfort of a distended bladder or rectum, and Geschwind (56) drew attention to the difficulty in diagnosing acute surgical conditions due to the diminished pain sensitivity. The concept of disturbed sensory input in schizophrenia was put forward by Venables (213). These clinical observations have been confirmed by studies of experimentally induced pain which showed that schizophrenics are less responsive to

thermal pain, pain reactivity and pain discrimination compared to normal subjects (70,144). Meanwhile, workers in other disciplines, notably Reynolds (177) showed that electrical stimulation of the periaqueductal grey matter of the rat produced sufficient analgesia to permit surgery. In human subjects with intractable pain, Richardson and Akil (178,179) obtained relief for up to 24 hours following low voltage stimulation of the periaqueduct grey matter and periventricular grey matter particularly the medial thalamus in the region of the third ventricle. They also showed that the analgesia produced by electrical stimulation could be reversed by giving the patient 1 mg of naloxone, a narcotic antagonist. It appeared that the brain has its own "built-in" analgesic system and it remained for Hughes (95) in 1975 to isolate an endogenous compound with pharmacological properties similar to morphine. Hughes and his co-workers (96) identified two pentapeptides which they named "enkephalins" and demonstrated their powerful opiate agonist activity. These lipo-proteins of approximately 600 daltons molecular weight have since been isolated from human cerebrospinal fluid (CSF) by Terenius (204). Enkephalins are not evenly distributed in the brain but are abundantly found in the caudate nucleus, the medial central grey areas including medial thalamus and the amygdala. The substantia nigra, locus coeruleus and dorsal horns of the spinal cord are also rich in enkephalin receptors. According to Kahuar et al. (122) the receptors are located in the membrane of the synaptosomal region.

Clinical application of this new knowledge quickly followed and gave rise to the endorphin (a collective name for all opioid proteins in the brain) hypothesis for schizophrenia, which suggests an excess of

endorphin in the brains of schizophrenics and the implication that endorphin antagonists may provide effective treatment. Naloxone and naltrexone, both narcotic antagonists have been shown to alter pain perception both in normal subjects (22) and in schizophrenics (35) and Gunne et al. (68) published the first report of an endorphin antagonist used in the treatment of schizophrenia. Unfortunately his small sample of six patients and the fact that neuroleptic drugs were also given deters somewhat from the success claimed. Subsequent studies were reviewed by Davis et al. (36) in 1979 and they concluded that the results of endorphin-antagonist treatment were poor. However, Lindstrom and his colleagues (133) demonstrated elevated endorphin levels in the CSF of schizophrenic patients compared to normal and thereby have helped to sustain the hypothesis. Akil (1) suggested that the brain enkephalin system may act as a "brake" when pain becomes excessive and disruptive. The fact that naloxone is an enkephalin antagonist *in vitro* and has no effect when given systemically suggests that enkephalins are only released under special conditions after which they can be blocked by antagonists.

Recently claims have been made for an antipsychotic property of fractions of the endorphin molecule. Verhoeven and his co-workers (211, 214) have observed similarities between neuroleptic drug action and the effect of des-tryosine-γ-endorphin (DTγE) and des-enkephalin-γ-endorphin (DEγE). In a double blind cross-over study of unmedicated schizophrenics, they obtained significant improvement in 50% of the patients. They concluded that a disorder of central endorphin metabolism played a role in the aetiology of schizophrenia.

Immunology and Viral Infection

As early as 1901 Metchnikov demonstrated the cytotoxic effect of certain sera to brain tissue which suggested the possibility of autoimmune mechanisms in psychiatric disorders (Haggard: Devils, Drugs and Doctors). Since then numerous brain specific proteins have been isolated but their relationship to brain pathology has not been demonstrated. Lehman-Facius (126) in 1937 reported an antibrain factor in the blood of schizophrenics and this served to stimulate further research and many reports which were often contradictory. The differences however were often due to different laboratory techniques and differences in patient samples. Haddad and Robe (69) noted an antigenic abnormality in the serum of chronically ill schizophrenics and Liedeman and Prilipko (132), Luria et al. (140,141) Vartanian et al. (212) and Goldstein et al. (64) have all reported abnormal lymphocyte responses in schizophrenic blood. In a controlled study of 26 schizophrenics and 25 healthy controls, Goldstein found serum factors in schizophrenics which were cytotoxic to thymocytes but after treatment with chlorpromazine, a neuroleptic drug, the cytotoxicity dropped. This immunosuppressive effect of antipsychotic medication suggests a disturbance of immune regulation in schizophrenia.

Heath and his colleagues (81,82,84) injected antibrain antibodies into the ventricles of rhesus monkeys with implanted electrodes and produced a catatonic state in the animals and spike and slow wave EEG discharges in the caudate region. They believed that the septal-striatal region is the antigenic part of the brain and that the antibodies are only found in schizophrenics who have full blown secondary symptoms including delusions and hallucinations. This is supported by work of

Pandy et al. (162) who found higher titres of antibody in chronic schizophrenics who had had several admissions to hospital compared to acute schizophrenics. One might propose that recurrent episodes of florid illness serve to stimulate the immune mechanism. Vartanian et al. (212) prepared a fractionation column of proteins in schizophrenic serum and have identified an α_1-glycoprotein as being the specific protein involved in the schizophrenic autoimmune process.

The possibility that the immunological component of schizophrenia may be hereditary has brought attention to genetic studies. Cassullo et al. (25) and Kyner et al. (123) have done statistical analysis of HLA antigens and found significant differences from normal subjects. Baron et al. (11) found antibrain factor in the sera of 17% of the relatives of schizophrenics compared to 2% in a control group and Pandy et al. (162) obtained higher titres of antibrain antibody in schizophrenics who had a family history of the disease. They believed this may be a valuable genetic marker of vulnerability to schizophrenia. Luchins and his co-workers (137,138) noted significant increase of HLA-A_2 antigen in black schizophrenic patients who had reversed cerebral hemispheric asymmetry on CT scan compared to black schizophrenics with normal asymmetry. Differences for white patients did not reach a significant level but the results were in the same direction. These are interesting observations when we relate them to the findings of C.T. scan studies in schizophrenia (62,136,219).

Clinical observations relating schizophrenia to other diseases which have an established immunological component have produced interesting findings. Mellsop and his colleagues (150) in Australia made clinical, radiological and serological examinations of 301 middle aged

schizophrenic women and could find no evidence of rheumatoid arthritis. Since the expected prevalence is 7.7%, this represents a highly significant dissociation of the two diseases, which raises the question of one disease having a protective effect on the other. Schizophrenia generally occurs at an earlier age than rheumatoid arthritis, but one must bear in mind that schizophrenics tend to be less mobile and do less manual labour than healthy subjects and both of these factors are important in the aetiology of rheumatoid arthritis. In addition there is the immunosuppressive effect of long term antipsychotic medication. Fieve et al. (46) have reported abnormal lymphocytes in patients taking chlorpromazine and Ananth and Minn (3) and Dubois et al. (42) have reported the development of lupus erythematosus (LE) in similar patients. These patients showed antinuclear antibodies in addition to LE cells.

While the weight of evidence for an autoimmune disorder in schizophrenia is impressive, there have been dissenters (185,226) who disclaim a specific antibrain antibody, but the method of assay of these workers has been criticized. Identification of a specific antibody to an anatomical region of the brain has not been established with any certainty. Pandy (162) found no differences in antibody titre to frontocortical, limbic and extra-pyramidal antigens. Although the data are far from conclusive, they are sufficiently encouraging to merit further studies into the immune mechanism of schizophrenics.

Somewhat related to research in immunology has been the search for a virus by both serological and cytological studies. Gajdusek (55) pointed out that an unconventional virus such as those associated with Creutzfeldt-Jakob disease, Kuru, scrapie in sheep and transmissible mink

encephalopathy may take years or decades before producing demonstrable cell damage and there is no inflammatory response in the tissues such as is seen following infection with conventional viruses. What is seen is a spongiosal degeneration of grey matter without any perivascular cuffing with mononuclear cells. Gajdusek suggested that the chronic poor prognosis type of schizophrenia may be due to such a virus although apart from the localised degenerative changes described by Averback (10), no cellular pathology has yet been identified in schizophrenia. However, Tyrrell (208) studied tissue cultures inoculated with CSF from schizophrenic patients and one-third of the specimens produced cytopathic effects. Although no virus particles have been identified by electron microscopy, the cytotoxic agent in the CSF is held back by a 50 nm filter but passes a 200 nm filter, which for size is compatible with a virus particle. In other studies Tyrrell et al. (207) deposited CSF from 38 schizophrenics on tissue cultures of human lung fibroblasts and rhesus monkey kidney cells grown on fetal bovine serum and in 13 cases a persistent (reproducible) cytopathic effect resulted. Cells became distorted, granular and degenerated. The extent of the effect varied from a local action to complete destruction of the whole culture and was more marked in the human fibroblasts. Tyrrell compared the "virus-like agent" to a rhinovirus which passes a 100 nm filter but is stopped by a 50 nm filter. He ruled out a mycoplasma since the agent was chloroform stable and resisted tylosin. A control group of 25 non-psychotic, non-neurological patients produced only one cytopathic CSF. Crow et al. (32) did a similar study on 47 acute schizophrenic patients of mixed types of whom 18 had CSF with a cytopathic effect. They suggested the possible presence of a

slow virus in some types of schizophrenia with a characteristic insidious onset and a slow episodic clinical deterioration. They noted that patients with CSF which was cytopathic had a poorer response to drug treatment and a poorer prognosis than the other patients in the group.

The possibility of a virus infection in schizophrenia raises questions of its possible relationship to the disease. Perhaps the organism is universal and is activated by damaged neural tissue in schizophrenics or on the other hand there may be a causal relationship. Since it is well known that neurotropic viruses show a predilection for certain regions of the nervous system, e.g., poliomyelitis in the motor cells of the aqueduct region and herpes in sensory ganglia, it is not unreasonable to suspect that a schizophrenia virus may also have a primary effect on a specific region such as the septal-striatal area.

Neuroanatomy

The search for structural abnormalities in the brains of schizophrenics goes back to the beginning of this century and each new investigative tool or technique has produced a spate of reports both supporting and denying morphological differences from the accepted normal. The first report of cerebral atrophy in schizophrenia is credited to Jacobi and Winkler (107,108) who in 1927 published the result of their study of 19 chronic schizophrenics using pneumoencephalograms (PEG). They found that 18 of the patients had unquestionable internal hydrocephalus and offered the opinion that the pathological changes were due to atrophy which developed in the course of the disease. This work was quickly followed by reports on larger series of patients by Moore et al. (154,155) and by

Lemke (130). Moore et al. (154, 155) found atrophy in all of 60 patients, most marked in the parietal regions and 25 patients had enlarged ventricles. They claim that the amount of atrophy is related to the degree of mental deterioration. Similarly, Lemke (130) found 50 out of 100 patients had enlarged ventricles which was also related to personality disintegration. He proposed a congenital cerebral anomaly which predisposes to schizophrenia and suggested that PEG studies were useful as a prognostic aid. Huber (94) studied the PEGs of 190 schizophrenics of mixed types and reported abnormalities in two-thirds of them, the pathological changes being most marked in the ventricles. In a subgroup with features of dementia (poverty of thought, psychomotor retardation, emotional flattening and lack of drive and initiative), 81.8% had enlarged ventricles. He also noted that enlarged ventricular size is associated with the degree of deterioration in the clinical state and is therefore part of the schizophrenic process and indicative of organic cerebral disease. Furthermore he compared schizophrenics who had been treated with electroconvulsive therapy (ECT) with those who had not received ECT and found no significant differences in ventricular size. Haug (73,74) also found no difference in ventricle size between patients treated with ECT and insulin coma therapy (ICT) and those who did not receive these treatments. Of his 101 cases, 58 had an abnormal PEG. Cortical atrophy was most marked in the frontal and temporo-parietal areas, and 43 had enlarged ventricles. The third ventricle was enlarged in 22 cases with a mean width of 8.7 mm. Haug noted that the "abnormal changes are mainly in the central parts of the brain which are of particular importance for affective functions". Like Lemke (130) he supported the idea of a congenital

hypoplasia in the process type of schizophrenia and discounted age as a factor.

Numerous other reports (8,41.43,53,73.119,191,120) have supported the finding of enlarged ventricles in chronic schizophrenia although Peltonen (165) compared 86 schizophrenics with a normal group and found no significant differences on PEG examination. However he does confirm that ECT, ICT and age have no effect on third ventricle size. Storey (202) in a small group of 18 schizophrenics also failed to find any enlargement of ventricles. It seems very probable that different findings by various authors are dependent on the diagnostic types of patients selected. Several authors (8,73,74,94,130) have emphasized that enlarged ventricles are associated with the process type of schizophrenia with clinical features of dementia rather than the schizophreniform types. Studies of groups of mixed psychiatric diagnosis by Wagner (216) and Van Boxel et al. (210) have demonstrated cerebral atrophy in psychoses other than schizophrenia and also point out that age and past treatment with ECT or ICT is not a relevant factor in ventricular size. Particular attention has been focused on the third ventricle by Lönnum and his colleagues (43,134,197) who claimed that prognosis was worse when the third ventricle is enlarged and the clinical features included impaired emotional control, depression, lack of drive, difficulty in handling social problems and inability to work. They suggested that a large third ventricle indicated pathology in structures surrounding the ventricle and Kiev et al. (119) stated that such patients showed increasing impairment of the highest integrative functions such as capacity for expression of needs, drive, goal achievement, learning, adaptation and the ability to deal with

stress. This has been confirmed by Matthews and Booker (146) who examined neurological patients with enlarged third ventricles.

Some disagreement exists among workers studying third ventricle width. Davidoff and Dyke (34) and Engeset and Lönnum (43) accepted 8 mm as maximum normal width while Robertson (182) claimed a variation from 3 to 9 mm with the usual measurement being 4 to 6 mm. They do agree that age is not a significant factor in ventricular size, or as Bruijn (21) states "...it is clear that only after the age of 60 years an increase in ventricular volume in some (not all) cases is to be found". Another possible reason for the differences and disagreements among various workers may be related to technical problems and deficiences of the PEG examination. Pumping air into the lumbar theca of the spinal column in order to procure an x-ray outline of cerebral ventricles demands considerable skill with a certain amount of discomfort for the patient both at the time of the procedure and for possibly several days afterwards. In addition the mortality rate has been reported at 0.29% (34). Measurements of structures on an x-ray film can be difficult since sharp well defined boundaries are seldom seen and Lönnum (134) admits a technical error of measurement up to 2 mm. This difficulty is increased if there is not complete filling of the ventricles with air. For this reason the present study utilised ultrasound as a simple, fast and inexpensive method of accurately measuring the width of the third ventricle, and having an additional advantage of causing no discomfort, inconvenience or risk to the patient. However since this study began, computerised axial tomography (CT scan) has been introduced to large medical centres and this provides accurate measurement of brain structures although its use has been

handicapped by its cost and the expense of operation. Nevertheless, some studies of ventricles in schizophrenics have been reported but unfortunately the results are still conflicting.

The first controlled study using CT scan was published in 1976 by Johnstone et al. (110) who compared lateral ventricle sizes of 18 chronic schizophrenics with eight healthy volunteers. They found a significant enlargement of the ventricles of the schizophrenics and state that previous treatment with drugs and ECT was not related to the results. Hill (92) however pointed out the difficulty of separating on clinical grounds true schizophrenics from schizophrenia-like psychosis and reminded us that many pathological processes can produce a schizophrenia-like illness, e.g., encephalitis, rheumatic encephalopathy, Sydenham's chorea, toxic encephalopathies and metabolic disorders. Jellinek (109) reported that concentration camp victims after repeated trauma, malnutrition and infection showed brain atrophy on PEG examinations. Marsden (144) suggested that morphological changes in the brains of schizophrenics may be related to long term drug action since neuroleptics are known to act on mesolimbic-cortical dopamine receptors. However, he conceded that there is no evidence to support his idea and admitted there may be a "pathological process as yet unknown".

In the last two years or so, research in this area has been mainly concentrated in two centres: the laboratories of Johnstone and her colleagues in the U.K. (33,112,161) and of Weinberger and his associates in Washington D.C. (40,218,223). Johnstone's group compared a second group of 18 chronic schizophrenics to 10 age-matched controls and confirmed their original findings of enlarged ventricles in the schizophrenics.

They added that the ventricular size did not correlate with ECT, ICT or drug treatment but was strongly associated with intellectual impairment. They concluded that schizophrenics who have an unremitting and progressive illness showed an increase in ventricular size (112). They emphasized that treatment did not interfere with the relentless progress of brain atrophy but schizophrenics with normal size ventricles responded better to drug treatment, as do acutely ill patients with positive symptoms (delusions, hallucination, thought disorder). They also considered the possibility of a slow virus type of encephalitis as the cause of cerebral atrophy and the subsequent 'defect' symptoms of chronic schizophrenia. The Weinberger group has confirmed many of the findings of Johnstone and co-workers (33,112,161). Comparing 73 schizophrenics (of whom 58 were chronic) with 56 healthy controls, they noted a significant enlargement of ventricles in the schizophrenics which was not related to the duration of the disease or the length of hospitalization (218). In another group of 75 patients and 62 controls they compared widths of the Sylvian and interhemispheric fissures on CT scan and found that two-thirds of the schizophrenics had abnormalities and highly significant widening of the fissures. They pointedout that the cortical findings did not correlate with ventricular size (220). The relationship of ventricular size to pre-morbid adjustment (223) and response to drug treatment (221) were also examined. In a retrospective study of 51 schizophrenics with evidence of brain atrophy it was found that these patients had a poorer score on the Phillips (167) and Cittelmen-Klein (58) adjustment scales. Similarly, patients with enlarged ventricles showed a poorer responce to drug treatment as measured by the Brief Psychiatric Rating Scale (159,221).

In a recent study, Tanaka et al. (203) divided schizophrenics and controls into two groups, one younger than 40 years and the other older. In the younger group they found no differences in cortical atrophy or third ventricle size but in the older group there were significant differences in both measurements. They concluded that there is a positive correlation between the size of the third ventricle and the duration of illness. The cortical atrophy was most marked in the frontal and temporal lobes. In this regard it is interesting that Golden et al. (62), using CT scan, found lower density in the left anterior area of schizophrenic brains compared to normals and concluded that there are structural deficits in this part of the brain associated with the schizophrenic disease process. Various workers have demonstrated a relationship between cerebral atrophy and intellectual impairment (38,40,61,180). Golden et al (61) tested schizophrenics with enlarged lateral ventricles and noted impaired performance on the Luria-Nebraska battery of tests (60). Donnelly et al. (40) also tested schizophrenics with lateral ventricular enlargement and Reider et al. (180) selected patients with enlarged cerebral sulci. Both groups used subtests of the Halstead-Reitan Battery (70,170-175) and demonstrated impaired function. Unfortunately their samples of patients were very small and they made no attempt to relate areas of psychological impairment to specific regions of the cerebrum.

Conflicting reports have come from Kingsley and Trimble (120) and from Gluck et al. (59) who could find no significant difference in ventricle size between schizophrenics and normal controls, although Gluck and his co-workers reported third ventricle widths up to 11.6 mm in some of the patients. In an excellent review of CT scan studies in schizophrenia,

Weinberger and Wyatt (219,222) concluded that in schizophrenia the consensus of opinion indicates an increase in the size of cerebral ventricles, a dilatation of fissures on the surface of the brain and atypical asymmetries between aspects of the cerebral hemispheres. Furthermore the increased ventricular size was associated with poor pre-morbid adjustments, poor response to treatment, soft neurological signs and psychological impairment. There was no correlation however with age, duration of illness, drug treatment or duration of hospitalization. They concluded that schizophrenia is not a unitary disease but perhaps a heterogeneous collection of abnormalities affecting higher brain function. Figures 5 to 9 show the location of the third ventricle and its anatomical relationships.

FIG. 5. Sagittal section of brain. Enlarged view of medial aspect of the left hemisphere showing important structures surrounding the third ventricle.

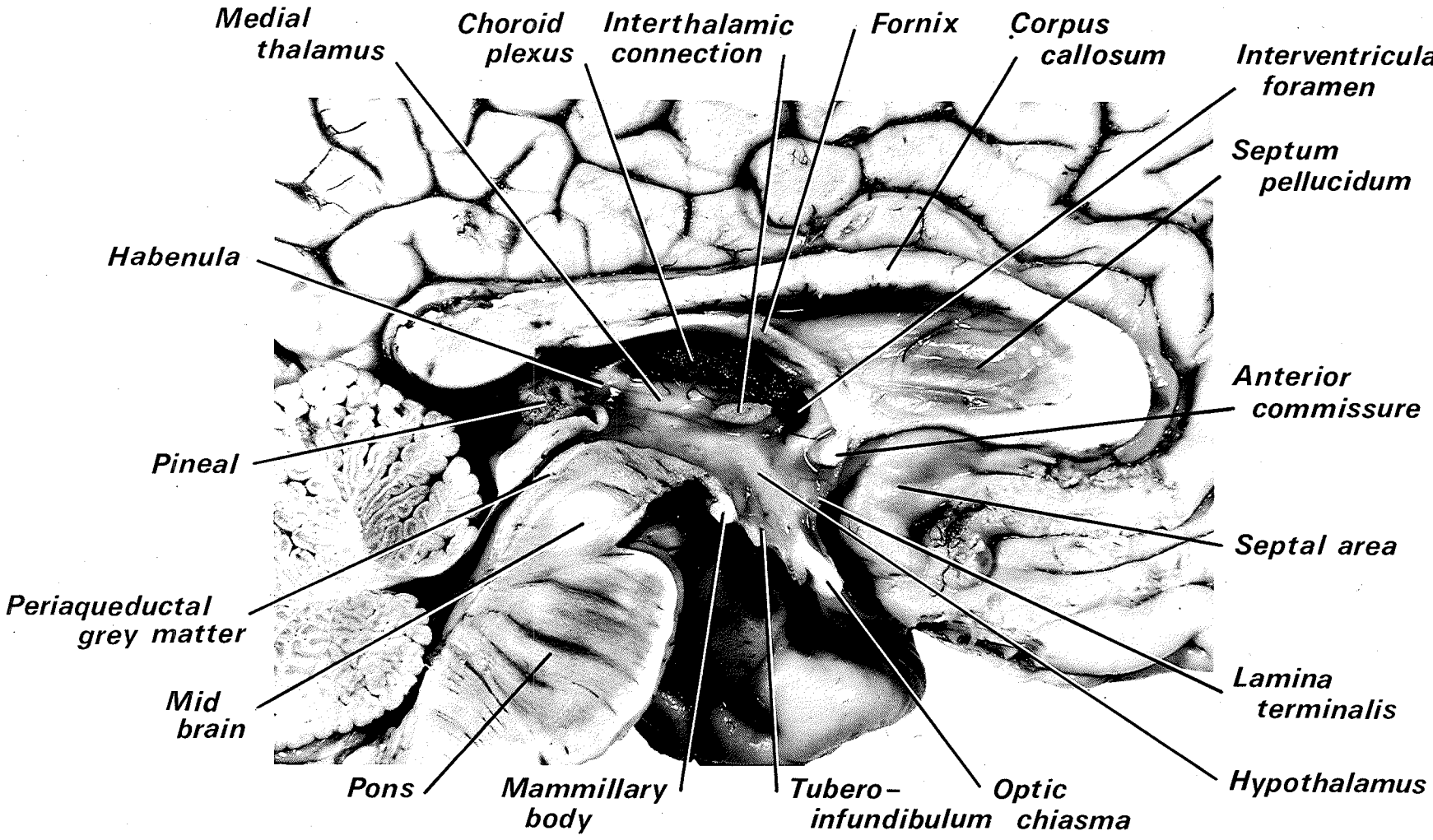

Medial thalamus
Choroid plexus
Interthalamic connection
Fornix
Corpus callosum
Interventricular foramen
Septum pellucidum
Habenula
Anterior commissure
Pineal
Septal area
Periaqueductal grey matter
Lamina terminalis
Mid brain
Hypothalamus
Pons
Mammillary body
Tubero-infundibulum
Optic chiasma

FIG 6. Sagittal section of the brain showing the medial aspect of the left hemisphere and location of the third ventricle.

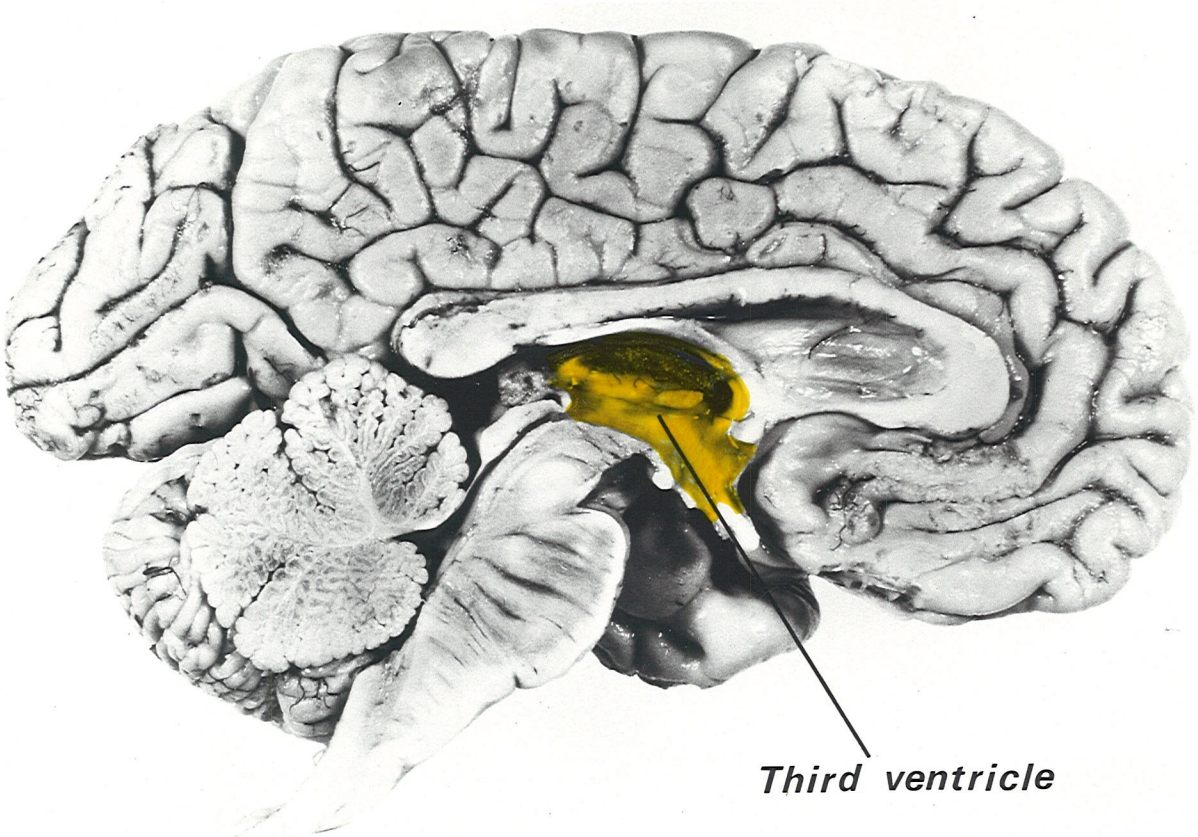

Third ventricle

FIG. 7. Anatomical Relations of the Third Ventricle. Medial aspect of the right hemisphere showing relationship to caudate nucleus and septal area.

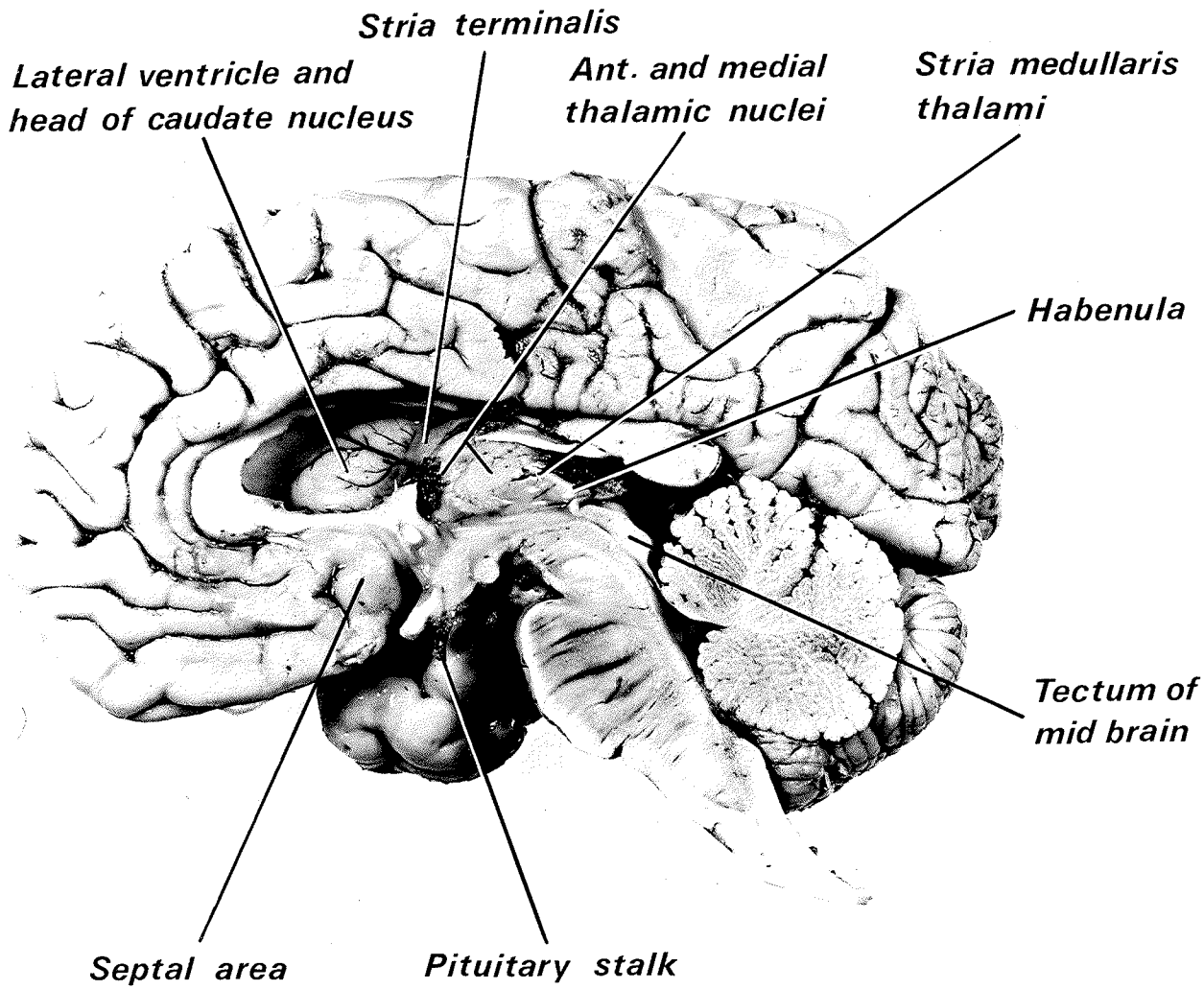

Stria terminalis
Lateral ventricle and head of caudate nucleus
Ant. and medial thalamic nuclei
Stria medullaris thalami
Habenula
Tectum of mid brain
Septal area
Pituitary stalk

FIG. 8. Anatomical Relations of the Third Ventricle. Coronal section at level of the upper pons.

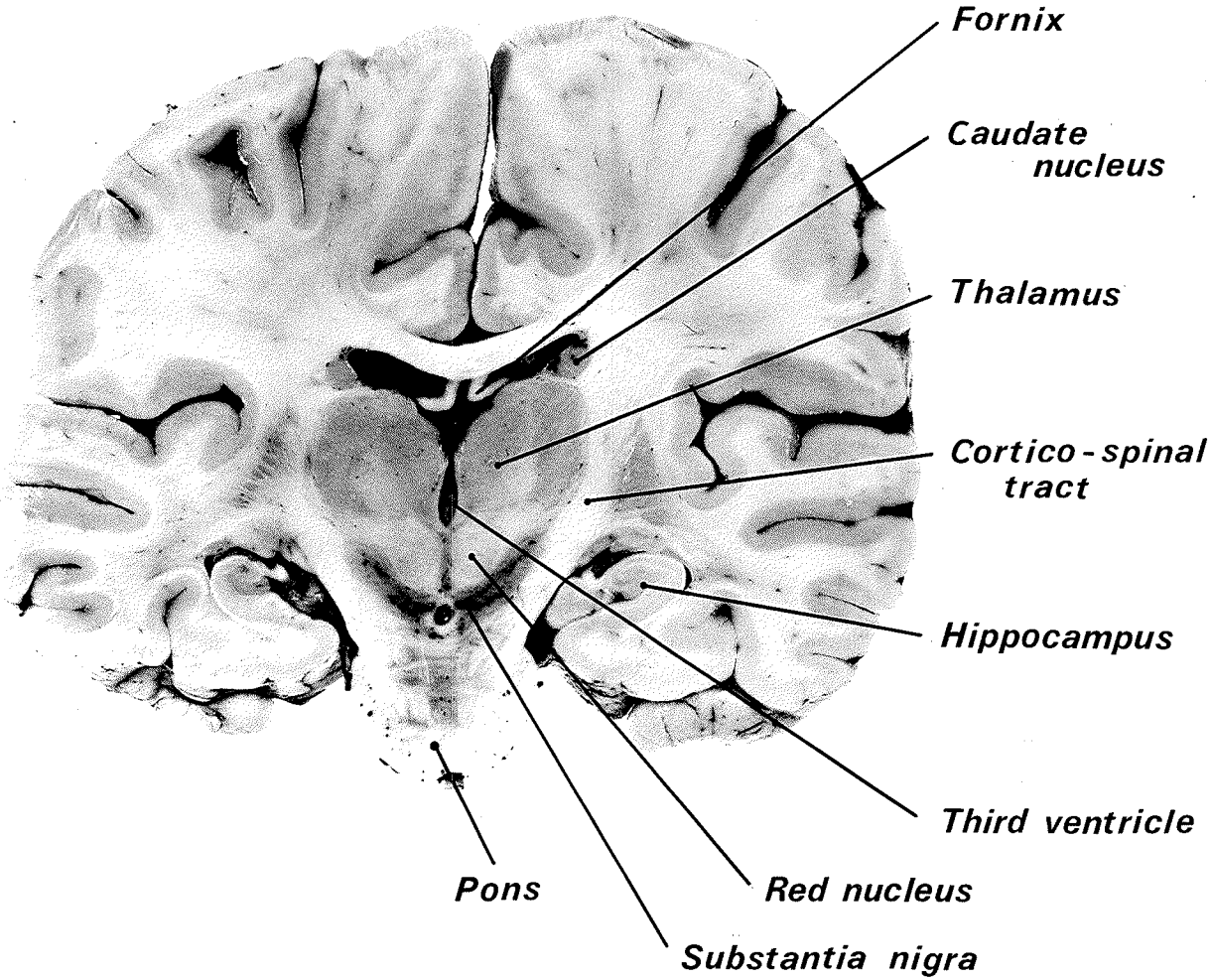
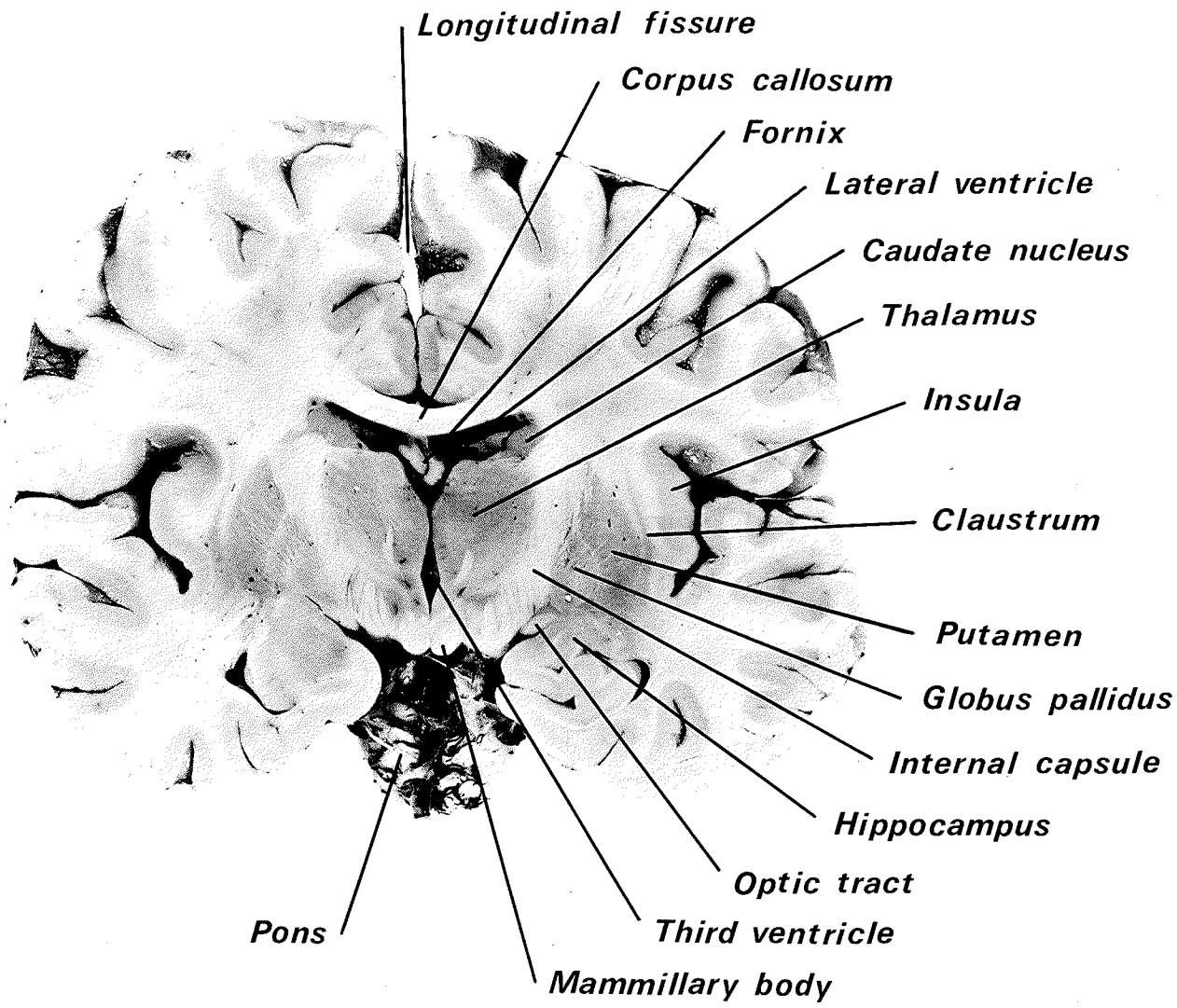

Fornix
Caudate nucleus
Thalamus
Cortico-spinal tract
Hippocampus
Third ventricle
Red nucleus
Substantia nigra
Pons

FIG. 9. Anatomical Relations of the Third Ventricle. Coronal section through the mammillary bodies.


Longitudinal fissure
Corpus callosum
Fornix
Lateral ventricle
Caudate nucleus
Thalamus
Insula
Claustrum
Putamen
Globus pallidus
Internal capsule
Hippocampus
Optic tract
Third ventricle
Mammillary body
Pons

HYPOTHESIS

In the review of neurobiological factors related to schizophrenia, attention has been focused on those studies which report plausible findings. Reported results are often conflicting and inconclusive but in general all tend to implicate the upper brain stem, the medial diencephalon of which the third ventricle occupies a central position, and the medial frontal cortex or septal area. It has been suggested that an enlarged third ventricle is a consequence of a progressive pathological process in schizophrenia which accounts for the 'defect' symptoms (thought disorder, lack of initiative, emotional blunting and psychomotor retardation) commonly seen in the later stages of the disease. There is difficulty in accepting this conclusion for various reasons. First of all, the reports in the literature already described have shown considerable variation in the percentage of chronic schizophrenics with an enlarged third ventricle. This may in part be explained by different methods of measurement but it makes one question a true relationship between the disease process and third ventricle size.

Secondly, although all chronic schizophrenics show clinical evidence of organic brain impairment, not all of them develop an enlarged third ventricle.

This study was undertaken to determine whether:

1. there is any relationship between third ventricle size and the psychopathology of chronic schizophrenia.
2. there is any significant difference in organic brain impairment between those subjects with enlarged third ventricles and those whose third ventricles are within the generally accepted limits

of normality.

In other words, the value of the third ventricle size as a diagnostic and prognostic factor in schizophrenia is being investigated.

METHODOLOGY

Subjects

Three groups of subjects were studied. Group 1 consisted of 50 normal volunteers selected from hospital staff, relatives of staff and university students who were given a token payment for their cooperation. Volunteers were carefully screened and no subject was accepted who had a personal or family history of psychiatric or neurological illness, epilepsy, head injury or intracranial infection. Twenty males and 30 females were selected and the mean age of the group was 28.46 years (S.D. 8.68).

Group 2 consisted of 43 chronic schizophrenics who were inpatients in a mental hospital. Through the courtesy of the Medical Director of Selkirk Mental Hospital, Manitoba, permission was granted to review the records of 142 patients and those patients were excluded who had epilepsy, mental retardation, neurological disease, or a history of head injury or intracranial infection. Twenty-eight males and 15 females were selected having a mean age of 40.47 years (S.D. 7.37). All of the patients were receiving neuroleptic drug treatment and most of them had in the past been treated with electroconvulsive therapy and/or insulin coma therapy.

Group 3 was selected from acutely ill schizophrenics recently admitted to hospital. Every patient was interviewed as soon as possible after admission and was screened according to the same selection criteria applied to Group 2. In addition, no patient was selected unless the admitting psychiatrist, the treating psychiatrist and the writer were all

in agreement that the patient had unequivocal signs and symptoms of schizophrenia which included a thought disorder, inappropriate affect, auditory hallucinations, impaired judgement and a history of behavioural change. Twenty-six males and 19 females were accepted, the total of 45 having a mean age of 24.60 (S.D. 6.99) years. For the purposes of this study, an acute schizophrenic is defined as a patient whose illness, according to the medical history, began less than two years previously.

Measurement of Third Ventricle

The width of the third ventricle was measured by means of an 'Ekoline 20' Diagnostic Ultrasonoscope purchased from Smith Kline Instrument Company (Fig. 11). This instrument transmits sonic pulses of ultrahigh frequency into tissue and receives echoes reflected from tissue interfaces. The interfaces may be soft tissue/bone, soft tissue/fluid or soft tissue/soft tissue and the echoes are displayed on a cathode ray oscilloscope along a distance-calibrated trace. Amplification of echoes can be precisely controlled in order to obtain an optimal display or dampen down unwanted echoes or artefact. The tissue depth trace is calibrated in 2 mm and 10 mm gradations and a fixed-focus polaroid camera is used to obtain a permanent photographic record of the desired echo display (Fig. 12). The technique is quick, causes no discomfort to the subject and can be mastered after a short period of training and experience. The writer obtained considerable experience in the routine use of this instrument before engaging in this study.

For the purposes of this study the desired echo display demonstrating the width of the third ventricle was obtained by placing the

FIG. 10. Ecoline-20 Ultrasonoscope.

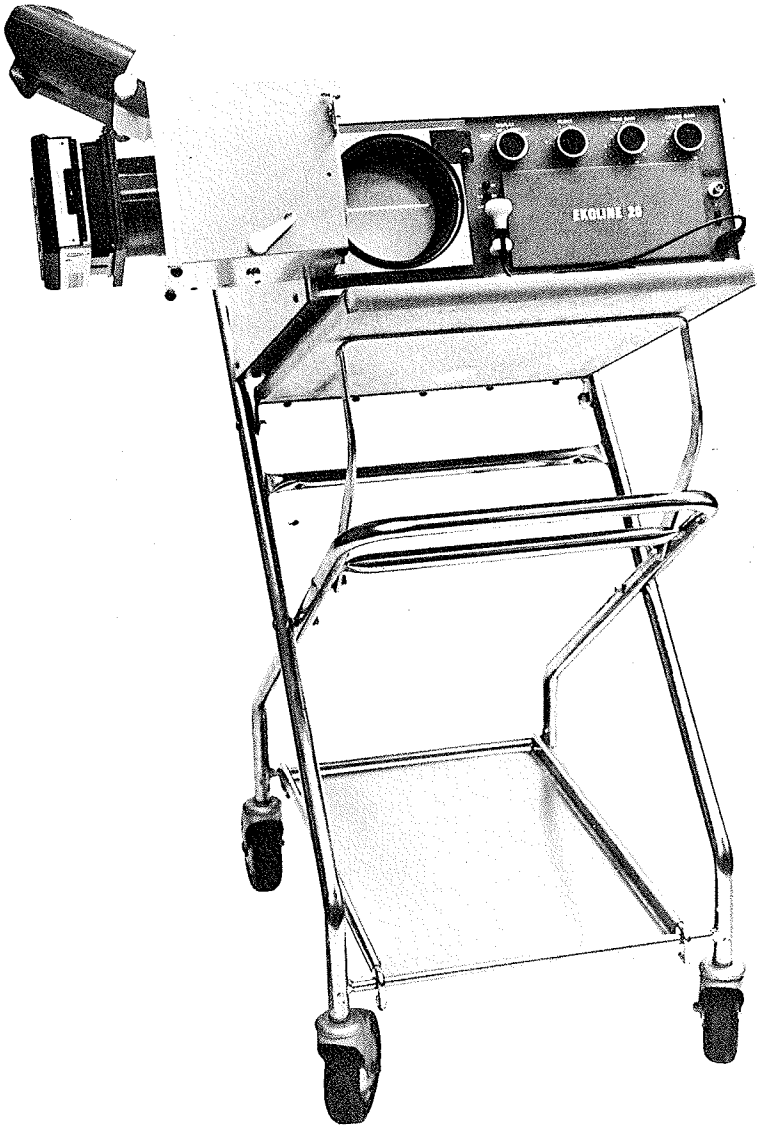


FIG. 11. Echogram of a subject from group 1 (normals) showing third ventricle of 4 mm width (centre). The echoes on either side probably relate to the lateral ventricle.

Scale shows 2 mm and 10 mm calibrations.

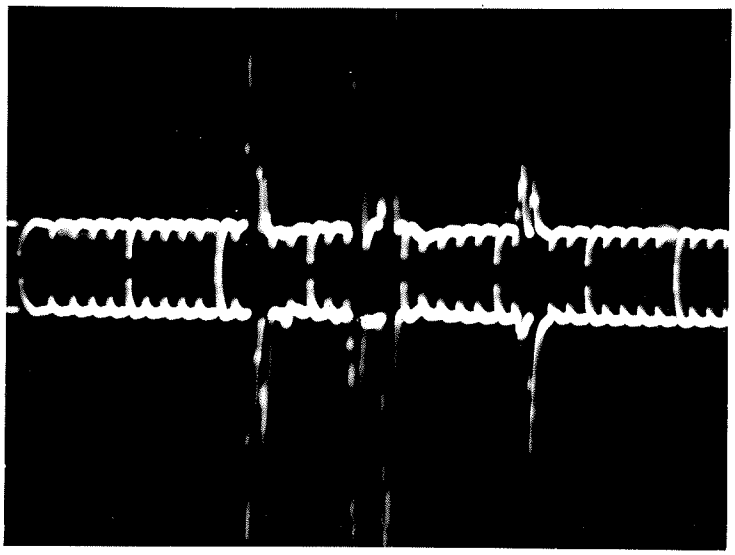


FIG. 12. Technique of using the Ecoline-20 Ultrasonoscope.

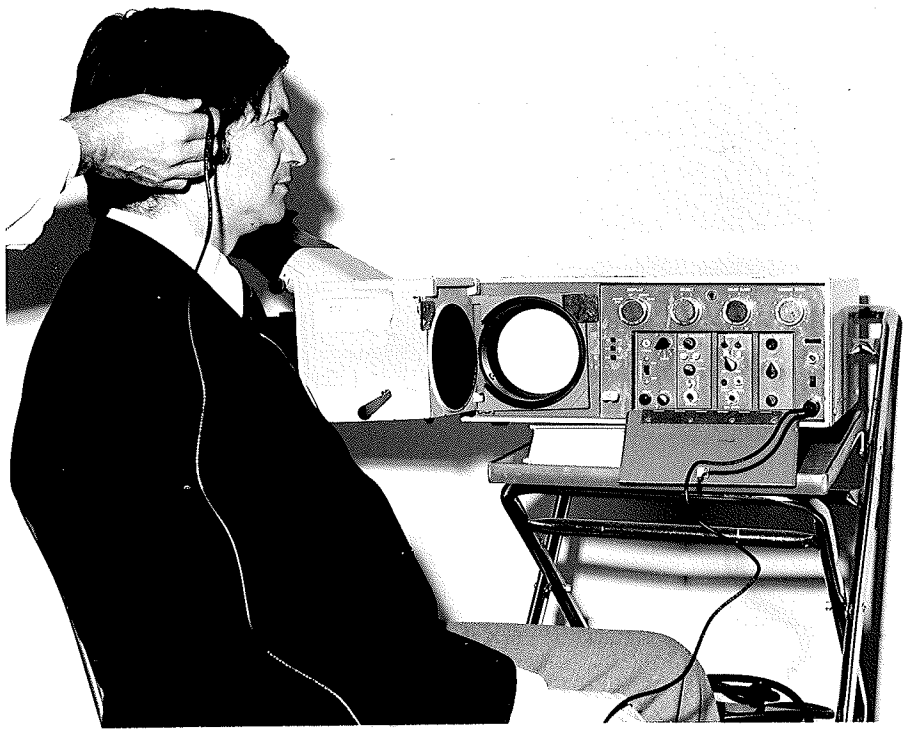
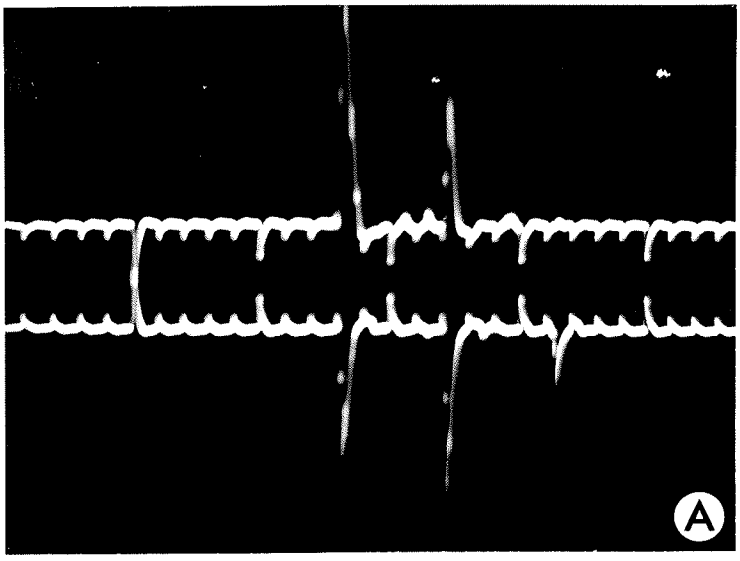


FIG. 13. Echograms of chronic schizophrenic patients showing third ventricle widths of 8 mm (A) and 11 mm (B). Scale shows 2 mm and 10 mm calibrations.


A

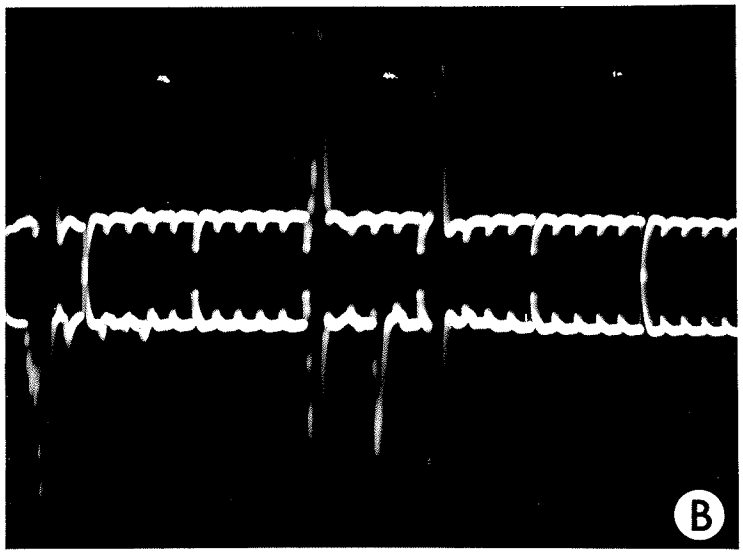

B

FIG. 14. Diagram showing the outline of cerebral ventricles in relation to the ear.

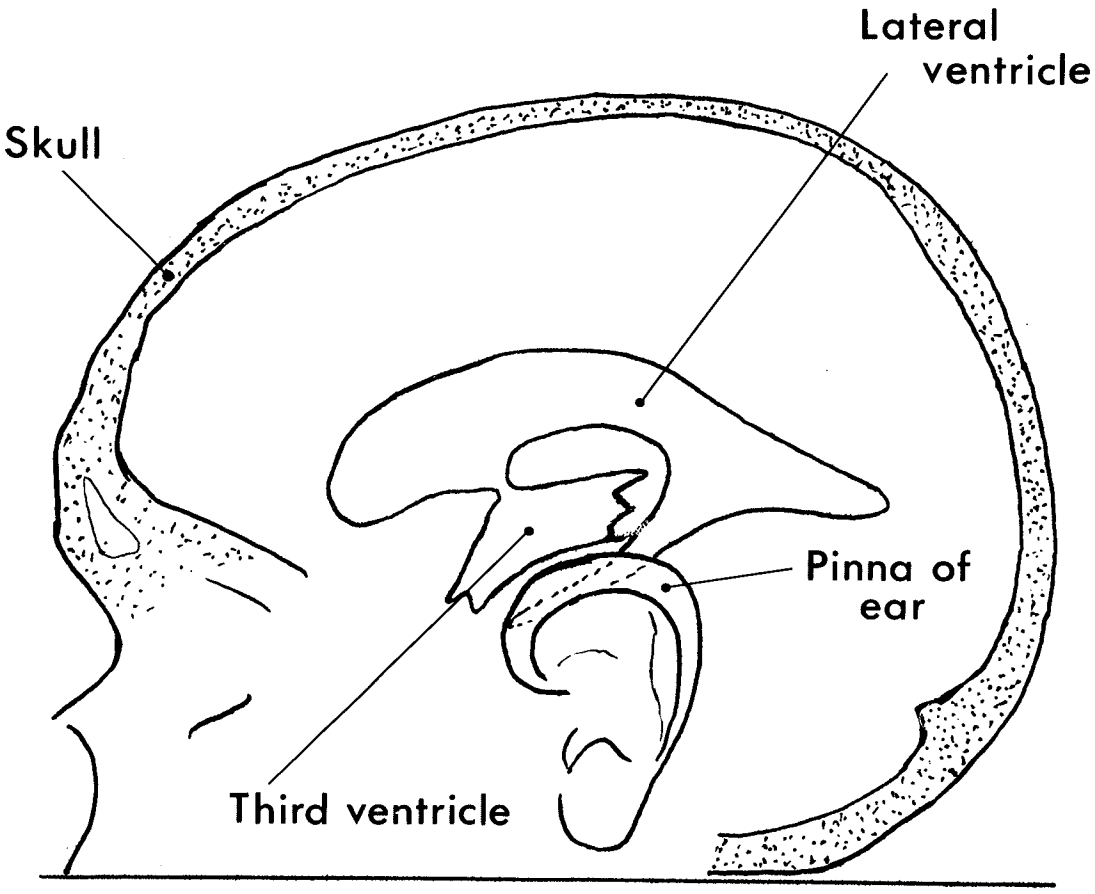
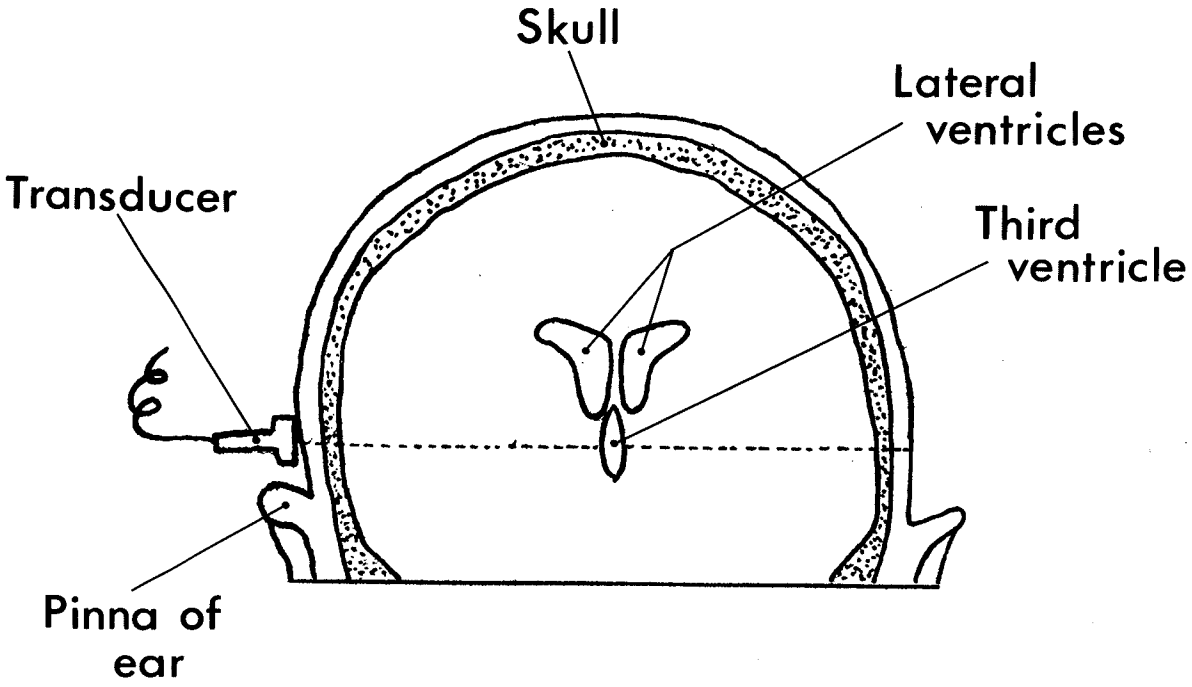
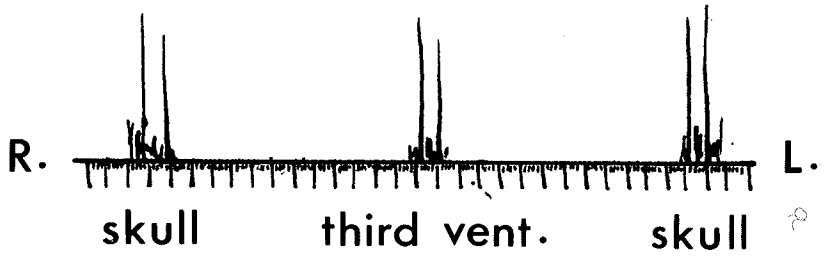

Lateral
ventricle
Skull
Pinna of
ear
Third ventricle

FIG. 15. Diagram relating ultrasonic echoes to intra-cranial structures.


Skull
Lateral ventricles
Transducer
Third ventricle
Pinna of ear


R.
L.
skull
third vent.
skull

transducer on the temporal area immediately above the upper anterior attachment of the pinna of the ear (Fig. 13). As a precaution, echoes were obtained first from right to left and then from left to right both being recorded on the same photograph and thus serving as a 'double check' of third ventricle width. To facilitate accurate measurement between echoes, it is possible to 'spread' the calibrated trace so that the gradations are wider apart (Fig. 14). Further details of ultrasound and echoencephalography are given in Appendix II.

Tests of Brain Function

Subjects of the three study groups were submitted to batteries of neuropsychological tests. The tests selected were the Halstead-Reitan Neuropsychological Battery (HRNB) and the Wechsler Adult Intelligence Scale (WAIS) both of which are well established as valid measures of brain function. Owing to the multiplicity of functions carried out by the brain, many of which can be ascribed to specific anatomical regions, it was necessary to select a diverse group of subtests which would effectively identify areas of impaired psychological function. This unfortunately meant a testing period of approximately eight hours total and several visits to the laboratory. For restless, acutely ill schizophrenics and for the poorly motivated uninterested chronic patient, this in some cases meant that some of the tests were not completed. Loss of interest, poor attention, sudden exits from the laboratory, failure to keep appointments, etc. are just some of the difficulties encountered by clinical researchers. In addition, patients developed physical illnesses or were discharged from hospital. Even among the normal controls staff

changed shifts or jobs, left the district or returned back to university. The result of these difficulties was a variation in the "n" value for different subtests but fortunately since the total "n" was large, at no time did the number of subjects drop low enough to preclude statistical analysis.

The purpose of the psychological tests was to identify 1) brain-damaged subjects, 2) lateralization of brain dysfunction, and 3) localization of brain dysfunction. The subtests of the HRNB and the WAIS will be briefly described.

(a) The Category Test consists of seven subtests each based on a principle which allows the subject to select a number (1 to 4) for each item projected on a screen. Selecting the correct number produces a bell sound while a buzzer signals an error. This is a test of abstract reasoning and concept formation which is either reinforced or modified by the bell and buzzer. It is a sensitive test of general brain dysfunction which can effectively discriminate 90% of brain damaged individuals from normal subjects.

(b) The Tactual Performance Test employs a board with cut-outs into which wooden blocks of various shapes can be placed. The subject has to place the blocks correctly while blind-folded and therefore relies entirely on somatosensory cues. The dominant hand, the non-dominant hand and then both hands are used and the total time taken is noted. Following this the board and blindfold are removed and the subject is asked to draw the shapes of the blocks (memory score) and their position (location score) on the board. The total time and location scores are highly discriminatory for brain damaged subjects.

(c) The Rhythm Test consists of 30 pairs of rhythmic beats and the subject has to decide whether the members of each pair are the same or different.

(d) The Speech Perception Test consists of 60 nonsense words all containing the same "ee" vowel. The subject listens to the auditory stimulus and has to match the sound with one of four choices on a list provided. This tests auditory discrimination and the ability to match auditory and visual stimuli.

(e) The Trail Making Test consists of two parts, A and B. Part A consists of 25 circles on a sheet of paper, the circles being numbered 1 to 25. The subject must connect the circles in the correct sequence beginning at 1. In Part B, 13 of the circles are numbered 1 to 13 and 12 are lettered A to L. The subject must connect the circles by alternating between numbers and letters, e.g., 1-A-2-B-3, etc. This is a useful test of brain damage and Part B particularly is 88% effective. However there is a correlation between test performance and both age and I.Q. which must be taken into account.

(f) The Finger Tapping Test examines the subjects ability to rapidly depress a telegraph key with the index finger of first the dominant and then the non-dominant hand. Five 10 second trials are allowed with each hand and the number of taps per trial is noted.

(g) The Impairment Index is computed from the results of the individual tests by dividing the number of tests which indicate brain damage by the total number of tests employed. For example, if 10 tests are used and five of the scores indicate brain damage, the Impairment Index would be 5/10 or 0.5. According to Reitan (170-172) the most valuable

tests of generalised brain dysfunction are the Halstead Impairment Index, the Category test, tactual performance (localisation), trail making test (total) and four or more dysphasic symptoms. Tests indicative of localised brain damage are listed in Table 6, page 93.

(h) The Asphasia Screening Test examines for language and related deficits and covers such areas as naming objects, spelling, reading, speaking, drawing, right-left orientation, calculation and comprehension. The probability of brain damage increases with the number of aphasic symptoms and with four deficits present reaches 100% probability.

(i) Sensory Perceptual Tests consist of a number of examinations to test sensory function. These include double simultaneous stimulation for vision, hearing and touch to elicit suppression, finger agnosia, finger-tip writing and tactile form recognition (astereognosis). The tests are applied to both hands.

(j) The WAIS, although primarily a test of intelligence, also gives valuable information concerning brain function. The verbal portion consists of six subtests covering information, comprehension, arithmetic, similarities, digit span and vocabulary. In the performance portion the subtests are digit symbol, picture completion, block design, picture arrangement and object assembly. The scores for the verbal and performance portions are calculated and from these the full scale I.Q. is derived. Large differences between the verbal and performance scores may be significant for the diagnosis and lateralization of brain damage. Of the subtests, block design, digit span and digit symbol are the most sensitive indicators of brain damage showing discrimination at the 80%

level. In some instances it has been found useful to calculate a "deterioration index" by comparing subtests which are sensitive to brain damage, the "don't hold" tests (digit span, digit symbol, arithmetic, and block design), with subtests which are relatively insensitive to brain damage the "hold" tests (information, comprehension, picture completion, and object assembly). However, the value of the deterioration index is disputed.

Appendix III illustrates sheets used in the Halstead-Reitan Neuropsychological Battery of tests.

RESULTS

Data from the three groups of subjects studied were derived from 56 variables which were then examined statistically in the Computer Department of the University of Manitoba Medical School. Tests applied were Analysis of Variance (ANOVA), Discriminant Analysis and Factor Analysis. ANOVA compares the mean scores for each variable among the groups while Discriminant Analysis studies the variables together in order to determine any significant correlations among them. Factor Analysis serves to identify clusters of variables which are arranged in order of their importance to the function of the set. While ANOVA establishes any significant difference which may exist among the groups, Discriminant Analysis and Factor Analysis help us to identify which variables or cluster of variables contribute most to the differences. This useful statistical technique effectively reduces a large number of variables, such as scores on neuropsychological tests, to a smaller more manageable number of clusters.

Examination of the data using the ANOVA showed that the majority of the means of the variables were significantly different in the three groups (Appendix I). The levels of statistical significance between paired groups showed that Group 2 (Chronic Schizophrenics) had the most deviant values and differed more from groups 1 and 3 than did 1 and 3 from each other. However, many of the subtests of the Halstead-Reitan Neuropsychological Battery are sensitive to age and education and these two variables were significantly different among the groups. It was therefore decided to adjust the means of the variables to allow for age and education differences and to repeat the ANOVA. Table 1 shows

the adjusted means and standard deviations. The ANOVA again showed significant differences among the three groups of subjects and the chronic schizophrenics were more deviant from group 1 (normal subjects) and group 3 (acute schizophrenics). A few of the subtests (digit symbol, spelling apraxia, agraphia, tactile suppression - right, auditory suppression) showed diminished probability but all other relationships remained the same. This would seem to confirm that in this study at least, age and education cannot account for the significant differences among the study groups.

Since the width of the third ventricle is of primary interest in this study, the distribution of measurements for each group of subjects is illustrated (Fig. 16) and the statistical difference between chronic schizophrenics and normal subjects is shown in Appendix I p.117 ($p<0.5$). While the chronic schizophrenics showed a definite shift to the right compared to the normal subjects and the acute schizophrenics, only six (14%) of the chronic patients (n=43) had a third ventricle width greater than the accepted normal of 8 mm. None of the normal subjects (n=48) in this study had a ventricle width greater than 8 mm. The acute schizophrenics did not differ significantly from the normal subjects and only one acutely ill patient had an enlarged ventricle.

A major hypothesis of this study was to demonstrate that although chronic schizophrenic patients show marked evidence of impaired brain function, this is not related to the size of the third ventricle. It was therefore decided to compare the chronic schizophrenics who had large third ventricles with those who had a normal size ventricle. Accordingly, subjects with a third ventricle of 8.0 mm or more (n=10) were compared statistically with those who had a third ventricle of less than 8.0 mm (n=33). The results of the ANOVA

MEANS AND STANDARD DEVIATIONS OF GROUPS
ADJUSTED FOR AGE AND EDUCATION

TABLE 1 SHOWING LEVELS OF STATISTICAL SIGNIFICANCE BETWEEN GROUPS (ANOVA)

	Means & Standard Deviations			Tests of Hypothesis		
Variable	Group 1	Group 2	Group 3	1/2	1/3	2/3
04	11.6 ± 16.7	117.5 ± 57.1	52.1 ± 25.0	**	**	**
05	29.3 ± 49.3	296.5 ± 153.1	126.8 ± 64.2	**	**	**
06	32.3 ± 65.6	446.2 ± 211.5	188.5 ± 91.2	**	**	**
07	-0.2 ± 1.8	8.6 ± 1.5	6.1 ± 2.3	**	**	*
08	7.7 ± 1.6	8.1 ± 1.9	8.4 ± 2.7			
09	14.0 ± 22.5	110.6 ± 30.9	68.6 ± 27.7	**	**	**
10	125.8 ± 13.7	72.6 ± 14.5	100.8 ± 13.0	**	**	**
11	122.5 ± 11.5	66.7 ± 15.9	89.1 ± 11.2	**	**	*
12	126.3 ± 11.8	68.0 ± 15.0	95.5 ± 11.9	**	**	*
13	44.9 ± 338.5	1743.5 ±1681.2	590.4 ± 404.9	**	**	**
14	-49.1 ± 162.0	1550.9 ±1170.9	531.1 ± 587.1	**	**	**
15	17.0 ± 164.6	864.8 ± 653.3	307.7 ± 267.6	**	**	**
16	2.0 ± 6.2	39.6 ± 30.0	13.3 ± 10.4	*	**	**
17	8.71 ± 1.5	3.4 ± 1.5	6.3 ± 2.3	**	*	*
18	6.37 ± 2.2	0.4 ± 1.5	3.0 ± 2.1	*	*	*
19	1.1 ± 2.4	14.6 ± 6.7	6.5 ± 4.8	**	**	**
20	1.5 ± 2.9	18.7 ± 11.4	9.4 ± 8.0	**	**	*
21	57.7 ± 7.4	29.6 ± 10.2	38.6 ± 11.6	*	**	*
22	50.3 ± 7.1	29.3 ± 8.5	37.4 ± 8.7	*	**	*

..cont'd.

TABLE 1 (cont'd)

Variable	Means & Standard Deviations Group 1	Group 2	Group 3	Tests of Hypothesis 1/2	1/3	2/3
23	13.2 ± 2.5	6.5 ± 2.9	11.2 ± 3.2	**	*	**
24	15.4 ± 3.4	3.8 ± 3.0	9.5 ± 3.5	*	**	*
25	13.6 ± 2.7	6.2 ± 3.1	9.5 ± 3.2	*	**	*
26	14.7 ± 2.7	4.5 ± 3.4	10.6 ± 2.4	**	**	*
27	12.1 ± 3.0	7.7 ± 2.8	9.5 ± 2.7	*	*	*
28	13.3 ± 2.4	6.6 ± 2.9	11.4 ± 2.8	**	*	**
29	14.2 ± 2.5	2.4 ± 2.8	7.0 ± 2.6	*	**	*
30	12.7 ± 2.7	3.1 ± 2.6	7.5 ± 1.9	**	*	*
31	14.1 ± 3.0	4.4 ± 3.0	10.3 ± 2.5	**	*	*
32	12.6 ± 2.8	4.5 ± 3.0	8.9 ± 2.4	**	*	*
33	15.3 ± 4.0	5.8 ± 3.1	9.2 ± 3.0	**	*	*
34	0.3 ± 0.7	2.0 ± 1.3	0.4 ± 1.1	*	NS	*
35	-0.1 ± 0.3	0.8 ± 0.5	0.02 ± 0.3	*	NS	*
36	-0.0 ± 0.5	0.7 ± 0.8	0.4 ± 0.7	*	*	NS
37	0.03 ± 0.4	0.6 ± 0.9	0.1 ± 0.3	*	NS	*
38	-0.2 ± 0.2	0.7 ± 0.9	0.1 ± 0.5	*	NS	*
39	0.1 ± 0.4	1.0 ± 0.8	0.3 ± 0.5	*	NS	*
40	-0.02 ± 0.5	1.2 ± 0.8	0.4 ± 0.6	*	*	*
41	-0.03 ± 0.3	0.8 ± 0.5	0.4 ± 0.3	*	*	*

..cont'd.

TABLE 1 (cont'd)

	Means & Standard Deviations			Tests of Hypothesis		
Variable	Group 1	Group 2	Group 3	1/2	1/3	2/3
42	-0.02 ± 0.01	0.1 ± 0.2	-0.02 ± 0.01	*	NS	*
43	0.04 ± 0.4	1.0 ± 0.8	0.3 ± 0.5	*	NS	*
44	0.03 ± 1.9	8.1 ± 4.1	3.2 ± 2.6	*	*	*
45	-0.7 ± 0.8	4.2 ± 4.1	0.4 ± 1.2	*	NS	*
46	-0.7 ± 0.8	3.3 ± 3.9	0.5 ± 1.2	*	NS	*
47	-0.3 ± 2.2	6.1 ± 4.1	3.7 ± 3.1	*	*	*
48	-1.1 ± 1.6	6.5 ± 4.2	3.4 ± 2.5	*	*	*
49	17.2 ± 8.2	48.7 ± 10.9	22.8 ± 8.4	*	NS	*
50	15.3 ± 5.8	30.6 ± 4.7	15.5 ± 1.5	*	NS	*
51	-0.3 ± 0.5	1.5 ± 2.4	0.4 ± 1.2	*	NS	*
52	-0.3 ± 0.4	1.7 ± 2.2	0.1 ± 0.7	*	NS	*
53	0.04 ± 0.6	0.3 ± 1.2	0.1 ± 0.4			
54	-0.1 ± 0.1	0.6 ± 1.3	0.03 ± 0.2	*	NS	*
55	-0.2 ± 0.2	1.2 ± 2.1	0.01 ± 0.6	*	NS	*
56	-0.3 ± 0.1	1.2 ± 2.2	0.1 ± 0.6	*	NS	*

Group 1: Normal subjects
Group 2: Chronic Schizophrenics
Group 3: Acute Schizophrenics

*:$p<0.05$
**:$p<0.01$

FIGURE 16 Distribution of third ventricle measurements in the three study groups.

Fig. 16

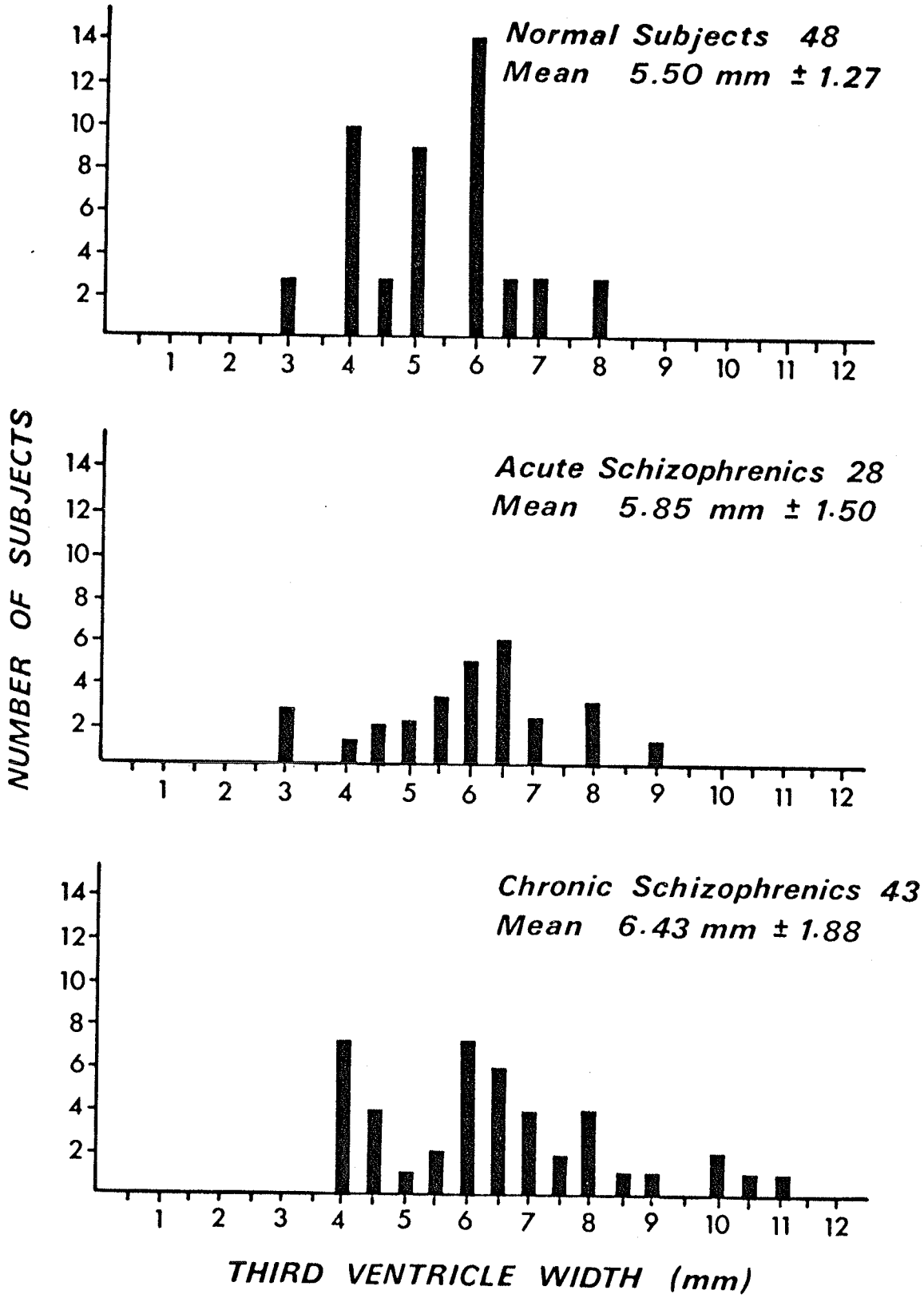

Normal Subjects 48
Mean 5.50 mm ± 1.27
Acute Schizophrenics 28
Mean 5.85 mm ± 1.50
Chronic Schizophrenics 43
Mean 6.43 mm ± 1.88
NUMBER OF SUBJECTS
THIRD VENTRICLE WIDTH (mm)

TABLE 2

STATISTICAL COMPARISON OF CHRONIC SCHIZOPHRENICS WITH NORMAL SIZE THIRD VENTRICLES (GROUP 2<8.0) AND THOSE WITH LARGE VENTRICLES (GROUP 2≥8.0) AFTER ADJUSTMENT FOR AGE AND EDUCATION

	Means & Standard Deviations			Tests of Hypothesis		
Variable	Group 1	Group 2<8.0	Group 2≥8.0	1 vs 2<8.0	1 vs 2≥8.0	2<8.0 vs 2≥8.0
04	11.6 ± 16.7	111.9 ± 60.7	132.8 ± 39.8	*	*	NS
05	29.3 ± 49.3	280.6 ± 150.2	351.4 ± 169.5	*	*	NS
06	32.3 ± 65.6	404.0 ± 224.7	590.7 ± 164.8	*	*	*
07	-0.2 ± 1.8	9.1 ± 1.4	7.0 ± 1.7	*	*	*
08	7.7 ± 1.6	6.5 ± 1.4	13.2 ± 1.4	*	*	*
09	14.0 ± 22.5	105.7 ± 32.0	130.7 ± 23.3	*	*	*
10	125.8 ± 13.7	73.5 ± 14.7	69.6 ± 14.3	*	*	NS
11	122.5 ± 11.5	66.2 ± 15.4	68.3 ± 18.7	*	*	NS
12	126.3 ± 11.8	68.1 ± 14.9	67.5 ± 16.7	*	*	NS
13	44.9 ± 338.5	1858.6 ± 1879.3	1372.7 ± 803.9	*	*	NS
14	-47.1 ± 162.0	1680.8 ± 1329.8	1146.9 ± 364.5	*	*	*
15	17.0 ± 164.6	957.3 ± 717.5	539.0 ± 259.6	*	*	*
16	2.0 ± 6.2	41.9 ± 33.6	31.2 ± 8.33	*	*	NS
17	8.7 ± 1.5	3.4 ± 1.6	3.4 ± 1.0	*	*	NS
18	6.4 ± 2.2	0.2 ± 1.6	0.9 ± 0.8	*	*	NS
19	1.1 ± 2.4	15.1 ± 6.9	12.3 ± 6.1	*	*	NS
20	1.5 ± 2.9	18.1 ± 11.0	20.3 ± 13.6	*	*	NS
21	57.7 ± 7.4	30.2 ± 9.8	27.6 ± 12.1	*	*	NS
22	50.3 ± 7.1	29.2 ± 8.6	29.6 ± 8.5	*	*	NS

TABLE 2 (cont'd)

Variable	Means & Standard Deviations			Tests of Hypothesis		
	Group 1	Group 2<8.0	Group 2≥8.0	1 vs 2<8.0	1 vs 2≥8.0	2<8.0 vs 3
23	13.2 ± 2.5	6.4 ± 2.8	6.7 ± 3.7	*	*	NS
24	15.4 ± 3.4	4.2 ± 3.1	2.1 ± 2.8	*	*	NS
25	13.6 ± 2.7	6.7 ± 3.3	4.4 ± 1.2	*	*	NS
26	14.7 ± 2.7	4.9 ± 3.3	2.9 ± 3.7	*	*	NS
27	12.1 ± 3.0	7.6 ± 3.0	8.1 ± 2.3	*	*	NS
28	13.3 ± 2.4	6.3 ± 3.0	7.5 ± 2.5	*	*	NS
29	14.2 ± 2.5	2.7 ± 2.9	1.2 ± 2.7	*	*	NS
30	12.7 ± 2.7	2.8 ± 2.1	4.4 ± 3.9	*	*	NS
31	14.1 ± 3.0	3.9 ± 3.1	6.4 ± 2.1	*	*	*
32	12.6 ± 2.8	4.7 ± 2.9	3.6 ± 3.3	*	*	NS
33	15.3 ± 4.0	5.8 ± 3.2	6.0 ± 3.2	*	*	NS
34	0.3 ± 0.7	1.7 ± 1.2	2.9 ± 1.6	*	*	*
35	-0.1 ± 0.3	0.8 ± 0.5	0.8 ± 0.6	*	*	NS
36	-0.01 ± 0.5	0.7 ± 0.9	0.9 ± 0.7	*	*	NS
37	0.03 ± 0.4	0.51 ± 0.8	0.8 ± 1.1	*	*	NS
38	-0.2 ± 0.2	0.8 ± 1.0	0.4 ± 0.6	*	*	NS
39	0.1 ± 0.4	1.1 ± 0.8	0.6 ± 0.6	*	*	NS
40	-0.02 ± 0.5	1.2 ± 0.9	1.4 ± 0.7	*	*	NS
41	-0.03 ± 0.3	0.8 ± 0.5	0.8 ± 0.5	*	*	NS

TABLE 2 (cont'd)

	Means & Standard Deviations			Tests of Hypothesis		
Variable	Group 1	Group 2<8.0	Group 2≥8.0	1 vs 2<8.0	1 vs 2>8.0	2<8.0 vs 3
42	-0.02 ± 0.01	0.1 ± 0.3	0.01 ± 0.1	*	NS	NS
43	0.04 ± 0.4	1.0 ± 0.7	1.2 ± 0.9	*	*	NS
44	0.03 ± 1.9	7.8 ± 4.2	9.0 ± 4.2	*	*	NS
45	-0.7 ± 0.8	4.1 ± 4.3	4.3 ± 3.5	*	*	NS
46	-0.7 ± 0.8	2.8 ± 3.7	4.8 ± 4.8	*	*	NS
47	-0.3 ± 2.2	5.8 ± 4.1	7.2 ± 4.5	*	*	NS
48	-1.1 ± 1.6	5.9 ± 4.6	8.6 ± 2.4	*	*	*
49	17.2 ± 8.2	51.8 ± 11.5	36.1	*	N/A	N/A
50	15.3 ± 5.8	29.9 ± 5.5	33.4	*	N/A	N/A
51	-0.3 ± 0.5	1.4 ± 2.6	2.0 ± 1.9	*	*	NS
52	-0.3 ± 0.4	1.6 ± 2.1	9.5 ± 2.4	*	*	*
53	0.04 ± 0.6	0.5 ± 1.3	-0.2 ± 0.7			
54	-0.1 ± 0.1	-0.04 ± 0.5	2.4 ± 2.4	NS	*	*
55	-0.2 ± 0.2	1.3 ± 2.3	0.9 ± 1.6	*	*	NS
56	-0.3 ± 0.1	1.1 ± 2.3	1.4 ± 2.3	*	*	NS

Group 1: Normal subjects
Group 2<8.0: Chronic schizophrenics; Third ventricle less than 8.0 mm in width.
Group 2≥8.0: Chronic schizophrenics; Third ventricle equal to or greater than 8.0 mm in width.

*:$p<0.05$
**:$p<0.01$

using means adjusted for age and education for the two subgroups and normal subjects are shown in Table 2. We see that while each subgroup of chronic schizophrenics retains its significant difference from the normal subjects, there are a few significant differences between the two subgroups. The variables which did show a significant difference were:

(6) Total Trail Making Time

(7) Impairment Index

(9) Category Test

(14) Tactual Performance - left

(15) Tactual Performance - both

(31) WAIS - Block Design

(34) Constructional Apraxia

(48) Finger-tip Writing - left

(52) Tactile Suppression - left

(54) Auditory Suppression - left

These represent only 19% of the total number of neuropsychological tests employed and considering the small n(=10) in the subgroups with large ventricles, one must interpret the results cautiously. Reitan(173, 176) considers Total Trail Making Time, the Impairment Index and the Category Test to be valid indicators of generalised brain damage. The results of this study do not provide any conclusive evidence to suggest a significant difference between patients with large third ventricles and those with normal size ventricles. The apparent increased impairment of left sided sensory perception (variables 14,48,52,54), presumably implicating the right hemisphere is an interesting finding which is difficult to understand.

When the data were subjected to discriminant analysis it was found

that the following variables were the best discriminators between the two subgroups of chronic schizophrenics:

(4) Trail Making - part A

(7) Impairment Index

(24) Comprehension

(29) Digit Symbol

(37) Agraphia

These statistical results suggest a general impairment of brain function in chronic schizophrenia with little evidence to support cerebral lateralisation.

Using Discriminant Analysis it was found that the following set of 22 variables was the best discriminator of the three study groups:

(3) Education

(4) Trail Making - part A

(6) Total Trail Making Time

(7) Impairment Index

(8) III Ventricle

(11) Performance I.Q.

(14) Tactual Performance - left

(16) Tactual Performance - total time

(20) Speech Perception

(24) Comprehension (WAIS)

(29) Digit Symbol (WAIS)

(35) Anomia

(37) Agraphia

(38) Alexia

(40) Acalculia

(43) Right left disorientation

(45) Finger agnosia - right

(48) Finger tip writing - left

(52) Tactile suppression - left

(54) Auditory suppression - left

(55) Visual suppression - right

(56) Visual suppression - left

Using this set of variables it was possible to classify correctly 85.7% of the normal group, 100% of the chronic schizophrenics and 89.5% of the acute schizophrenics. As in the univariate analysis it was easier to discriminate groups 1 and 2. The Standardised Discriminant coefficients (Table 3) of these 22 variables are shown with their discriminant scores, the magnitude of the coefficient giving an idea of how much each variable contributes to the function of the set. We note that the third ventricle contributes a relatively low value of -0.28 and that neither the third ventricle nor the impairment index contribute as much as left auditory suppression and left visual suppression.

Taking the 22 variables identified by discriminant analysis we found four clusters for the whole set (Table 4) while factor analysis applied to each group separately showed some clusters appearing in all three groups (Table 5). These are Tactual Performance Time (TPT) -

left and Total TP time; Performance I.Q. and Comprehension, Trail Making A and Total Trail Making Time; Auditory Suppression Right; Visual Suppression right and left. The third ventricle grouped with different variables in each group and appears to be more important in the chronic schizophrenics (factor 3) than in the acute schizophrenics (factor 4) or in the normal subjects (factor 6). Factor 1 consists of those variables which are of most importance to the function of the groups while factors 2, 3, 4, etc. are of diminishing value.

Univariate analysis within each group shows significant correlations between third ventricle size and some of the neuropsychological tests. In the normal subjects with dysarthria ($p<0.05$), Audioverbal agnosia ($p<0.01$), astereognosis - left ($p<0.01$); in the acute schizophrenics with spelling apraxia ($p<0.01$), agraphia ($p<0.01$), acalculia ($p<0.01$) and finger tip writing - left ($p<0.05$). These tests can be related neuroanatomically to both left and right hemisphere function (Tables 6 and 7) suggesting a global or generalized brain dysfunction.

Looking again at the 22 variables from our discriminant analysis of which 20 were tests, we can relate them to brain dysfunction as follows (Reitan 171,173,176):

General brain dysfunction:

- Trail Making total time
- Impairment Index
- Comprehension

Left hemisphere dysfunction:

- Total TPT time

TABLE 3. STANDARDIZED DISCRIMINANT COEFFICIENTS

VARIABLE	
Education	0.77
Trail A	-0.80
Trail Total	1.39
Impair Index	-0.72
III Ventricle	-0.28
Performance I.Q.	-0.39
Tactual Performance--Left	1.33
Total Tactual Perception Time	-1.67
Speech Perception	-1.87
Comprehension	0.99
Digit Symbol	1.05
Anomia	-0.61
Agraphia	1.19
Alexia	0.48
Acalculia	0.59
Right-Left Disorientation	-0.40
Finger Agnosia--Right	-0.62
Finger Tip Writing--Left	0.20
Tactile Suppression--Left	-0.98
Auditory Suppression--Left	3.98
Visual Suppression--Right	0.75
Visual Suppression--Left	-3.72

TABLE 4. FACTOR ANALYSIS--CLUSTERING OF 22 VARIABLES (n=71)

FACTOR 1	FACTOR 2	FACTOR 3	FACTOR 4
Education	Alexia	TPT-Lt.	Tactile Supp. Lt.
Trail A	Finger Agnosia Rt.	Total TPT Time	
Trail Total	Aud. Supp. Lt.	Speech Perception	
Impair T Index	Visual Supp. Rt.	Agraphia	
III Ventricle	Visual Supp. Lt.	R-L Disorientation	
P-I.Q.			
Composition			
Digit Symbol			
Anomia			
Acalculia			
Finger Tip Writing Lt.			

TABLE 5. FACTOR ANALYSIS--CLUSTERING OF 22 VARIABLES WITHIN EACH EXPERIMENTAL STUDY GROUP.

GROUP 1 (NORMALS)

1	2	3	4	5	6
TPT-Lt.	Education	Trail A	Acalculia	Impair Index	III Ventricle
Total TPT Time	P-I.Q.	Trail Total	Finger Tip Writ. Lt.	Speech Percep.	Alexia
Anomia	Comprehension	R-L Disorientation			
	Digit Symbol	Finger Agnosia Rt.			
	Agraphia				

GROUP 2 (CHRONIC SCHIZOPHRENIA)

1	2	3	4	5	6
Trail A	Alexia	Education	Impair Index	TPT-Lt.	Tactile Supp. Lt.
Total Trail	Finger Agnosia Rt.	III Ventricle	Digit Symbol	TPT-Total Time	
Impair Index	Aud. Supp. Rt.	P-I.Q.	Finger Tip Writ. Lt.	Speech Percep.	
Anomia	Visual Supp. Rt.	Comprehension		R-L Disorient.	
Agraphia	Visual Supp. Lt.				
Acalculia					

GROUP 3 (ACUTE SCHIZOPHRENIA)

1	2	3	4	5	6	7
Trail A	Tactile Supp. Lt.	Speech Perception	III Ventricle	TPT-Lt.	Education	Digit Symbol
Total Trail	Aud. Supp. Lt.	Agraphia	Alexia	Total TPT Time	R-L Disorientation	
Impair Index	Visual Supp. Rt.	Acalculia	Finger Agnosia Rt.			
P-I.Q.	Visual Supp. Lt.	Finger Tip Writ. Lt.				
Comprehension						

TABLE 6. NEUROPSYCHOLOGICAL FINDINGS INDICATIVE OF LOCALISED BRAIN DYSFUNCTION.

LEFT TEMPORAL LOBE:

.similarities poor on W.A.I.S.

.right auditory suppression

.left upper quadrant visual suppression

LEFT POSTERIOR TEMPORAL CORTEX; ANGULAR GYRUS:

.auditory verbal and number agnosia

.visual form and letter agnosia

.dyslexia

.speech perception impaired

LEFT POSTERIOR FRONTAL CORTEX:

.aphasia (expressive)

.anomia

.spelling dyspraxia

.dysgraphia

RIGHT TEMPORAL LOBE:

.left auditory suppression

.right upper quadrant visual suppression

RIGHT ANTERIOR TEMPORAL CORTEX:

.picture arrangement poor on W.A.I.S. (little difference between VIQ and PIQ)

- continued -

TABLE 6 .(Cont'd)

LEFT PARIETAL AREA:

.finger-tip writing impaired on right

RIGHT PARIETAL AREA:

.finger-tip writing impaired on left

.block design poor on W.A.I.S.

ANTERIOR TO CENTRAL FISSURE:

.finger tapping worse than Tactual Performance Test with same hand (contralateral)

.Category Test and Trail B Test both impaired suggests both frontal lobes affected

POSTERIOR TO CENTRAL FISSURE:

.Tactual Performance Test worse than finger tapping with same hand (contralateral)

.auditory, visual and tactual suppression

- Speech perception (temporo-parietal area)
- Digit symbol
- Anomia (posterior frontal area)
- Agraphia (posterior frontal area)
- Alexia (posterior parietal area)
- Acalculia (posterior parietal area)
- Right-left disorientation (posterior parietal area)
- Right finger agnosia (posterior parietal area)
- Visual suppression - right (temporo-parietal area)

Right hemisphere dysfunction:

- Trail Making Part A
- Performance I.Q.
- TPT left (parietal area)
- finger-tip writing - left (parietal area)
- tactile suppression - left (parietal area)
- auditory suppression - left (posterior temporal area)
- visual suppression - left (temporo-parietal)

The cerebral localization of these cortical functions has been established over the years by clinical neuroscientists and is of paramount importance in the diagnosis of localized brain disease (Table 6). As can be seen, the temporo-parietal areas appear to be incriminated as the primary areas of dysfunction but we must accept this cautiously and bear in mind the limitations of the test battery. The temporo-parietal areas have close connections with the thalamus (posterior ventral), the hippocampus, the amygdala, and the basal ganglia. In the left hemisphere list we have the cluster of symptoms known clinically as Gerstmann's syndrome

(dyslexia, dyscalculia, right-left disorientation and finger agnosia) which is related to pathology in the left angular gyrus. The finding of auditory and visual suppression directs our attention to the temporo-parietal areas and also to the geniculate bodies and the peri-aqueduct area. Although there are test results suggestive of right hemisphere dysfunction it is surprising that the classic disturbances are not evident. One would expect apraxias, poor scores on rhythm, block design, picture arrangement, TPT location and TPT memory which all deal with spatial concepts. This may mean that the disturbance is primarily subcortical.

Table 7 gives subtests of the Halstead-Reitan Neuropsychological Battery grouped according to function tested and shows their relationship to the right and left hemispheres of the brain. Results from the study seem to implicate the left hemisphere more than the right and on both sides it appears that the temporo-parietal areas (and the posterior frontal on the left side) are more impaired. Anomia and agraphia are related to motor function of the left (dominant) hemisphere but unfortunately there are no available tests for the corresponding areas of the right hemisphere. While cerebral lateralisation may influence test findings, particularly in the diagnosis of individual cases, it was felt not to be significant in this study. Only 12 of a total of 138 subjects were left handed (four of the normal subjects, five chronic schizophrenics and three acute schizophrenics). Furthermore the work of Milner (153) in Montreal showed that 75% of left handed persons had left cerebral dominance, 15% had mixed dominance and only 15% had right hemisphere dominance.

TABLE 7.. SUBTESTS OF THE HALSTEAD-REITAN NEUROPSYCHOLOGICAL BATTERY GROUPED ACCORDING TO FUNCTION TESTED AND SHOWING RELATIONSHIP TO IMPAIRMENT OF CEREBRAL HEMISPHERES.

RIGHT HEMISPHERE

Construction Dyspraxia	Part B > Part A	Slower With Left Hand		Dystereognosis Lt. Finger Dysgnosia Lt. Tactile Supp. Lt. Auditory Supp. Lt. Visual Supp. Lt.	VIQ > PIQ
APHASIA SYMPTOMS	TRAIL MAKING	TACTUAL PERFORMANCE	FINGER TAPPING	SENSORY PERCEPTION	W.A.I.S.
Dysnomia Dyslexia Dysgraphia Dyscalculia	Part B < Part A	Slower With Right Hand		Dystereognosis Rt. Finger Dysgnosia Rt. Tactile Supp. Rt. Auditory Supp. Rt. Visual Supp. Rt.	VIQ < PIQ

LEFT HEMISPHERE

< = less (worse) than

> = more (better) than

DISCUSSION

The results of this study suggest that while chronic schizophrenics suffer some degree of deterioration of brain function as measured by psychological tests, only a small percentage of these patients have an enlargement of the third ventricle. If we accept 8 mm as the maximum normal width of the third ventricle then only six (14%) of the chronic schizophrenics in this study have an enlarged third ventricle. This is in marked contrast to the majority of reports in the literature where other techniques have been used, but is in agreement with the findings of Peltonen (165), Storey (202), Kingsley and Trimble(120) and Gluck et al. (59). We are reminded of the cautionary statements of Hill (92), Jellinek (109) and Marsden (144) that there are many causes of cerebral ventricular enlargement. Since it is generally accepted that age (at least not until after 60 years) and treatment modalities used in schizophrenia do not influence the size of the cerebral ventricles we are left with the puzzling question of why some chronic schizophrenics and other mentally ill patients (211,217) have an enlarged third ventricle. The small percentage of patients affected suggests that there is little if any relationship between schizophrenia and ventricle size. The proposal of Haug (74) and Lemke (130) that schizophrenia is associated with a congenital hypoplasia of the diencephalon certainly gains no support since all but one of the acute schizophrenics and the great majority of chronic schizophrenics have normal size third ventricles.

The more popular suggestions that a central atrophic process in the brain is associated with a progressive schizophrenic illness leaves unanswered the question of why only some patients are affected. All 43 chronic patients in this study had been ill for many years (an average of 19 years) and all were in hospital because they showed the "defect"

symptoms with poor prognosis for social rehabilitation (110,112,143, 219,222,230). Yet 86% of them had normal size third ventricles! Atrophy of the brain resulting from an auto-immune process would be expected, if we consider the usual course of established auto-immune diseases, to be relentlessly progressive with ultimately a common pathology in all patients. There is no evidence in this study that all schizophrenics will ultimately develop enlarged cerebral ventricles.

The theory of a slow acting neurotropic virus is more difficult to discard although one would still wonder about the small percentage of patients with gross pathology. Virus diseases are well known for producing varied clinical pictures and great differences in severity of symptoms, e.g., poliomyelitis, and also show a predilection for certain cell types. It is conceivable that chronic schizophrenia is the late stage of a progressive slow virus infection which varies in severity from patient to patient. The demonstration of a cytotoxic cerebrospinal fluid by Tyrell (208) and the cellular pathology recently reported by Averback (10) and Stevens (201) would support the theory of a virus infection having an affinity for periventricular and periaqueductal grey matter. It is interesting that the work of Heath and his colleagues (75-78,81,83) with depth electrodes also suggested pathology in the same regions of the brain.

While there is a great deal of evidence to support a biochemical disorder in schizophrenia, particularly a disturbance of dopaminergic neurons, it is difficult to relate such a disorder to an atrophic process in the diencephalon. Dopamine-rich regions of the brain are numerous and widespread and undoubtedly have many different functions. The concept of cellular degeneration subsequent to collapse of the

neurotransmitter system leading ultimately to atrophic changes and enlarged ventricles is not supported by this or other studies. Crow (29) in a recent paper would have us believe that there are two syndromes in schizophrenia; one with positive symptoms due to a neurochemical disturbance which responds to drugs and a second with negative symptoms due to a degenerative process and not responding to treatment. However, it should be pointed out that 1) not all schizophrenics with positive symptoms (delusions, hallucinations, thought disorder) respond to drugs, 2) many chronic schizophrenics with negative symptoms (lack of drive, emotional flattening, poverty of thoughts) do respond to medication, and 3) only a small percentage of schizophrenics show evidence of degenerative organic brain damage.

In an effort to identify specific regions of the brain affected in schizophrenia a broad battery of neuropsychological tests was employed in order to test as many as possible of the numerous and varied functions of the brain. The results showed that chronic schizophrenics differed markedly from both normal subjects and acutely ill patients, most of the subtests showing a significant difference at the 1% level of probability. Even after adjustment to allow for age and educational differences among the study groups the chronic schizophrenics remained significantly different. Parsons and Prigatano (164) warn us of variables which may influence score results on neuropsychological tests. In addition to age and education, localised brain lesions, physical illness, aphasia, visual defects, emotional distress, alcoholism and handedness (already discussed) are notable. By careful screening and selection of the chronic patients both as to physical health and

behavioural patterns these problems were hopefully eliminated. However, two other possible variables have to be considered when assessing the test results. First, there is the effect of neuroleptic drugs which were being administered to all of the patients. If anything, one would expect neuroleptics to enhance test performance since by their action these drugs improve perception of reality and the milieu and in many cases make the patient more alert. Golden (61), Johnstone et al(110), and Weinberger and Wyatt (219, 222) were concerned about drug effect and reported from their studies that drugs used in schizophrenia have no significant effect on test performance.

Second, there is the effect of duration of disease which, in chronic schizophrenics, is often analogous to length of hospitalisation. Clinically, in the writer's experience, schizophrenics do not show any evidence of becoming progressively mentally impaired but tend to 'plateau' after a few years and then maintain their level of function until the effects of senility cause further deterioration. The chronic patients in this study were under 60 years of age and had been ill for a mean period of approximately 20 years, varying from nine years to 28 years. The effects of "institutionalisation" may also be over-rated. Some 20 years ago psychiatrists 'discovered' that the chronic symptoms of schizophrenia were not due to the disease at all but merely the result of prolonged hospital care. Consequently hospital wards were rapidly closed down and chronic patients quickly placed in the 'healthier' environment of the community. Today it is generally conceded that this policy has done little if anything to correct the situation; the chronic patient with his 'defect' symptoms is still with us and it seems to be part of the disease process after all. Weinberger and Wyatt (219,222) found no significant relationship between test performance and duration of hospitalisation.

In an effort to identify specific regions of the brain affected in schizophrenia the data were submitted to discriminant analysis and factor analysis and in this way the variables which were of most importance in distinguishing one study group from another were identified. We have seen that 22 variables (of which 20 were neuropsychological tests) were identified in this way (Table 3) and that nearly all of these tests suggest impairment of the posterior temporal and posterior parietal regions of both hemispheres and the left posterior frontal region. The discriminant coefficients of these variables tend to suggest that the left hemisphere is more impaired than the right (speech perception, tactual performance and agraphia all having relatively high coefficients) but the overall results give more support to a global disturbance of brain function. These test results are compatible with the clinical features of chronic schizophrenia although they do not explain the emotional flattening.

While the analysis of the data is an interesting scientific exercise one must be cautious before relating the results to specific anatomical areas of the brain. The Halstead-Reitan Neuropsychological Battery is perhaps the best comprehensive psychological test battery available to measure organic brain impairment but like all behavioural tests it has its limitations. For example, excluding motor activity there are no reliable tests for the frontal lobes in the Halstead-Reitan battery. On the other hand, the results of statistical analysis in this study show an interesting correlation with the findings reported by Golden (62) who found less density of brain tissue on C.T. scan studies of the left frontal region in chronic schizophrenics. Also Ingvar (97,98) and Mathew et al. (145) reported a bilateral increase of cerebral blood flow posterior to the central sulcus in schizophrenics compared to normal subjects. This suggests a higher metabolic rate (rather than an atrophic process) in the

parietal and posterior temporal regions of schizophrenic brains. Haug (73,74) in his pneumoencephalographic studies found cortical atrophy to be more marked in the temporal and parietal areas bilaterally in his group of chronic schizophrenics.

A statistical comparison of the data from the two subgroups of schizophrenics (those with large third ventricles versus those with normal size third ventricles) failed to reveal any convincing statistical differences. This would seem to support the hypothesis that the dementia of chronic schizophrenia is not related to third ventricle size and we note that the discriminant coefficient for third ventricle size was of relatively low value.

Accepting the results of this study as valid, we are now faced with the dilemma of trying to correlate the findings of basic neuroscience studies with the results of clinical and neuropsychological studies. To date there have been no reports in human subjects which shed any light on the problem but recently Phillipson and Pycock (168), using techniques of microdissection and microradiochemical assay of catecholamines in rats, have revealed a new dopamine pathway which has its origin in neurons of the ventral tegmentum of the midbrain and project to the medial and medial aspect of the lateral habenular nuclei. They point out that the habenular nuclei are rich in dopamine and they believe that these nuclei may act as a control centre which regulates dopaminergic activity in limbic forebrain areas including the frontal cortex, the cingulate gyrus and the nucleus accumbens. Figure 4 shows us the numerous connections of the habenular nuclei and the central position they occupy in the diencephalon. Brodal (20) refers to important connections between the rostral brain stem and the hypothalamus and septal areas. He

also points out that there are well established connections between the temporo-parietal cortex (Brodmann's areas 21,39,40,41) and the cingulate gyrus which in turn has strong connections with the pre-frontal cortex.

Since the neuroanatomical connections have been established we are now in a position to make cautious speculations. Perhaps the clinical features of chronic schizophrenia which are manifestations of the temporo-parietal cortex are really secondary manifestations of a disease which has its primary pathology in the upper brain stem and diencephalon. In other words, the functional collapse, whatever its cause, is projected via the habenula and the cingulate gyrus to the more remote neo-cortex of the temporal and parietal lobes. As a somewhat crude analogy we may think of renal disease producing hypertension which in turn creates an invalid suffering from cardiac failure. Or, disease of the pancreas leading to diabetes mellitus resulting in blindness. A more pertinent example may be the 'kindling effect' of creating a cortical epileptic focus by repeated and persistent electrical stimulation of the homologous cortex of the opposite hemisphere.

Future Avenues of Research

This and similar studies make it very evident that a longitudinal study over a period of several years is desirable but this unfortunately is fraught with difficulties. After only a few years an attempt was made to locate the patients of the acute schizophrenic group (Group 3) but only three could be located. Schizophrenics are notorious 'drifters', frequently moving from one address to another, from town to town and often from hospital to hospital. Furthermore, the clear cut classification of schizophrenia described at the beginning of this century (simple,

hebephrenic, catatonic and paranoid types) is of little value today, perhaps because schizophrenics are often subjected to 'multi-pharmacology' at an early stage in their illness. What we tend to find is a mixed clinical picture of 'undifferentiated' type. However a follow-up study of a large sample of acute young schizophrenics with careful documentation of symptoms and annual measurement of the third ventricle over a period of 10 or 15 years could only be rewarding. The techniques of ultrasonography (2,38,49,66,188,209,225) as used in this study are very reliable and provide a quick, non-intrusive and inexpensive method to study a large population.

The field of neurochemistry offers tantalising opportunities: for example the role of serotonin in schizophrenia and its relationship to the dopaminergic system; studies of melatonin and its possible relationship to the abnormal sleep patterns of schizophrenics. Immunological studies of families to identify anti-brain antibodies requires further investigation particularly in view of the evidence which exists for a hereditary factor in schizophrenia.

In our present state of knowledge and clinical practice it would appear that anti-psychotic medication serves to counteract the effects of the primary pathological process but in the majority of cases is doing little if anything to arrest the disease process.

CONCLUSIONS

In conclusion, the results of this study indicate:

1. Only a small percentage (14%) of chronic schizophrenics have an enlarged third ventricle judging from measurement of the width of the ventricle. The technique of using ultrasound has proved to be a reliable, valid, inexpensive and non-intrusive method of obtaining measurements of ventricular width. In addition there is no pain or discomfort to the patient.
2. Acutely ill schizophrenics do not have enlarged third ventricles compared to a group of normal subjects. The majority (81%) of third ventricles in normal subjects have a width of 3 mm to 6 mm.
3. Both acutely ill and chronic schizophrenics showed evidence of impaired brain function when subjected to a broad range of neuropsychological tests but the chronic group of patients was significantly more impaired than the acute group. Discriminant analysis of the neuropsychological data showed that the best discriminators of the study groups were tests related to functions of temporal, parietal and left frontal lobes of the brain but these findings must be interpreted with caution.
4. Statistical comparison of the neuropsychological data from chronic schizophrenics with large third ventricles versus those with normal size ventricles showed only a few variables which differed significantly. This suggests that the dementia of chronic schizophrenia is not related to third ventricle size.

APPENDIX I

Statistical data for the three study groups showing means of the variables and the levels of statistical significance between groups.

GROUP 1. NORMAL SUBJECTS - STATISTICAL VALUES.

VARIABLE	N	$\bar{X}$	S.E.	S.D.
Age	50	28.45	1.23	8.68
Sex	50	0.50	0.00	0.49
Education	48	11.02	0.20	1.36
Trail Making Part A	50	31.23	1.39	9.80
Trail Making Part B	49	80.34	5.55	38.82
Trail Making Total	49	111.55	5.93	41.48
Impairment Index	50	1.90	0.25	1.77
Third Ventricle Width	48	5.50	0.18	1.27
Category Test	50	34.89	2.99	21.14
Verbal I.Q.	47	114.63	1.90	12.77
Performance I.Q.	47	109.53	1.54	10.57
Full Scale I.Q.	47	113.74	1.54	10.55
Tactual Performance--Right	50	346.19	29.95	211.78
Tactual Performance--Left	49	265.12	18.51	129.58
Tactual Performance--Both	46	147.97	12.37	85.29
Tactual Performance--Total Time	50	11.05	0.46	18.60
Tactual Performance--Memory	49	7.75	0.18	1.21
Tactual Performance--Location	47	5.04	0.32	2.02
Rhythm Test	50	3.62	0.33	2.36

- continued -

GROUP 1. NORMAL SUBJECTS - STATISTICAL VALUES

VARIABLES	N	$\bar{X}$	S.E.	S.D.
Speech Perception	50	4.68	0.29	2.02
Finger Tapping--Right	50	50.50	0.99	6.97
Finger Tapping--Left	50	45.15	0.98	6.92
WAIS: Information	49	12.00	0.37	2.56
WAIS: Comprehension	49	13.02	0.47	3.25
WAIS: Arithmetic	14	11.50	0.67	2.50
WAIS: Similarities	49	12.85	0.35	2.42
WAIS: Digit Span	15	10.80	0.79	3.05
WAIS: Vocabulary	14	12.35	0.63	2.37
WAIS: Digit Symbol	48	11.43	0.39	2.72
WAIS: Picture Completion	48	10.56	0.36	2.46
WAIS: Block Design	49	11.85	0.39	2.60
WAIS: Picture Arrangement	15	11.00	0.71	2.75
WAIS: Object Assembly	15	12.60	0.96	3.69
Constructional Apraxia	46	0.58	0.11	0.74
Anomia	45	0.05	0.03	0.20
Spelling Apraxia	45	0.13	0.08	0.50
Agraphia	43	0.09	0.06	0.36
Alexia	45	0.04	0.03	0.20

- continued -

GROUP 1. NORMAL SUBJECTS - STATISTICAL VALUES

VARIABLES	N	$\bar{X}$	S.E.	S.D.
Dysarthria	45	0.15	0.05	0.36
Acalculia	45	0.20	0.06	0.40
Auditory Verbal Agnosia	45	0.11	0.05	0.31
Ideokinetic Apraxia	45	0.00	0.00	0.00
Right-Left Disorientation	45	0.20	0.07	0.45
Total Items Failed (Anomia - Right-Left Disorientation)	43	1.58	0.24	1.54
Finger Agnosia--Right	44	0.11	0.07	0.49
Finger Agnosia--Left	44	0.11	0.07	0.44
Finger Tip Writing--Right	44	1.11	0.30	2.00
Finger Tip Writing--Left	44	0.43	0.19	1.22
Astereognosis--Right	25	20.23	1.31	5.44
Astereognosis--Left	27	16.03	1.02	5.28
Tactile Suppression--Right	45	0.04	0.04	0.29
Tactile Suppression--Left	45	0.00	0.00	0.00
Auditory Suppression--Right	45	0.08	0.09	0.59
Auditory Suppression--Left	45	0.00	0.00	0.00
Visual Suppression--Right	45	0.02	0.02	0.14
Visual Suppression--Left	45	0.00	0.00	0.00

GROUP 2. CHRONIC SCHIZOPHRENICS - STATISTICAL VALUES

VARIABLES	N	$\bar{X}$	S.E.	S.D.
Age	43	40.46	1.12	7.37
Sex	43	0.67	0.07	0.47
Education	36	8.22	1.78	2.88
Trail Making Part A	42	90.33	13.20	72.90
Trail Making Part B	40	232.84	24.70	152.00
Trail Making Total	40	321.54	50.87	209.19
Impairment Index	42	7.14	0.26	1.31
Third Ventricle Width	43	6.43	0.28	1.88
Category Test	41	90.26	4.89	31.35
Verbal I.Q.	41	82.63	2.74	17.59
Performance I.Q.	41	77.80	2.61	16.75
Full Scale I.Q.	40	80.04	2.67	17.13
Tactual Performance--Right	38	1379.55	277.21	1708.85
Tactual Performance--Left	37	1140.72	188.59	1147.18
Tactual Performance--Both	34	688.17	109.47	638.36
Tactual Performance--Total Time	43	41.45	5.00	34.97
Tactual Performance--Memory	34	4.20	0.34	1.98
Tactual Performance--Location	34	1.44	0.24	1.41
Rhythm Test	42	11.61	1.02	6.64

- continued -

GROUP 2. CHRONIC SCHIZOPHRENICS - STATISTICAL VALUES

VARIABLES	N	$\bar{X}$	S.E.	S.D.
Speech Perception	41	15.21	2.01	12.89
Finger Tapping--Right	42	34.95	1.58	10.25
Finger Tapping--Left	41	33.34	1.33	8.51
WAIS: Information	41	7.87	0.59	3.80
WAIS: Comprehension	41	6.02	0.55	3.56
WAIS: Arithmetic	36	6.97	0.50	2.99
WAIS: Similarities	41	6.48	0.64	4.12
WAIS: Digit Span	37	8.05	0.47	2.87
WAIS: Vocabulary	37	7.10	0.55	3.35
WAIS: Digit Symbol	41	4.46	0.41	2.66
WAIS: Picture Completion	41	5.09	0.41	2.68
WAIS: Block Design	41	6.17	0.50	3.23
WAIS: Picture Arrangement	37	4.91	0.46	2.82
WAIS: Object Assembly	36	6.47	0.56	3.28
Constructional Apraxia	41	1.46	0.21	1.39
Anomia	41	0.56	0.09	0.59
Spelling Apraxia	40	0.62	0.14	0.89
Agraphia	39	0.48	0.14	0.88
Alexia	41	0.46	0.14	0.89

- continued -

GROUP 2. CHRONIC SCHIZOPHRENICS - STATISTICAL VALUES

VARIABLES	N	$\bar{X}$	S.E.	S.D.
Dysarthria	41	0.73	0.12	0.80
Acalculia	41	0.97	0.13	0.85
Auditory Verbal Agnosia	41	0.58	0.07	0.49
Ideokinetic Apraxia	41	0.04	0.03	0.21
Right-Left Disorientation	41	0.85	0.11	0.76
Total Items Failed (Anomia - Right-Left Disorientation)	41	6.75	0.72	4.66
Finger Agnosia--Right	36	3.02	0.67	4.01
Finger Agnosia--Left	37	2.56	0.63	3.83
Finger Tip Writing--Right	38	4.86	0.65	4.03
Finger Tip Writing--Left	38	5.18	0.75	4.67
Astereognosis--Right	4	32.87	7.47	6.61
Astereognosis--Left	5	25.79	3.18	7.12
Tactile Suppression--Right	35	1.22	0.41	2.43
Tactile Suppression--Left	35	1.28	0.37	2.30
Auditory Suppression--Right	35	0.34	0.19	1.16
Auditory Suppression--Left	35	0.31	0.22	0.82
Visual Suppression--Right	36	0.66	0.33	1.98
Visual Suppression--Left	36	0.66	0.35	2.00

GROUP 3. ACUTE SCHIZOPHRENICS - STATISTICAL VALUES

VARIABLES	N	$\bar{X}$	S.E.M.	S.D.
Age	45	24.59	2.42	6.99
Sex	45	0.58	0.19	0.49
Education	41	10.53	0.25	1.64
Trail Making Part A	43	45.83	2.83	18.60
Trail Making Part B	43	120.44	8.10	53.13
Trail Making Total	43	166.25	9.49	62.27
Impairment Index	43	4.58	0.38	2.25
Third Ventricle Width	28	5.85	0.28	1.50
Category Test	38	59.44	4.39	27.09
Verbal I.Q.	42	104.35	2.05	13.31
Performance I.Q.	40	93.79	1.71	11.58
Full Scale I.Q.	42	99.92	1.87	12.17
Tactual Performance--Right	42	560.73	51.46	333.54
Tactual Performance--Left	42	528.88	80.06	518.89
Tactual Performance--Both	41	284.90	37.98	243.23
Tractual Performance--Total Time	45	24.73	1.53	30.49
Tactual Performance--Memory	40	6.65	0.37	2.35
Tactual Performance--Location	40	3.62	0.35	2.23
Rhythm Test	43	5.97	0.71	4.66

- continued -

GROUP 3. ACUTE SCHIZOPHRENICS - STATISTICAL VALUES

VARIABLES	N	$\bar{X}$	S.E.M.	S.D.
Speech Perception	43	8.00	1.21	7.94
Finger Tapping--Right	43	41.41	1.70	11.15
Finger Tapping--Left	43	39.13	1.25	8.23
WAIS: Information	42	11.59	0.53	3.14
WAIS: Comprehension	43	10.58	0.53	3.52
WAIS: Arithmetic	37	9.67	0.49	2.67
WAIS: Similarities	43	11.23	0.36	2.36
WAIS: Digit Span	37	9.62	0.43	2.63
WAIS: Vocabulary	38	11.18	0.44	2.72
WAIS: Digit Symbol	43	8.20	0.35	2.29
WAIS: Picture Completion	43	8.18	0.28	1.88
WAIS: Block Design	43	10.41	0.36	2.41
WAIS: Picture Arrangement	38	8.86	0.39	2.46
WAIS: Object Assembly	37	9.40	0.48	2.95
Constructional Apraxia	28	0.67	0.20	1.05
Anomia	28	0.07	0.05	0.26
Spelling Apraxia	28	0.28	0.12	0.62
Agraphia	28	0.07	0.05	0.26
Alexia	28	0.17	0.54	0.10

- continued -

GROUP 3. ACUTE SCHIZOPHRENICS - STATISTICAL VALUES

VARIABLES	N	$\bar{X}$	S.E.M.	S.D.
Dysarthria	28	0.25	0.08	0.44
Acalculia	28	0.35	0.10	0.55
Auditory Verbal Agnosia	28	0.28	0.08	0.46
Ideokinetic Apraxia	28	0.00	0.00	0.00
Right-Left Disorientation	28	0.28	0.10	0.53
Total Items Failed (Anomia - Right-Left Disorientation)	28	2.85	0.55	2.92
Finger Agnosia--Right	23	0.52	0.21	1.03
Finger Agnosia--Left	23	0.56	0.22	1.07
Finger Tip Writing--Right	24	3.00	0.67	3.29
Finger Tip Writing--Left	25	2.32	0.51	2.41
Astereognosis--Right	5	23.20	3.26	7.30
Astereognosis--Left	4	16.37	0.74	1.49
Tactile Suppression--Right	26	0.35	0.21	1.09
Tactile Suppression--Left	26	0.15	0.12	0.61
Auditory Suppression--Right	25	0.08	0.08	0.40
Auditory Suppression--Left	25	0.04	0.04	0.20
Visual Suppression--Right	26	0.15	0.12	0.61
Visual Suppression--Left	26	0.19	0.11	0.56

LEVELS OF STATISTICAL SIGNIFICANCE BETWEEN GROUPS.

VARIABLE	Gps 1/2	Gps 1/3	Gps 2/3
1. Age	**	*	**
2. Sex	*		
3. Education	**		**
4. Trail Making Part A	**		**
5. Trail Making Part B	**	*	**
6. Trail Making Total	**	*	*
7. Impairment Index	**	**	**
8. Third Ventricle Width	*		
9. Category Test	**	**	**
10. Verbal I.Q.	**	**	**
11. Performance I.Q.	**	**	**
12. Full Scale I.Q.	**	**	**
13. Tactual Performance--Right	**		**
14. Tactual Performance--Left	**		**
15. Tactual Performance--Both	**		**
16. Tactual Performance--Total Time	**	*	**
17. Tactual Performance--Memory	**	**	**
18. Tactual Performance--Location	**	**	**
19. Rhythm Test	**	*	**

- continued -

LEVELS OF STATISTICAL SIGNIFICANCE BETWEEN GROUPS (CONT.)

VARIABLE	Gps 1/2	Gps 1/3	Gps 2/3
20. Speech Perception	**		**
21. Finger Tapping--Right	**	**	**
22. Finger Tapping--Left	**	**	**
23. WAIS: Information	**		**
24. WAIS: Comprehension	**	**	**
25. WAIS: Arithmetic	**	*	**
26. WAIS: Similarities	**	*	**
27. WAIS: Digit Span			**
28. WAIS: Vocabulary	**		**
29. WAIS: Digit Symbol	**	**	**
30. WAIS: Picture Completion	**	**	**
31. WAIS: Block Design	**	*	**
32. WAIS: Picture Arrangement	**	**	**
33. WAIS: Object Assembly	**	**	**
34. Constructional Apraxia	**		**
35. Anomia	**		**
36. Spelling Apraxia	**		*
37. Agraphia	**	**	
38. Alexia	*		

- continued -

LEVELS OF STATISTICAL SIGNIFICANCE BETWEEN GROUPS (CONT.)

VARIABLE	Gps 1/2	Gps 1/3	Gps 2/3
39. Dysarthria	**		**
40. Acalculia	**		**
41. Auditory Verbal Agnosia	**		**
42. Ideokinetic Apraxia			
43. Right-Left Disorientation	**		**
44. Total Items Failed (35-43)	**		**
45. Finger Agnosia--Right	**		**
46. Finger Agnosia--Left	**		**
47. Finger Tip Writing--Right	**	*	*
48. Finger Tip Writing--Left	**	*	**
49. Astereognosis--Right	*		*
50. Astereognosis--Left	*		*
51. Tactile Suppression--Right	**		*
52. Tactile Suppression--Left	*		**
53. Auditory Suppression--Right			
54. Auditory Suppression--Left	*		*
55. Visual Suppression--Right			
56. Visual Suppression--Left			

*: $p<0.05$

**: $p<0.01$

Group 1: Normal Subjects

Group 2: Chronic Schizophrenics

Group 3: Acute Schizophrenics

APPENDIX II: ECHOENCEPHALOGRAPHY

Ultrasound is defined as sound with a frequency over 20,000 cycles per second (20 KHz). The use of ultrasound to demonstrate mid-line structures in the skull was first described by Leksell in 1956. The Curie brothers in 1880 first discovered the piezo-electric effect of some crystals which when stressed generated an electrical potential across opposing surfaces. Ultrasonic waves are produced by applying short pulses of high frequency electrical energy to a piezo-electric crystal. In the Ecoline-20 model used in this study (Fig. 11) barium titanate crystal is used and the transducer functioned at a frequency of 1 megacycle per second. Since the vibrations produced on the crystal are intermittent, the crystal can act as a receiver of the reflection of the pulses (echoes) as well as transmit them. The echoes are converted into electrical signals which are amplified and fed into a cathode ray oscilloscope.

The frequency of ultrasound used in diagnostic machines is harmless to patients but at very high frequencies, heat is produced and tissue damage can result.

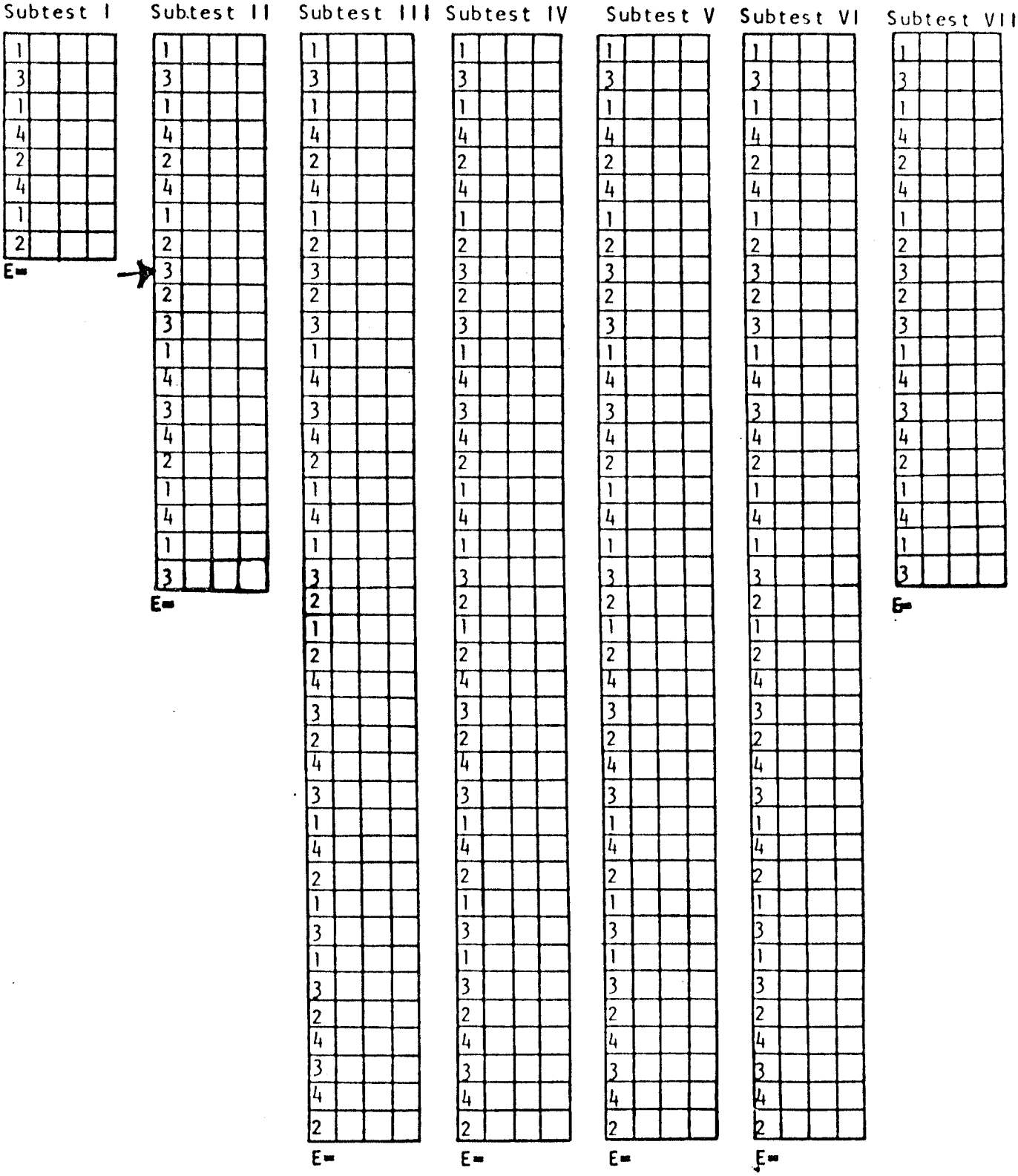
APPENDIX III: SCORE SHEETS USED WITH THE HALSTEAD-REITAN BATTERY OF NEUROPSYCHOLOGICAL TESTS.

HALSTEAD CATEGORY TEST

Adult Form

e_____ Date_____ Examiner_____ Total Number of Errors_____

m



e right-hand column for each subtest is used to check correct responses and the left-hand umn to record each incorrect response by number. The middle column merely separates the umns in which the results are recorded.)

TACTUAL PERFORMANCE TEST

Name_____ Date_____ Examiner_____

Indicate form used:

_____ 10-figure board - Ages 15 years & older
_____ 6-figure board - vertical position - Ages 9 through 14 years
_____ 6-figure board - horizontal position - Ages 5 through 8 years

Trial	Hand	Circle	Time	
1	Dominant Hand	R L	' " =	_____
2	Non-dominant Hand	R L	' " =	_____
3	Both Hands		' " =	_____

Total Time:_____

Memory:_____

Localization:_____

Comments:

USE REVERSE SIDE FOR DRAWING

SEASHORE RHYTHM TEST

Name: _____ Date: _____ Errors: _____

	A	B	C
1			
2			
3			
4			
5			
6			
7			
8			
9			
10			

Adult Form

Speech-sounds Perception Test

e_____Date_____Examiner_____Score_____

ections: Underline the syllable which you hear.

Series A	Series B	Series C
theeks zeeks theets zeets	1. peem beem peen been	1. deeld deel beeld beel
weech yeech weej yeej	2. theez theerz feez feerz	2. weev heev weef heef
leeg bleeg leeng bleeng	3. sheesh sheez zeesh zeez	3. thee fee theer feer
peez peest teez teest	4. veef weef veeth weeth	4. neeld neel meeld meel
freeb fleeb freep fleep	5. theel feel theeld feeld	5. seed zeed seet zeet
pleeb preeb pleed preed	6. peet peent beet beent	6. yeeg yeek heeg heek
seek seech sheek sheech	7. treep treeb teep teeb	7. meen meem neen neem
neek neenk meek meenk	8. steets speets steeks speeks	8. theerd theer teerd teer
wheech heech wheesh heesh	9. beert beerd peert peerd	9. heez wheez heev wheev
preet preekt peet peekt	10. sheed zeed sheend zeend	10. neep teep neet teet

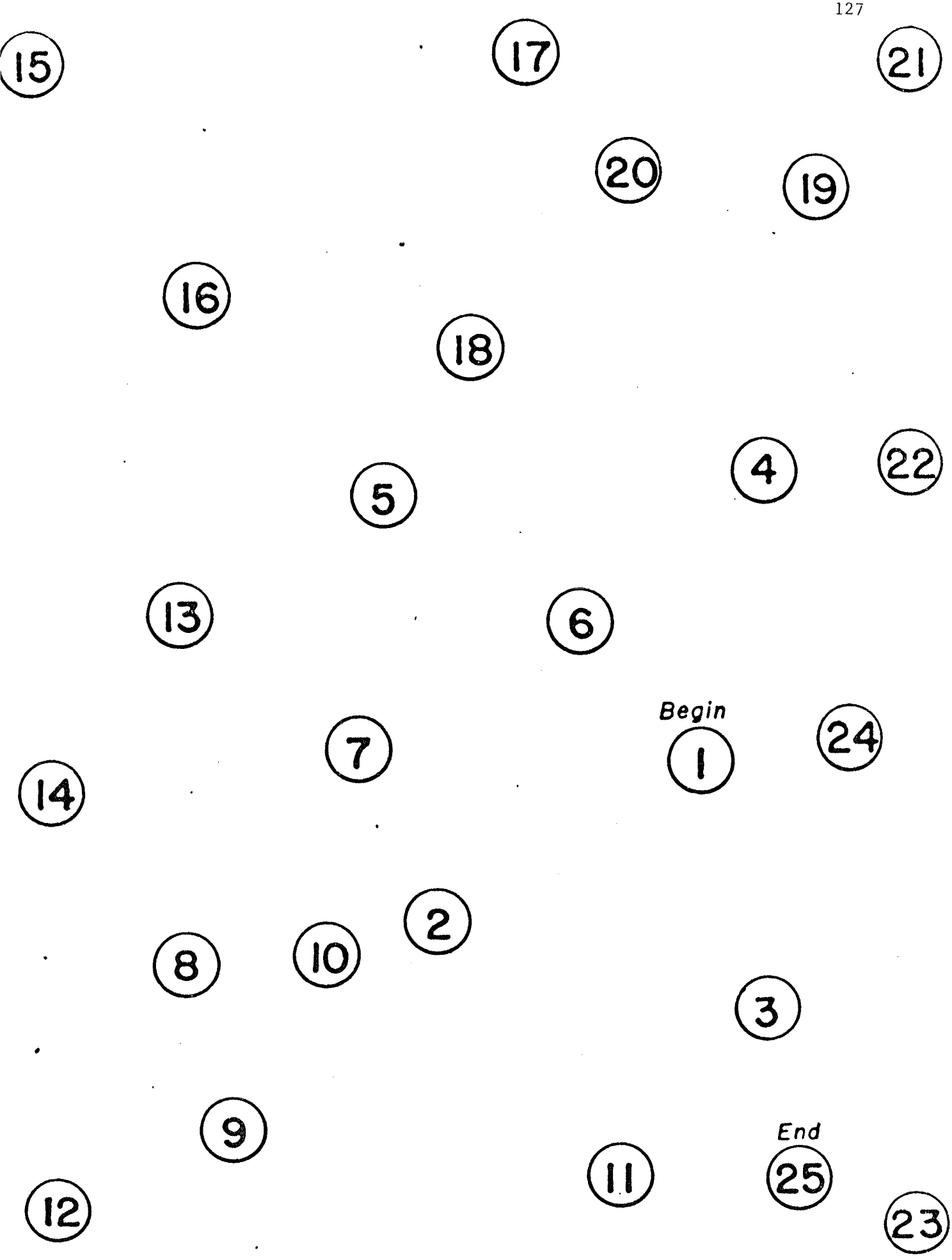
Series D	Series E	Series F
heep heet wheep wheet	1. seeng sheeng seen sheen	1. yeem yeen heem heen
keev keem feev feem	2. geerd keerd geer keer	2. leern theern leer theer
neek neeg meek meeg	3. keen geen keem geem	3. feeth fees theeth thees
cheem cheen sheem sheen	4. ween weeng heen heeng	4. reeg treeg reek treek
feep theep feet theet	5. teed teet peed peet	5. yeed yeet weed weet
heeld weeld heel weel	6. keets keez teets teez	6. meep meet deep deet
deed teed deend teend	7. theet theent zeet zeent	7. deez dees beez bees
teesh peesh teez peez	8. beep peep beet peet	8. teeld teel peeld peel
weef veef weev veev	9. tee pee teer peer	9. meel meer feel feer
leen heen leeng heeng	10. beeb beed deeb deed	10. ween wheen weem wheem

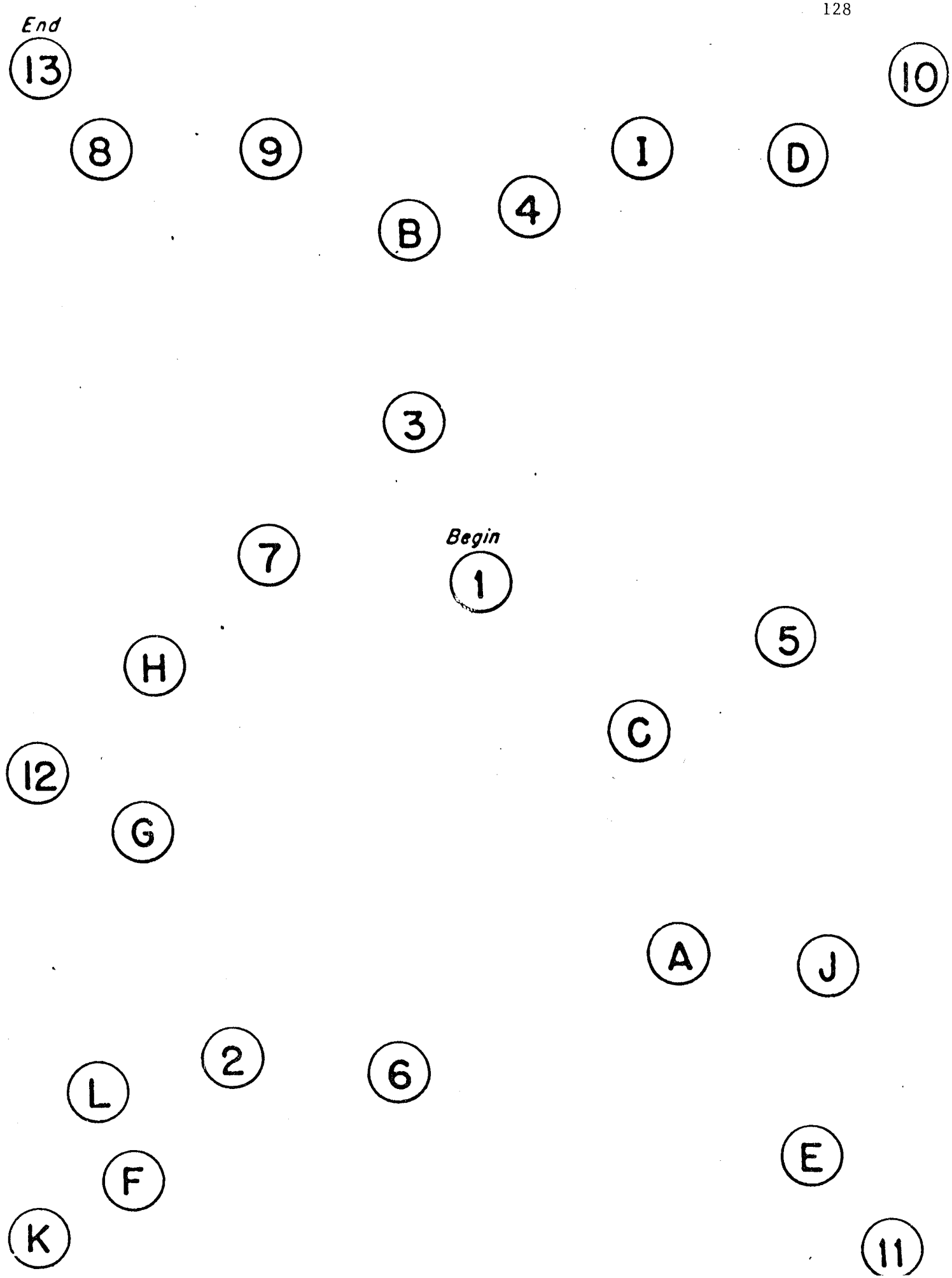
FINGER TAPPING TEST

E: _____ DATE: _____ EXAMINER: _____

HANDEDNESS: _____

LEFT HAND	RIGHT HAND
1.	1.
2.	2.
3.	3.
4.	4.
5.	5.
OTAL: _____ / 5	TOTAL: _____ / 5
EAN: _____	MEAN: _____


15
17
21
20
19
16
18
4
22
5
13
6
Begin
24
7
1
14
2
8
10
3
9
End
11
25
12
23


End
13
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K
11

APHASIA SCREENING TEST

ame: _____ Date: _____ Examiner: _____

1. Copy SQUARE - *Construction Apraxia*	18. Repeat TRIANGLE - *Central Dysarthria*
2. Name SQUARE - *Anomia*	19. Repeat MASSACHUSETTS - *Central Dysarthria*
3. Spell SQUARE - *Spelling Apraxia*	20. Repeat METHODIST EPISCOPAL - *Central Dysarthria*
4. Copy CROSS - *Construction Apraxia*	21. Write SQUARE - *Agraphia*
5. Name CROSS - *Anomia*	22a Read SEVEN - *Alexia*
6. Spell CROSS - *Spelling Apraxia*	22b Repeat SEVEN - *Auditory Verbral Agnosia*
7. Copy TRIANGLE - *Construction Apraxia*	23. Repeat-Explain: HE SHOUTED THE WARNING - *Central Dysarthria & Verbal Agnosia*
8. Name TRIANGLE - *Anomia*	24. Write HE SHOUTED THE WARNING - *Agraphia*
9. Spell TRIANGLE - *Spelling Apraxia*	25. Compute 85 - 27 - *Acalculia*
0. Name BABY - *Anomia*	26. Compute 17 X 3 - *Acalculia*
1. Write CLOCK - *Agraphia*	27. Name KEY - *Anomia*
2. Name FORK - *Anomia*	28. Demonstrate use of KEY - *Ideokinetic Apraxia*
3. Read 7 SIX 2 - *Letter/Number Agnosia & Alexia*	29. Draw KEY - *Construction Apraxia*
4. Read M G W - *Letter Agnosia*	30. Read PLACE LEFT HAND TO RIGHT EAR - *Alexia*
5. Reading I - *Alexia*	31. Place LEFT HAND TO RIGHT EAR - *Right-Left Disorientation & Body Agnosia*
6. Reading II - *Alexia*	32. Place LEFT HAND TO LEFT ELBOW - *Right-Left Disorientation & Auditory Verbal Agnosia*

Italic type indicates neurological disability being tested.

Indicate instance in which stimulus is not perceived or is incorrectly perceived.

FINGER AGNOSIA:

	2	4	1	3	5	2	5	3	1	4	2	4	1	3	5	2	5	3	1	4
RIGHT																				
LEFT																				

FINGER-TIP NUMBER WRITING:

		4 6 3 5		3 5 4 6		6 5 4 3		5 4 6 3		6 3 5 4	
RIGHT	1		2		3		4		5		
LEFT	1		2		3		4		5		

ASTEREOGNOSIS:

RIGHT I ○ □ △ + II + ○ □ △ Total Time: _____

LEFT I △ + ○ □ II □ △ + ○ Total Time: _____

TACTILE SUPPRESSION:

1	RH	LH	BH	LH	BH	RH	LH	RH	BH	LH	RH	BH
2	RF	LH	FH	LH	FH	RF	LH	RF	FH	LH	RF	FH
3	LF	RH	FH	LF	FH	RH	LF	RH	FH	LF	RH	FH

AUDITORY SUPPRESSION:

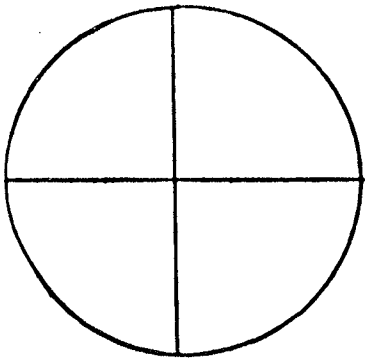
RE	LE	BE	LE	BE	RE	LE	RE	BE	LE	RE	BE

VISUAL SUPPRESSION:

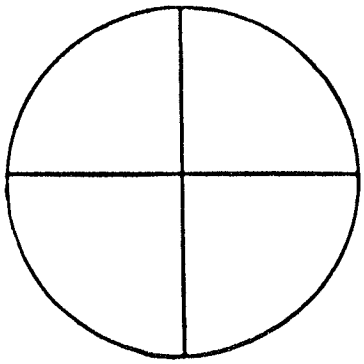
1	RV	LV	BV	LV	BV	RV	LV	RV	BV	LV	RV	BV
2	RV	LV	BV	LV	BV	RV	LV	RV	BV	LV	RV	BV
3	RV	LV	BV	LV	BV	RV	LV	RV	BV	LV	RV	BV

VISUAL FIELDS:

LEFT EYE



RIGHT EYE



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