STUDIES OF THE PSYCHOSES OF EPILEPSY

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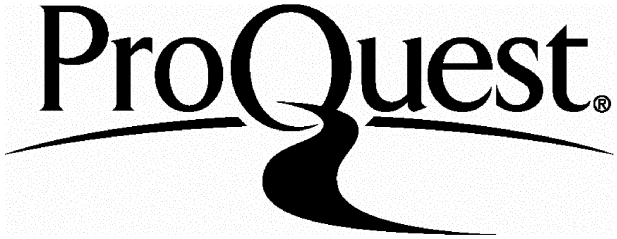

ABSTRACT

There are two components to this Thesis. The first is a review of the literature. Associations between epilepsy and psychiatry have been known since historical times, but most interest in the psychopathology associated with epilepsy emerged in the French, German and English literatures of the nineteenth century. This is the first substantial literature review which has been carried out in this area, and the author has gone to original sources where that has been possible. Following the literature review a number of conclusions about relationships between epilepsy and psychoses are made. One of these is that patients with temporal lobe epilepsy have an increased liability to develop psychoses.

Four studies are presented. In the first, an attempt was made to classify the types of psychoses that patients with epilepsy present and their relationship to psychosis in the absence of epilepsy. It is concluded that patients with temporal lobe epilepsy are more likely to present with nuclear schizophrenia, and that this form is most likely to be present with a left sided lesion.

This is followed by three imaging studies. Two of these relate to structural imaging, namely a CT study and an MRI study, and examine the hypothesis that an organic structural brain disorder underlies the development of these psychoses. Essentially, few significant differences are found which support the hypothesis. The third study is a Positron Emission Tomography study, examining changes of brain function in patients with epileptic psychosis. Here, significant associations are noted between altered cerebral metabolic rate of oxygen use and the presence of psychosis.

The final part of the thesis is a discussion of these findings in relationship to the literature review of the first section. It is concluded that the schizophrenia-like psychoses of epilepsy form a good biological model to further our understanding of schizophrenia.

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SECTION 1:

HISTORICAL INTRODUCTION

HISTORICAL INTRODUCTION

The history of epilepsy is closely associated with that of psychiatry. Both have links with gods, demons, witches and the supernatural, and have evoked prejudice, disaffection and malediction from other members of society. Reference to psychiatric illness and epilepsy can be found in the earliest of medical writings, but further, their symbiotic relationship has been a persistent historical theme.

It is widely acknowledged that the disease the Greeks called "sacred" referred to epilepsy, and the first monograph on the subject was that of Hippocrates (460-358 BC). "On the Sacred Disease" was a medical text written largely for lay readers, and its central theme was that epilepsy was not sacred or divine, but a natural affection with an hereditary origin. The Greeks it seems surmised that epilepsy was divine because it was wonderful: only a God could throw a man to the ground, convulse him and then restore him to normality.

Hippocrates noted that epilepsy did not affect all men equally; it attacked the phlegmatic and not the bilious. This was associated with its pathogenesis which was due to disease of the brain. However, Hippocrates also pronounced:

> "and men ought to know that from nothing else but thence (from the brain) comes joys, delights, laughter and sports and sorrows griefs,

> despondency, and lamentations ... and by this same organ we become mad and delirious, and fears and terrors assail us ... As long as the brain is at rest, the man enjoys his reason, but the depravement of the brain arises from phlegm and bile (Hippocrates 1939 p 366)

The brain was thus the seat of both the falling sickness and madness, and both were related to phlegm. There are early examples of the association of the sacred disease to madness. Herodotus, discussing the mad behaviour of the Persian King Cambyses, says that from birth he suffered from:

> " ... A certain great disease ... which some people call sacred. And thus it would not be unlikely that if the body suffered from a great disease the mind was not sound either". (Temkin 1971 p 15).

Hippocrates himself mused on the lay notions of the disease, stating that:

> "Terrors which happen during the night, and fevers, and delirium, and jumpings out of bed, and frightful apparitions, and fleeing away, - all these they hold to be plots of Hecate, and the invasions of the Heroes ..." (p 358).

Hecate was the moon goddess, sometimes merged with Artemis, to whom was attributed, amongst other things, raving and madness.

Hercules, whose birth was delayed by Hera to favour the earlier delivery and hence succession of Eurystheus to the title of ruler of Greece, may have had epilepsy, and is said to have killed his own children in a seizure of madness. The supposition that this was epileptic related to a comment in a Hippocratic treatise that:

> "When the uterus is near the liver and the hypochondrium and

> produces suffocation, the woman turns up the white of her eyes, becomes cold, gnashes her teeth, saliva flows into her mouth and she resembles the persons seized by the Herculean disease". (Hippocrates 1839-1861 vol 8 p 32-34: Temkin p 20).

Although this does not definitively state that Hippocrates was referring to epilepsy, it is suggestive. This quote also serves to illustrate another historical link between epilepsy and psychiatry, namely that between hysteria and epilepsy (Trimble 1981: 1989).

Further evidence comes from the writings of Aristotle. In considering the question of why talented individuals are always melancholic, he gives Hercules as an example.

> "For he apparently had this constitution and therefore epileptic afflictions were called after him "the sacred disease" by the ancients. His made fit in the incident with the children points to this ..." (Aristotle, quoted by Simon 1978 p 229).

Aretaeus noted that people with epilepsy were:

> "Languid, spiritless ... unsociable, and not disposed to hold intercourse, nor to be sociable, at any period of life; sleepless, subject to many horrid dreams and without appetite". (Adams 1856).

These ideas link with the Galenic concept of humours, and their relationship to temperament. The latter was construed as a somatic rather than a psychological state, and was derived by combination of four basic humours: phlegm, blood, black bile and yellow bile. The melancholic disposition was related to black bile, but it was also related to "raving", and to epilepsy. For

Galen, the two had a related pathogenesis:

> "This humour arises in some people in large quantity either because of their original humoural constitution or by their customary diet which is transformed into this humour by digestion in the blood vessels. Like thick phlegm, this heavy atrabilious blood obstructs the passage through the middle or posterior cavity of the brain and sometimes causes epilepsy. When its excess pervades the brain matter itself, it causes melancholy ..." (Siegel 1970)

Lunatics

There is a clear association in historical writings between the moon, epilepsy and insanity. The gospels provide an early example. The ninth chapter of St Marks Gospel, with additions from St Matthew's and St Luke's versions of the same incident reads as follows:

> "Master I have brought to thee my son for he is a lunatic and sore vexed and hath a dumb spirit. And wheresoever he taketh him he teareth him and bruising him hardly departeth from him; and he foameth and gnasheth with his teeth and pineth away. And they brought him unto Him, and when He saw him straightaway the spirit take him and he fell to the ground and wallowed foaming. And He asked his father, "How long is it since this came unto him?", And he said, "Of a child, and of times it has cast him into the fire and into the water to destroy him".

Jesus rebuked the spirit, which then left the boy, and he was "as one dead ... but Jesus took him by the hand, and lifted him up; and he arose".

In Rome epilepsy was known as "morbidus lunaticus". Araeteus referred to it as an affliction of persons who have sinned against the moon and it was a widely held belief that the timing of seizures was related to the light of the

moon, with a tendency to have attacks at full moon. The term lunatic thus embraced periodic affections, including epilepsy, but also varieties of mental illness. The astrologist Julius Firmicius Maternus in the forth C. A.D. noted that the moon made people convulsed or lunatic, and referred to "lunaticos epilempticos" (Temkin p 94).

Middle Ages

With the waning of Greek influence on Roman scholars, few advancements in medical thinking emerged until the Renaissance. The centre of the learning moved to the Arab world, and few new ideas on epilepsy emerged. The great Rhazes (A.D. 865-925) believed in lunar theories, and the associations between demons, madness and epilepsy remained. The writer Ali B. Rabban al-Tabari referred to epilepsy as "the diviner's disease" emphasising the prophetic powers of some epileptics (Temkin l971). Although the relationship between religiosity and epilepsy is referred to later, the visions of many soothsayers and prophets have been suggested as manifestations of epilepsy. A good example from this era is Mohammed (570-623). Born in Mecca, his possible epilepsy seems to have been denied by the Islamic tradition, and promulgated largely by Christian writers. He is reported to have had attacks in which he became pale, resembled a drunkard, fell down and sweated profusely. At such times he had visual and auditory hallucinations. After several years of such attacks, in which the angel Gabriel came before him, he

came to see himself as a prophet. Nonetheless, the inhabitants of Mecca considered him to be a madman and one possessed, and his wife thought he was a fanatic deceived by the artifices of a demon (Howden 1873).
A christian equivalent was St Paul of Tarsus (Landsborough 1987). He too had ecstatic visions, was spurned by the Galatians because of some illness, and certainly during his conversion he "dropped to the ground and heard a voice" (Acts 9:18).

Thus Mohammed and St Paul were possible examples of people with epilepsy who had episodes which would today be referred to as psychotic, but with associated religiosity. There is a considerable amount of ancient literature emphasising the associations between epilepsy, ecstasy and prophesy (Temkin 1971), themes which are continually revived up to the present day.

More specific associations of epilepsy and insanity are hard to find in the Middle Ages. Benivieni described automatic behaviour, and early accounts of what are now referred to as partial seizures are recorded. Such observations allowed Marci (1995-1667) to broaden the definition of epilepsy, "To any affection of the body where the victims are disordered in their minds, while the members (of the body), be it all, or some, are moved against their will (quoted by Temkin 1971 p 192).

Shakespeare however may have had insights:

Iago.	My Lord is fallen into an epilepsy, This is his second fit, he had one yesterday.
Cassio	Rub him about the temples. No, forbear:
Iago	The lethargy must have its quiet course: If not, he foam at the mouth; and by and by breaks out to savage madness.

Othello iv i

The Eighteenth Century

With the enlightenment came attempts to oppose supernatural and demonic explanations for disease, but epilepsy was bound by its historical association with possession. This extended far beyond lay and theological considerations, and was reflected in the writings of such physicians as Stahl (1695-1734), Hoffmann (1660-1742), van Swieten (1700-1772) and even Willis (1621-1675). In 1729 an English doctor, Harle wrote:

> "Tis true, in one place a person is said to have a devil, and be mad, and other to be demoniac, and yet is called a lunatic, or one troubled with the falling sickness. If we take in both texts, we have the full meaning, which is, that the madness and epilepsy these people labour'd under were caus'd by the devil". (Harle 1729 p 22).

The influence of the moon was still in evidence. Richard Mead (1673-1754) in his "Treatise Concerning the Influence of the Sun and Moon upon Human Bodies, and the Diseases thereby produced", wrote that epileptic fits:

> "Do constantly recur every new and full moon ... the Latins (call sufferers)... Lunatici ... and it may not be improper to remark in this place, that the raving fits of mad people, who keep lunar periods, are generally accompanied with epileptic symptoms: which was attested to me as a constant observation by the late learned Dr Tyson, formerly

> physician to Bethlem hospital, who upon that account usually called such patients epileptic mad". (Mead 1748).

The first substantial treatise on epilepsy was that published by Tissot (1728-1797) in 1770. Although opposing the ideas of lunar influences, he introduced another obliquity, namely an association between masturbation and epilepsy. His book L'onanism (1782) spelled out the consequences of masturbation, which included epilepsy, venereal pleasures in general being one cause of sympathetic epilepsy (Tissot 1770). His ideas influenced thinking on epilepsy for over a hundred years, and were related to the later introduction of bromides for treatment. Likewise, the idea that masturbation caused insanity lived on for several generations.

The Nineteenth Century

The growth of the hospital system led to concentrations of patients with various problems coming under close medical scrutiny. Many patients with epilepsy previously incarcerated in prisons, along with the insane, were now to be found in hospital wards, the progression of their illnesses, if chronic, being observed and documented. Epilepsy was a particularly prominent diagnosis in the asylums, and in some epileptic patients were segregated into separate wards. The Commissioners in Lunacy reported that in 1887 there were 1294 patients with epilepsy in various asylums in England and Wales from a total of 14,336, and 9% of insane patients bought under treatment that

year had epilepsy (Savage 1892).

Older asylums, for example Bethlem, Bethel Hospital, Norwich and St Lukes excluded patients with epilepsy from admission. Griesinger (1867) recorded that the prognosis for epilepsy associated with insanity was so bad that asylums that were devoted to curable cases of insanity "shut their gates against all insane persons ... affected with epilepsy". (p 406).

The new county asylums built later however did admit epileptic patients, and for the first time the prognosis of the disease could be studied. One consequence was that asylum physicians saw severe cases, less affected patients staying under the care of general physicians and later, neurologists.

Pinel (1745-1826), one of the leading physicians in Paris, was physician in chief at the Bicêtre and at the Salpétrière. He is credited, along with William Tuke (1732-1822) and Connoly (1794-18566), with the so called unchaining of patients in the then asylum-work houses in which they were incarcerated. He recognised "insanity complicated with epilepsy" which he noted was frequent in the hospital setting, and was incurable. Interestingly he advocated separation of epileptic patients from others:

> "Few objects are found to inspire so much horror and repugnance amongst maniacs in general, than the sight of epileptic fits .. Hence it

> ought to be a fundamental law in all lunatic asylums, to insulate epileptics with great care, and to apportion for their exclusive use part of the establishment, which cannot be visited or seen into by the other classes of lunatics".

He later continued:

> "The duties of the superintendent, in respect to this class of maniacs, consists in guarding them against falls and bruises, obviating all causes of strong or intense emotions, preventing errors in regimen or diet, and prescribing exercises suitable to their inclinations and capacities" (Pinel 1801, 1962 p 204-205).

Esquirol (1772-1840), one of Pinel's pupils, also recognised insanity associated with epilepsy and psychiatric illness. He reported that of 339 woman at the Salpétrière with epilepsy, 12 were monomaniacs, 36 were manics, 34 were furious, and 145 were in a state of dementia.

Bouchet and Cazauvieilh (1825) presented pathological data on patients with epilepsy, epilepsy and insanity and insanity without epilepsy. Similar lesions were noted in all three groups, and they had several cases of epilepsy and insanity with pathology in the Cornés d'Ammon. They concluded that insanity was related to alterations of grey matter and epilepsy to change in white matter. Both were related to congestion and chronic inflammation.

Two other French physicians made a special study of psychiatric apsects of epilepsy, namely Morel (1809-79) and Falret (1825-1902). Falret, a student of Esquirol, introduced a classification of the mental disorders associated with

epilepsy that has had a lasting usefulness. Thus he recognised peri-ictal disorders, those associated in time with the seizure; those that were inter-paroxysmal; and patients who entered a prolonged delirium, folie épileptique, or epileptic insanity proper (Falret 1860:1861).

Morel seems to have been responsible for the initial concept of the epileptic character (Reynolds 1861). He noted:

> "Il est dans la nature des maladies nerveuses d'imprier à l'idiosyncrasie physique et moral des malades un cachet tout-à-fait particulier".

Included were anger, irritability and fury, and from these ideas grew the concept of epilepsie larvée - so called larval or masked epilepsy. Morel recognised that paroxysmal behaviour disturbances could coincide with the ictus, or be independent of it. It was a short step therefore to suggesting the concept of epilepsy without seizures, masked and identified by behavioural features only. Morel gave a list of these, discussed in more detail by Berrios (1979). They included marked instability of character, increased motor activity, polymorphic delusions, sudden explosive behaviour, episodic repetition of stereotyped insanity and sudden shouting. These were elements derived from his description of the epileptic character.

This idea received support from the writings of Falret. Under his third category, folie épileptique, he recognised cases in which the slight epileptic

paroxysms went unrecognised, or may develop later in the course of the illness. However, he also noted that in some cases "le delire épileptique se substitue en quelque sorte aux convulsions épileptiques". The convulsions and the delirium were thus both manifestations of the same underlying pathology. Falret further divided epileptic insanity into two forms, namely petit mal and grand mal intellectuel. The former were generally milder, although he recognised that in many cases the form was intermediate. The automatism, a subject not new to forensic medicine at that time, was a manifestation of the lesser attacks, and Falret stressed that during them there was a propensity for irrational and violent acts to be carried out.

These views did not receive universal approbation. Herpin (1799-1865), who wrote a major text on epilepsy published in 1857, in which prognosis was carefully considered, scarcely mentions psychiatric problems. Similarly, in England, several authors were sceptical. Reynolds (1851) actually produced statistics on his own patients. He concluded that "epilepsy does not necessarily involve any mental change", (p46), and that while depression of spirits and excitability of temper were common, "ulterior mental changes are rare". Unfortunately this view is biased since, as he noted, his statistics were on a group in which he excluded all cases of "positive insanity".

Sieveking (1861) explained the dilemma, still echoed in criticisms today:

> "There is some difficulty in obtaining satisfactory statistics on this point (insanity in epilepsy) .. because confirmed epileptics are so frequently removed from the observation of the physician who saw the commencement of the disease, to be placed in asylums; hence the statistics of these establishments only refer to a certain proportion, but by no means all epileptics, as they exclude nearly all cases that have been cured, or in whom the disease has not reached a maximum intensity". (p 78).

He went on to quote the figures given by Esquirol.

The most important English writer on epilepsy in the last century was Hughlings Jackson (1835-1911). He had much to say on the relationship between epilepsy and mental disorders, and his philosophy of cerebral function and how it was affected in disease embraced four main tenets. These were the evolution of nervous functions; the hierarchy of those functions; the negative and positive symptoms of dissolution; and the distinction between local and uniform dissolution. The brain was seen as developing in both space and time, and was not the static organ of the pathological laboratory. Further, it was hierarchically organised, not a simple collection of reflexes. With any lesion there are two effects, one due to the destruction of tissue resulting in negative symptoms, the other due to release of subjacent activity of other healthy areas of brain causing positive symptoms. Writing as a physician whose territory was the wards of the newly established National Hospital for the Paralysed and Epileptic, Hughlings Jackson saw patients with

self limited episodes of mental change. He advocated the study of mental diseases could well begin in such a setting. He quoted with approval the figure of Bucknill and Tuke and noted 6% of patients in asylums "owe their insanity to epilepsy" (Taylor 1958 vol 2 p 119). He felt that cases in which the manifestations of the epilepsy were slight where the worst for the mind, the discharging lesion in such cases being "in the highest and most intellectual of the nervous arrangements" (p121).

Hughlings Jackson referred to Falret's writings and gave the following classification of the association between the mental state and epilepsy;

1) The sudden and transient mental disorder after one or a few fits.
2) More lengthy infirmity after a rapid succession of numerous fits.
3) The persistent deterioration, the result of fits repeated for months or years.

He also initially subscribed to the doctrine of masked epilepsy, but expressed doubts. He said:

> "Epileptic mania, although it usually occurs after a fit ... sometimes replaces a fit ... It has been said that the patient who, is subject to attacks in which there is a convulsion of muscles may at another time have an attack in which there is a "convulsion of ideas", and corresponding excess of external action. I used to adopt the hypotheses of masked epilepsy. But I do not now think it possible ... I think another hypotheses is preferable. I think it probable that there is a transitory epileptic paroxysm in every case of mental automatism ..." (p 122)

His explanation for the behaviour was that the epileptic paroxysm had two effects. It resulted in loss of consciousness, with loss of control permitting

increased automatic action.

One of Hughlings Jacksons's patients, Dr Z, has recently been the subject of renewed interest (Taylor and Marsh 1980). Dr Z was Arthur Thomas Myers, and his case is described in Hughlings Jacksons's 1888 paper in Brain (Taylor 1958 p 385). In this he describes a form of epilepsy in which the "intellectual aura" or "dreamy state" is the striking symptom. His patient, and others mentioned in this paper describe what are now recognised as classical symptoms of temporal lobe epilepsy. Dr Z committed suicide from an overdose of chloral, and at post mortem was shown to have a small lesion in the left uncinate gyrus. Although Taylor and Marsh argue that this lesion was most probably an artefact, the case is important for several reasons. Dr Z helped Hughlings Jackson formulate more clearly this type of seizure, and distinguish it from other forms of partial epilepsy. One way Dr Z helped him was by his habit of recording his symptoms in extensive written accounts. In Dr Z's obituary, published in the British Medical Journal of January 27th 1894 we read that he:

> "With singular patience, minuteness, and fidelity ... invented a system of indexing ... he was much interested in some of the problems which the "psychical researchers" aspire to solve ... his history is tinged by a touch of melancholy ... destiny thought fit to inflict upon him that terrible and inscrutable nervous malady which occasionally harassed him in early youth, and of late years advanced with relentless dread, baffling the most devoted medical skill and ultimately involving a fine intellect in ruin and confusion ..."

It is further known that he never married, and had an interest in the mystical. His last paper was 50 pages long and titled "Mind-cure, Faith-cure and Miracles of Lourdes". Is it possible that we have here a description of the kind of person referred to as having epileptic personality changes? Is Dr Z with his hypergraphia, obsessionality and religiosity an exemplum of the characteristics of the Geschwind syndrome?

Another English author to discuss epilepsy and its consequences was Maudsley (1835-1918). He was especially interested in the forensic aspects of mental disease, and the question of individual responsibility. He described epileptic mania, "a most dangerous form of insanity", in which:

> "In a frenzy of excitement, unconscious of what he is doing, his senses perhaps possessed with frightful hallucinations, he is driven to most destructive acts of violence against both animate and inanimate objects" (Maudsley 1874 p 228).

He went on to describe the progression of epilepsy:

> "There may be no impairment whatever at first, although after the disease has lasted for sometime there will be a loss of memory and weakness of mind, deepening into actual dementia in the worst cases. It is one of the saddest experiences of asylum life to witness the pitiful fate of those patients who have not sunk below the consciousness of their condition. Gentle, amiable, and industrious through their long intervals of lucidity, they hope against hope that each recurring paroxysm will be the last; they eagerly try all remedies, in the hope of curing the disease; they see others leave the asylum restored to health, and confidently anticipate that their turn will come; but confidence wanes as the attacks recur, the mind is slowly weakened by the storms of fury through which it passes, and they sink finally into the apathy of

dementia ..." (p228)

Maudsley also accepted the concept of masked epilepsy and that changes of character and temperament could occur months or even years before distinctly epileptic seizures were manifest. He classified the mental disorders of epilepsy into four categories thus:

1) Prodromata or forerunners
2) Those corresponding in the mental sphere to the slight form of epilepsy known as petit mal.
3) More violent symptoms that would correspond to regular epileptic convulsions or grand mal.
4) Mental decay following long-continued epilepsy.

In type four, Maudsley specifically mentions the development of an exaggerated sentiment, visual hallucinations, and "like Swedenborg, they are sometimes carried up into heaven while yet in the flesh, and have conferences with the Supreme ..." (p 243).

Such religiosity was the subject of a study of Howden (1873). He set out to describe "a feature in the mental condition of epileptics", which he felt was not uncommon. He recognised these " ... Strong devotional feelings" which manifest either as simple piety or religious delusions. Several case histories were provided, emphasising differing shades of religiosity, and some support provided for the concept that "many religious fanatics were epileptics ..." The latter included Mohammed, Ann Lee, the mother of the shakers and

Swedenbourg.

Passages from the novels of Dostoievski, notably from "The Idiot", are reminiscent of some of these characteristics. Dostoievski was known to have epilepsy, and had personally experienced ecstatic moments. These have been described by his friend Trakhov as follows:

> "I had the feeling that the sky had descended to the ground and had swallowed me up. I truly felt the presence of God and he entered into me ..."

The saintly Prince Myshkin had similar auras in the "The Idiot".

The German Contribution

Towards the end of the nineteenth century, the medical hegemony moved away from France to Germany. Neuropsychiatry was no exception, and a number of German writers took an interest in epilepsy. A starting point is the work of Griesinger (1817-1868). He was professor of psychiatry and neurology in Berlin and clearly formulated the idea that normal mental processes are dependent on brain function, and that the latter was involved in insanity. His dictum was:

> "Insanity being a disease, and that disease being an affection of the brain, it can therefore only be studied in a proper manner from the medical point of view" (Griesinger 1857 p 9).

He recognised epilepsy as a cause of insanity, both acutely and chronically. He also suggested that psychical disturbances could occur before the epilepsy

was manifest, and that in established cases alternate with epileptic attacks. He noted that "a very great number of epileptics are in a state of chronic mental disease even during the intervals between attacks". He used the term "psychomotor symptoms" and accepted the idea that psychoses could substitute for seizures as shown in the following case history;

Case 1 (quoted by Griesinger 1857 p 297)

> "A peasant, born at Krumbach in Swabia, age 27, and unmarried, was subject from his eighth year to epileptic attacks. Two years ago, his disease changed its character without any one being able to account for it; and in place of epileptic attacks, the man found himself seized (sic) by an irresistible disposition to commit murder. He feels the approach of the fit several hours and sometimes a day, before it comes on. Immediately when he has the presentiment, he earnestly asks to be tied up and bound with chains, lest he commit some crime.
>
> He feels himself greatly exhausted, and experiences slight convulsive movements in the limbs ... The fit lasts one to two days".

Samt (1875/6), a psychiatrist from Berlin, elaborated the concept of epileptic equivalents in a study of over 40 cases. His classification of epileptic insanity recognised two major forms, namely psychic equivalents and post epileptic insanity. Psychic equivalents were recognised by their clinical form which included episodes of violence, religious ecstasy, anxious delirium and stupor.

Kraepelin (1856-25), professor of psychiatry at Munich and Heidleberg, whose work on classification has so profoundly influenced psychiatry in the twentieth century, also studied epileptic insanity. He recognised the latter as one of the

major forms of mental illness, alongside dementia praecox and manic depressive illness. He quotes Samt with approval, recognising the plemorphic forms of epileptic symptoms. He described cases of epileptic delirium, with religious hallucinations and delusions and emphasised how alcohol might exacerbate the psychopathology (Kraepelin 1904). He drew attention to the acute mood changes of epilepsy, which may be associated with more prolonged episodes of hallucinations and delusions. This state he noted may bear some resemblance to dementia praecox.

The periodic mood swings seen in patients with epilepsy were further discussed by Aschaffenberg (1906). He reported that 70% of his cases had such fluctuations of mood, with no obvious relationship to their seizures. The attacks had a sudden onset and termination without obvious cause, although they could be induced by small amounts of alcohol. Such mood swings were also noted by Gaupp (1903).

It was a short step to the concepts of such authors as Bratz and Leubuscher (1907) who defined "affect epilepsy" attacks precipitated by psychological factors which consisted of loss of consciousness, dizziness, hallucinations and rage.

The position at the end of the nineteenth century is best summed up by reference to Savage's (1892) contribution to Tuke's "Dictionary of Psychological Medicine". He accepted the hereditary principle, and that epilepsy "is almost important factor in the production" of insanity. He noted preictal, ictal and interictal associations, and noted that before a seizure "brief attacks of insanity, generally of a maniacal type", may be seen. He accepted the concept of masked epilepsy, and speculated on its pathogenesis:

> "In the two classes of cases (seizures, and impulsive destructive acts without convulsions) similar discharges of nerve force along paths of least resistance take place and may become habitual by recurrence; the difference is slight, whether there be a discharge of motor force, which is altogether purposeless, or whether there be a discharge, which, though unconscious, is still along certain definite lines, which may have been by use established". (p453).

Post-ictal automatisms were a well recognised cause of insanity, and he thought that many cases of so called masked epilepsy fell into this class. The post-epileptic symptoms were often violent, in many cases being epileptic mania, although melancholia was another variant. This was usually associated with ideas of persecution and strong religious tendencies.

Savage was of the opinion that successive attacks led to a gradual weaknening of the mind, with dementia being the inevitable outcome.

The Nature of the Link; The Twentieth Century

Along with these presentations of the clinical nature of epileptic insanity and its variants, there was much speculation on the nature of the link. To understand this, it is important to note that in the 19th Century there was considerable discussion on the nature of mental illness, and the differing forms of insanity. For some, such as Griesinger, there was only one major psychosis (Einheitpsychose). The disorder changed its manifestations over time, but what was viewed was only different stages of the same morbid process. Others, for example Kraepelin, defined several forms, all thought related to differing underlying disease states. Since, by the end of the 19th century, many writers recognised that epilepsy and insanity were somehow interlinked, the nature of this relationship became a matter for debate. Berrios (1979) has reviewed this, providing the following summary of the prevailing views:

1) THE LINK AS A CHANCE COMBINATION:

- A) As the result of defective statistics (Herpin)
- B) As the result of a chance genetic combination (Magnan)

2) THE LINK AS REAL:

- A) Epilepsy producing psychosis
  - i) By disrupting reality testing (Ziehan; Gaupp)
  - ii) By weakening the brain (Bucholz)
- B) Psychosis producing epilepsy (Clouston)
- C) Both being the result of a common organic factor (Jackson)

In the main, these hypotheses have been the ones considered ever since. Some further clarification is necessary. Magnan (1835-1912), a pupil of Falret, took up the principles of Morel (1809-1873), that degenerative hereditary strains were pathological variations which would get worse from one generation to the next. Epilepsy would be considered one reflection of such degeneraton, and, as Hill (1981) has pointed out, these ideas had a long lasting influence on psychiatry, but also influenced ideas about epilepsy. They were associated with the unitary view of psychosis, led to ideas of constitutional predisposition to epilepsy based on personality features and contributed to the continuing stigma attached to epilepsy by both the general public and the medical profession.

Morel's view was taken up by Maudsley (1879) and expressed as follows:

> "When epilepsy in young children leads to idiocy, as it often does, we must generally look for the deep root of the mischief in the family neurosis ... (p 45) ... epilepsy in the parent may engender the insane neurosis in the child, and insanity in the parent the epileptic neurosis in the child" (p65).

Another British physician influenced by these theories was Aldren Turner (1907), physician to the National Hospital, Queen Square, and consultant to the Colony for Epileptics, Chalfont St Peter, as it was then called.

> "In epilepsy, as in other degenerative neuroses, stigmata of degeneration are present ... (these) ... are deviations from the normal, and occur in those who are subjects of a hereditary degenerative predisposition ... " (p 17).

For Magnan, the combinations and metamorphic relationship between epilepsy and psychotic episodes were explained by the concept of double inheritance, one parent contributing to epilepsy, the other to the insanity.

The idea that a person could suffer from two psychoses led to discussion of the nature of the relationship between them. Stransky (1906) pointed out that one must separate the simultaneous from the successive, others questioned the pathoplastic effects of the one on the other (Gaupp 1903, Glaus 1931). The question of whether or not the psychosis produced epilepsy, or vice versa, was answered by individual case histories, and as psychiatric terminology changed the majority of papers concentrated on schizophrenia. The combination of schizophrenia and epilepsy was variously reported as common (Yde 1941) and rare (Krapf 1928: Glaus 1931), and the, by then well recorded observation that in some patients by the time the psychosis appeared the epilepsy had become quiescent, was used as an illustration of the incompatibility of the two psychoses.

If the psychosis bought with it seizures, the latter was viewed as part of the schizophrenic process, while various theories were put forward to explain how the epilepsy could damage the brain to lead to the psychosis, including via raised intracranial pressure, autointoxication and endocrine disturbances.

Others preferred more psychological explanations, for example that the recurrent psychic disorganisation of the ictus could lead to chronic illness (Ziehan 1902).

Conclusions

It has been shown that associations between epilepsy and mental illness have been observed since antiquity. The most important era historically is the 19th century, most notably with the observations of the mid-century French alienists and German neuropsychiatrists. All of the arguments that still pervade this subject can be seen to have been rehearsed over the ensuing decades, including the possibility that all is based on observational and statistical artifacts due to patients being observed and collected in the asylum setting.

The concept of epileptic equivalents had a profound effect on this debate. There can be no doubt that this idea was accepted by many highly experienced influential physicians such as Aldren Turner. As a topic it fell from favour in the early part of the twentieth century, but by then the notion had transmogrified into an acceptance of an explanation for interictal personality changes and hence psychoses. Further it accounted for other paroxysmal clinical phenomena, that may not even be associated with seizures, or a history of them, and that were often of a violent nature.

It seems to be the case that often observations of the coadunation of epilepsy and insanity were made by neuropsychiatrists in an asylum setting, although this was not always so. Krapelin was not an asylum physician, and Hughlings Jackson was a neurologist. Those who denied the association had, like Reynolds, to remove insane patients from their own statistics.

The debate over the association between epilepsy and schizophrenia moderated in the first half of the twentieth century, especially as the view that it was rare seems to have become established (section 2). A resurgence of interest occurred in the 1950's (section 3).

SECTION 2:

FORCED NORMALISATION AND ALTERNATIVE PSYCHOSES

FORCED NORMALISATION AND ALTERNATIVE PSYCHOSES

In contrast to the suggestion that there is an increased presentation of psychopathology in epileptic patients an alternative literature which suggested an antagonism developed in the early part of this century.

The idea that there could be some kind of antagonism between different illnesses, should not be mixed up with the related idea of an antagonism of symptoms at different stages of an illness. The latter concept has a longer medical tradition. It relates to the ancient concept of "sympathy", probably first hinted at in the writings of Hippocrates and Galen (131-200 AD). Essentially, physicians struggled to explain the presence of symptoms at sites distant from an impaired body part, prior to the discovery of hormones, bacteria or even the circulation of the blood. The body was seen as an organism, and its constituent parts seen as being in sympathy (consensus partium). The sympathetic nerves were given a major, if not exclusive role in this process (Reise 1959). This doctrine of sympathy, was also applied to epilepsy, and a classification into idiopathic and sympathetic epilepsy was predominant in the 18th and much of the 19th century.

In addition to the doctrine of sympathy, there was also the concept of conversion of diseases. Ferriar, who introduced the term conversion to

medicine a century before Freud, summed it up thus:

> "A disease is said to be converted, when new symptoms arise in its progress, which require a different designation, and which either put a period to the original disorder, or combining with it, alter the physician's views reflecting the prognostics, or the method of cure ..."

He went on to state the following:

> "It is so far certain, that medicines operate by producing conversions, that we perceive very considerable diseases resulting from the use of certain remedies ... as we judge of the extinction of the original complaint, in some measure, by the increase and permanency of the remedial disease".

He even anticipated convulsive therapy:

> " ... Some derangements of the mind cannot be removed, without exciting an artificial delirium ..." (p 1, 72,73).

An earlier example, with special reference to epilepsy, comes from Willis (1667). He noted that:

> "Epilepsy is sometimes cured by the help of medicines, experience doth testifie ... in the meantime, as to what further belongs to the prognostication of this Disease, if it end not about the time of ripe age, neither can be driven away by the use of medicines, there happens yet a diverse event in several sick patients, for it either ends immediately in Death, or is changed into some other Disease, to wit, the Palsie, stupiditie, or Melancholy, for the most part incurable" (p 18).

Doubts about the specificity of epileptic psychosis occurred at the end of the 19th century. Marchand and Ajuriaguerra (1948) noted several authors who had reported "une sorte de substitution alternante entre le delire et la manifestation convulsive". They went on to quote a case of Parant (1895).

> "Cette même alternance est signalée par Parant chez une épileptique qui, sous l'influence d'un traitement bromuré, voit ses crises disparaître, mais elles sont remplacées par des troubles, mentaux

> caractérisés par des hallucinations de l'ouöie et de la vue, des idées de persécution, de l'agitation maniaque alternant avec de la dépression; apres diminution de la dose de bromure, les acces convulsifs reparaissent et les troubles mentaux disparaissent" (p 168).

Savage (1892) wrote:

> "We have met with several instances of patients who have suffered from slight attacks of epilepsy, who having been relieved or cured of the fits of convulsions, have from that time begun to degenerate mentally, and we have elsewhere described cases in which epileptiform, if not epileptic, fits have been followed by mental improvement ... from some hitherto unexplained cause, severe convulsions may occur during some phases of insanity, which may be followed by recovery". (p 455)

In the early decades of this century, the doubts about the association between epilepsy and psychosis continued, and several authors noted a low frequency of seizures in psychotics. Krapf (1928) critically reviewed the published cases, and reported six cases of his own from the Munich University Clinic. He was doubtful about the diagnosis of either the epilepsy or the schizophrenia in many instances, for example referring to the attacks as hysteriform-tetanoid, or suggesting they were the result of hyperventilation. In his own series he either found similar objections, or explained the relationship away on the grounds of latent predisposition to schizophrenia temporarily awakened.

Glaus (1931) examined over 6,000 cases from the Zurich clinic. He commented that epileptiform seizures (epileptiformer Anfalle) occur rarely in schizophrenia, noting references to such attacks in approximately a dozen

cases, generally in catatonics in the acute stage of the illness. He thought this related to cerebral oedema. He commented that four cases had, in spite of complete absence of epileptic seizures, all the psychic features of epilepsy ("fast alle für Epilepsie bezeichnenden psychischen Eigenschaften" p 453). Here he was referring to hesitant speech, unconsciousness, circumstantiality, perseveration, irritability and intense affects. However, this was a combination of schizophrenia and psychic epilepsy. This he thought of as a specific form of psychopathology rather than an organic mental illness.

Glaus was unable to support the suggestion that epilepsy and schizophrenia occured in combination, except in epileptic twilight states, an exogenous reaction form. However, he did note that when such symptoms increase and group themselves into a characteristic pattern, then it was permissable to talk of a schizophrenic pathoplasticity, the existence of a schizophrenic constitution colouring the picture. Generally though he followed Bleuler, who said that in cases of epilepsy, where delusions of persecution and auditory hallucinations were present, one must assume schizophrenia.

The arguments these authors put forward related to the possible combination of two forms of endogenous psychoses simultaneously, obviously not compatible with ideas of unitary psychosis. Glaus also considered the

possibility of a successive combination, noting that this could occur, and usually it was in the order of the epilepsy appearing before the psychosis. In his paper he described eight cases in which a double diagnosis was made, in four there was a successive combination, the schizophrenia having developed and progressed whereas the epilepsy had not appeared for many years. Two other cases showed a similar improvement in the frequency of epileptic seizures when the schizophrenia developed. In one case he accepted the combination of epilepsy and schizophrenia. Thus, while the finding of only eight cases in 6,000 must be considered low, in seven, Glaus did observe either simultaneous or successive associations. The successive cases suggested some kind of antagonism, although his conclusion was that the two diseases do not significantly influence each other.

Several authors calculated the prevalence of epilepsy in schizophrenics and vice versa, the literature being reviewed by Davison and Bagley (1969). Tables 1 and 2 are taken from their review. The data on the prevalence of schizophrenia in epileptic patients does not reveal this to be greater than in the general population, a conclusion that Davison and Bagley found unreliable. Table 2 however clearly shows that several other authors also noted a low prevalence rate of epilepsy in schzophrenics, but here the figures are more variable. Kraepelin (1910-15), in contrast gave the figure as 16-19%, although

TABLE 1

PREVALENCE OF "SCHIZOPHRENIA" IN EPILEPTIC PATIENTS

No of Epileptic Patients	No With Schizophrenia	% ± SE	References
487	1	.2 ± .2	Ganter, 1925 (45)
2,000	15	.75 ± .2	Fürstenberg, l949 (44)
897	7	.77 ± .3	Alstöm, 1950 (44)
1,806	14	.8 ± .2	Gibbs, 1952 (13)
871	6	.7 ± .4	Lorentz de Haas et al, 1956 (93)
300	2	.7 ± .5	Loeb & Giberti, 1956 (91)
1,138	6	.5 ± .2	Lorentz de Haas and Magnus, l958 (94)
1,073	8	.75 ± .25	Bartlett, 1957 (17)

Prevalence of schizophrenia in general population .2 to .5 percent, Dunham (5)

TABLE 2

PREVALENCE OF EPILEPSY IN SCHIZOPHRENIC PATIENTS

No. of Schizophrenic Patients	No with Epilepsy	% ± SE	Reference
200 (females)	39	19.5 ± 2.8 }	
100 (males)	14	8.0 ± 2.7 }	Urstein, 1909 (136)
2,700	95	3.5 ± .35}	
347	30	8.6 ± 1.5	Giese, 1914 (52)
217	10	4.6 ± 1.4	Vorkastner, 1918 (140)
665	13	2.0 ± .5	Ballerini and Laszlo, 1964 (16)
715	20	2.7 ± .6	Yde et al, 1941 (143)
1,506	18	1.2 ± .3	Krapf, 1928 (79)
1,827	14	.77 ± .2	Perŝic, 1956 (105)
537	3	.3 ± .3	Smorto and Sciorta, 1955 (130)
6,000	20	.3 ± .07	Strauss, 1929 (132)
50,000	145-165	.3 ± .02	Kat, 1937 (73)
3,242	2	0.6 ± .04	de Boor, 1948 (25)
500	2	.4 ± .3	Hoch, 1943

Prevalence of epilepsy in general population .5 per cent, Brewis et al, 1966 (27)

he included syncope and vertigo, thus overestimating epileptic seizures. Nonetheless, these low prevalence figures appearing in the 1920's and 30's significantly altered the prevailing view of the relationship between schizophrenia and epilepsy from one association to one of antagonism.

Convulsive Therapy

Laszlo von Meduna (1896-1964) first induced a seizure in a patient with severe psychiatric illness with intramuscular camphor in 1934. He had been working in Budapest, as a pupil of Professor Schaffer, and was interested in the pathology of schizophrenia. Schaffer believed that hereditary diseases were characterised by selective and specific pathological changes, and that in schizophrenia neurones were destroyed, while glial cells were unaffected. von Meduna examined the brains of both schizophrenic and epileptic patients and noted that the changes in epilepsy were the opposite to those of schizophrenia, notably with loss of few neuronal cells but clear gliosis. He formulated a hypothesis that there was hypofunction of the glia in schizophrenia, and hyperfunction in epilepsy (von Meduna 1985). He then looked for other evidence of antagonism between the two disorders, and was encouraged by the paper of Nyiro and Jablonsky (1929). Thus in their hospital, they noted only 1.05% of epileptic patients were discharged as cured, while in epileptic patients with schizophrenia the figure was 16.5%. Von

Meduna said:

> "From his clinical data, Professor Nyiro concluded that there was an antagonism between epilepsy and schizophrenia, meaning that the schizophrenic process would work against the epileptic process" (p 54).

Nyiro, followed this, injecting the blood of schizophrenics into epileptic patients, with little success. However, von Meduna concluded:

> "I accepted the concept of a biological antagonism between the two diseases, but I thought it worked in the opposite direction" (p 54)

von Meduna sought a way to create artificial convulsions, and settled on camphor. Following experiments with guinea pigs, he treated his first patient in January 1934. The results of this and other experiments are written up in a series of papers (von Meduna 1935, 1937, 1938). Although on several occasions he makes strong statements about the biological antagonism between schizophrenia and epilepsy, his precise interpretation is unclear. Thus, as noted, he relied on the results of Nyiro and Jablonsky whose own paper (1930) noted that combinations of epilepsy and schizophrenia were by no means rare, and the 16.5% figure quoted above denotes cases of a combination of the two.

Thus it can be calculated that 95 of the series of 176 patients were considered to have only epilepsy, while 81 had the combination, of whom 13 were cured. Further, von Meduna concluded:

> "One group of schizophrenic patients are characterised by both a tendency to self recovery and a predisposition to epileptiform attacks ..." (p56)

In other words von Meduna, while writing of antagonism, based his theory in part on cases of combinations of the two states.

In an attempt to unravel this paradox further, Wolf and Trimble (1985) noted that von Meduna was a Hungarian, who wrote in German and was not always too precise with terminology. For example he used the terms Krankheit (disease) and Krankheitsbild (disorder), and seizures and epilepsy interchangeably. Further, he makes it clear that schizophrenia is a heterogenous condition with three forms, endogenous, exogenous and exo-endogenous. In the endogenous there was no hope of any cure, but the exogenous form was that most likely to be influenced. Thus, it is suggested that he recognised the association between epilepsy and schizophrenia, but that the antagonism referred to was not that between two diseases (epilepsy and schizophrenia), but between the symptoms, namely seizures and psychosis. This is compatible with the statements of Glaus (1931) that, in general,

> "in the cases of combinations of epilepsy and schizophrenia an alternating relationship is indeed the rule (p 499),

and Wrysch (1933) who rhetorically asked:

"But is it permissible to conclude from the syndromic antagonism, an antagonism of the basic disorders?"

Forced Normalisation

The interest in the antagonism between psychosis and seizures was renewed at a later date from a different perspective. Henrich Landolt, chief at the Swiss Asylum, for Epileptics in Zurich, had investigated epileptic patients with paroxysmal psychiatric disorders with the newly introduced EEG. He found at least two groups of patients, one in which the EEG showed an increase in activity during the behaviour disorder, and another in which epileptic activity, present when the patient was behaviourly normal, was absent (Landolt 1953, 1958). It is important to note his definition of psychotic episodes as "pathological mental changes which are more prolonged in time than the seizures and shorter than the chronic mental disorders seen in epilepsy ..." (p91). This was limited in time, from hours to weeks, and the changes were reversible.

Landolt reported EEG investigations of 107 cases of "epileptic twilight states and psychotic episodes and 42 cases of schizophrenic attacks". He excluded catatonics and demented patients. The term "twilight states", unlike the Anglo-Saxon meaning of an organic brain syndrome with alteration of consciousness, referred to an earlier Germanic meaning, namely of a productive psychosis in the setting of clear consciousness often

indistinguishable from schizophrenia.

Landolt described cases of preparoxysmal dysphoria showing "regression" of the pathological EEG with what he referred to as "forced normalisation". The dysphoria indicated that "defence mechanisms against the epilepsy are set in motion" (1958 p 101). Of the psychotic episodes, he identified four types: post-paroxysmal twilight states, petit mal status, psycho-organic episodes and productive psychotic episodes with "forced normalisation". This latter group he suggested formed the epileptic mania and epilepsie larveé of the last century. The features were polymorphous:

> "They may be continuously excited, talking and even screaming uninterruptedly, restless and in constant motion, and sometimes with an excessive increase in the dynamics of ideation, with a simultaneous reduction and concentration in the range of thought. Hallucinations, illusions, delusions and compulsive acts are seen ... most of them feel very lucid and have the impression that their thinking is particularly clear .. (amnesia) may be completely lacking ..
>
> Also within this category are the orientated and lucid twilight states in which the patients are quiet and composed, seemingly no more than slightly tense - a picture which is strikingly often almost indistinguishable from schizophrenic states". (Landolt 1958 p 111-2).

Landolt pointed out that these attacks could last several weeks, and may also occur in patients who have never suffered a seizure. Further, during such episodes in epileptic patients with frequent seizures, the latter were rarely expressed. The episodes could be provoked by anticonvulsant treatment, and interrupted by ECT, although the convulsive threshold for metrazol was

elevated.

With regards to the EEG, the epileptic activity and dysrhythmias regressed during these states, for their duration, the dysrhythmia returning on the recovery of mental normality. Landolt concluded:

> "Thus, these cases reveal an unmistakable correlation between the course of the psychotic process and changes in the EEG, in that the paroxysmal focus which is active before and after the twilight state dissolves during this twilight state and often so completely that the record is normalised. In other words, and putting it more crudely, there would seem to be epileptics who must have a pathological EEG in order to be mentally sane ..." (p114).

The term forced normalisation has given some problems, discussed by Wolf and Trimble (1985). Originally Landolt used the term "super-normal braking action" to express an excess of inhibition in these cases, but this was too speculative, and he preferred an empirical designation with fewer theoretical implications. He chose "forcierte Normalisierung", but on translation to the English "forced normalisation" the meaning slightly changed. The German does not, like the English imply some kind of definite force, or mechanism. Landolt defined it thus:

> "Forced normalisation is the phenomenon characterised by the fact that, with the occurrence of psychotic states, the EEG becomes more normal or entirely normal as compared with previous and subsequent EEG findings" (1958 p 114).

He thought it could represent the expression of a state of increased reactivity of normal tissue to the dysfunction of damaged tissue, the previous

abnormality being a prerequisite for its occurrence.

Landolt also reported on the EEG of non-catatonic schizophrenics, noticing normalisation during attacks of psychosis, temporal paroxysmal potentials or generalised or focal dysrhythmias often being noted at other times. He further supported his contentions by referring to others who had observed similar phenomena. The majority are case reports, and they are largely found in either the German or French literature of around that time. However, there were exceptions. Gibbs (1951) was experimenting with phenacetylurea (Phenurone) and reported intensification of psychiatric disorder in temporal lobe epilepsy on suppressing seizures. He observed that this sometimes happened with barbiturates and hydantoins, and that psychosis could be precipitated. Elimination of the drug resulted in reappearance of the seizures and resolution of the abnormal mental states. Gibbs refers to normalisation of the EEG.

Hill (1981) made similar observations but interpreted them differently. He emphasised the relevance of the onset and termination of these episodes, there being some "homoeostatic" function related to the process of recuperation and adaption.

Alternative Psychosis

It has to be stated that the documentation in the above literature is often poor, both with regards to the precise number of patients with differing clinical states and the accompanying EEG profiles. However, a fair summary would be that clinically it was well established that in some patients there was a reciprocal relationship between abnormal mental states, not necessarily always psychotic in nature, and seizures, and that in some there was documented EEG evidence of the forced normalisation of Landolt. Tellenbach (1965) thus introduced the term "alternative psychosis" on the grounds that it was inconvenient to always refer to "epileptic psychosis with forced normalisation of the electroencephalogram", and a shorthand term was desirable. Further, this designation did not emphasise the EEG, and was a clinical expression. Tellenbach did not imply any specific pathogeneses, but he did discuss the ideas of Landolt, and put forward the suggestion that in some cases the cessation of seizures did not necessarily mean there was an arrest of underlying disease process.

More Recent Studies

Since the early observations of Landolt, sufficient numbers of patients with alternating psychoses have been documented to put their existence beyond doubt. Further, in some the EEG accompaniment of forced normalisation has

been recorded. One such case was reported by Stevens (1966). Glaser (1964) studies 37 patients with episodes of psychosis and temporal lobe epilepsy. He did not record true normalisation, but noted, in four intensification of psychosis along with improvement of the EEG. Using intensive EEG monitoring, including prolonged video-EEG studies, Ramani and Gumnit (1982) clearly documented forced normalisation in a 21 year old female with complex partial seizures who had shown a consistent inverse relationship between psychosis and seizure frequency.

Dongier (1959-60) gathered information by questionnaire from participants at a colloquium convened to examine issues on the relationship between EEG findings and psychotic states. Five hundred and thirty-six psychotic episodes from 516 patients were documented, and 78 were identified in which there was disappearance of either a focal (50) or bisynchronous (28) discharge. Delusions were more frequent in those in which a pre-existing focal discharge disappeared, and the duration of the episode was longer (several days or weeks). Paranoid behaviour was most frequent.

Palkanis et al (1987) collected seven patients in the course of three years. They had no previous psychiatric histories, and their behavioural problems emerged shortly after starting or altering anticonvulsant therapy when seizure

control was achieved. Their EEG's, abnormal before therapy change, normalised during the psychotic episodes. The patients did not have an obvious structural cause for their attacks, and neither was a long history of uncontrolled seizures a typical finding. Three were diagnosed as atypical psychosis, two as paranoid schizophrenia, and two as organic psychosis. Six had complex partial seizures, all with temporal lobe abnormalities on the EEG.

Sander et al (1991) have recorded 15 cases of psychosis in patients taking vigabatrin, and in 4 the phenomenon of alternating psychosis was observed, in some cases with EEG normalisation.

These studies, and indeed the earlier work of Landolt tended to emphasise the temporal lobe/partial seizure association with this phenomenon. However, Landolt (1963) himself wrote:

> "In the first years, the cortical focal epilepsies prevailed amongst those who had forced normalisation. Later, the relation turned towards the generalised epilepsies. This was clearly correlated with the progress in the treatment of petit mal. When we, in 1954, introduce the succinimide drugs there was an immediate increase in cases of forced normalisation or productive psychotic twilight states of petit mal".

This view was supported by Tellenbach (1965), and was reinforced by the reports of Fischer et al (1965) and Roger et al (1968). The former group described three cases with five episodes of psychoses with visual and auditory hallucinations. They had previous psychiatric histories, but no prior psychotic

episodes. During the ethosuximide treatment the EEG was normal. Roger et al (1968) reviewed 20 cases from the literature, and added 15 of their own. In some, an EEG was taken in the psychotic episode and was normalised. The development of the psychosis was seen in 4.3% of their total population, the mean age of those affected being 22 years 8 months, the epilepsy being present for at least 14 years. Six cases had documented previous psychotic episodes. In 31 cases where information was available, there was loss of epileptic paroxysms in 22, and clinical improvement in seizures in 90% of cases. In 28 cases EEG data were available. In 20, paroxysms totally disappeared, and in 14 the traces were normalised.

Wolf (1986: 1990) has contributed several studies to this literature and has re-emphasised the importance of both generalised seizures and drugs in the development of these psychoses. He investigated psychosis and related disorders in 611 patients seen in the clinic in Berlin between July 1977 and July I983. There were 30 with psychotic syndromes, and 7 with other episodic psychiatric disorders. Five (0.85%) showed forced normalisation. The rate was higher in generalised epilepsies (1.7%). He also reported in his series, 19 alternative productive psychotic episodes, 12 were paranoid or paranoid-hallucinatory, four catatonic-like or ecstatic, two coenesthetic, and one delusional psychosis.

TABLE 3

CLINICAL SYNDROMES OF FORCED NORMALIZATION

SYNDROME	NO. OF PATIENTS
Productive psychotic episodes	19
"Prepsychotic dysphoria"	9
Hysterical episodes	5
Depressive states	3
Hypochondriacal states	3
Maniform states	2
Dysphoric states	2
Twilight state	1
Episodes of depersonalization	1

P. Wolf, unpublished data

In other study of adolescents and adults with absences that required intensive treatment, he noted forced normalisation in 7.9% of cases. He emphasised that several clinical pictures may evolve, not all psychotic, as shown in Table 3 (Wolf and Trimble 1985, p 275). He noted that Tellenbach pointed out that the development of psychotic symptomatology was preceded by premonitory symptoms, especially insomnia, anxiety, feelings of oppression and withdrawal. The insomnia, Wolf feels, is therapeutically important, since rapid administration of benzodiazepines may control this, and prevent the development of psychosis. Hysterical states (three patients developing non-epileptic "pseudoseizures") were prominent, affective disorder (two depressive, two manic), and depersonalisation and derealisation were other variants.

He noted an association between generalised idiopathic epilepsies and forced normalisation, and considered the role of anticonvulsant drugs. He accepted that most could be involved, but ethosuximide was most implicated. In his series, this was involved in all cases except one, and methsuximide in the remaining one. The phenomenon was not related to toxicity, and could be seen at low doses. In contrast, sodium valproate was not involved, and cases could be switched to this without difficulty. He speculated that this may be due to the differences between the succinimides and sodium valproate on sleep,

the former sometimes provoking arousal. However, this is not in accord with the report of Palkanis et al (1987). In their series, only two were given succinimides, and two were prescribed valproic acid.

Wolf also drew attention to social factors. He noted that unemployment was significantly higher in patients with alternative psychoses, and further commented on the lack of independence in this group. The way that social factors augmented the biological features were explained either on the grounds that social integration is a stabilising factor in a potentially psychotic patient, or that better integration reflects a more stable primary personality, one better able to cope with an impending psychosis and seek help before florid manifestations develop.

Pathogenesis

After review of the literature, Wolf (1990) preferred the term "paradoxical normalisation" to describe the phenomenon that Landolt observed, while approving of the use of alternative psychosis. He listed 11 possible mechanisms, which were as follows:

1) The psychotic state is a reaction to the sudden cessation of seizures. This stems from suggestions that patients with epilepsy fail to adjust to the sudden loss of their illness and all of the social consequences. This fails to account for the sudden rapid onset, or the possible relationship to the succinimides. Further, the episodes are short lived, and terminated by a seizure.

2) A true "biological antagonism" exists (see below)

3) The seizure may continue, partially suppressed, with a continuing confined limbic status epilepticus, the surface EEG recordings showing only desynchronisation. It has been known for a long time that the surface records give a poor reflection of what goes on in the depths, and abnormal electrical activity in limbic structures is correlated with aggression and psychosis.

4) The generator of the epileptic discharges is still active, but the activity of the latter is propagated along unusual paths. Both this and 3 place this phenomenon into the category of an ictal status.

5) Anticonvulsants only influence seizures, and underlying metabolic processes are readjusted by them resulting in psychoses. The fact that the psychoses are sometimes terminated by a seizure gives this some support.

6) There is a reaction of the healthy parts of the brain against the epileptic focus. This is similar to Landolt's own position, and is Jacksonian.

7) Improved seizure control and the psychoses are related to activation of the Reticular Activating System.

8) Since there are reciprocal links between the Reticular Activating System and hippocampal structures, a decrease of activity in the latter will increase RAS activity. This would not explain the state in association with control of generalised epilepsies.

9) The role of sleep (see above)

10) Increased epileptic activity is associated with increased inhibition, an electrobiological homeostasis being renewed at a new level of tension (attributed to Christian).

11) The abnormal EEG reflects a phylogenetic immaturity of the CNS, one not adapted to contemporary environment. Archaic experiences, latently present, are activated during the normalisation (attributed to Bilz).

The problem with most of these theories is their lack of validity, or even the

possibility of subjecting them to experimentation. Wolf tries to synthesise some of these, based on his own findings. He assumes that in paradoxical normalisation, the epilepsy is still active, but subcortical and restricted. At the same time, inhibitory processes are active. The latter lead to insomnia and possibly hypervigilance, with an associated dysphoria. At this point the psychosis is impending, but its development will depend on several other factors. These include general risk factors for psychosis, past psychotic experiences, premorbid personality, social competence and general life situation.

Biological Antagonism

The possible biological underpinnings of an antagonism between psychosis, especially schizophrenia-like states and seizures have been reviewed by Reynolds (1981). He had early on drawn attention to the fact that patients with epilepsy receiving anticonvulsant drugs became folate deficient, and that this was greater in those with severe psychiatric illness or dementia. Further, folate is convulsant, emphasising how folate deficient states could lead to a diminution of seizures in the presence of a psychosis.

Reynolds gives other examples of antagonisms, shown in Table 4 (from Reynolds p 275). These include methionine, and methionine-sulphoxamine. Trimble (1977) suggested that dopamine may be involved. Thus,

TABLE 4

EVIDENCE OF BIOLOGICAL ANTAGONISM BETWEEN EPILEPSY AND SCHIZOPHRENIA

Agent	Epilepsy	Schizophrenia
Anticonvulsant drugs, barbiturates	Therapeutic	?Aggravation
Phenothiazines	Convulsant	Therapeutic
Methionine	?Therapeutic	Aggravation
Methionine-sulfoximine	Convulsant	?Therapeutic
EEG	"Forced normalisation" (Landolt)	"Homeostatic" (Hill)
Folic acid	?Aggravation	??

? Implies need for more substantial evidence (Reynolds, 1968)

antipsychotic drugs are dopamine antagonists, and are known to provoke seizures. Dopamine agonists both increase the intensity of psychotic symptoms or can precipitate a psychosis while also possessing some anticonvulsant properties. However, alternative hypotheses might be constructed using GABA, or perhaps a peptide.

In general, the neurotransmitter based hypotheses have more merit for the kind of events that Landolt described, in the sense that changes in folate metabolism are not rapid, and short lived while a switch in neurochemical status within specified neurotransmitter pathways can occur rapidly, and are seen for example following the administration of a multitude of psychotropic drugs.

Conclusions

The literature reviewed in this chapter establishes one clear link between epilepsy and psychosis, namely that revealed through the phenomenon of forced normalisation. It also clarifies a misunderstanding of the associations between the two, namely that the antagonism is between symptoms viewed longitudinally rather than between two independent disease entities. Indeed, neither epilepsy nor schizophrenia can be viewed as diseases, they are both syndromes associated with several underlying disease processes, some of

which seem common to both.

It is often denied that forced normalisation, and its clinical counterpart alternative psychosis, occur, probably with good reason. Thus, they are certainly rarer than made out by Landolt, and studies are few and far between. It is difficult to document such cases precisely, and EEG recordings often cannot be obtained. However, another, less enlightened reason to ignore such findings is that their presence reveals too closely the association between seizures and psychosis and may have a profound effect on treatment. Thus, if in some patients suppression of seizures provokes psychopathology it means that seizures and epilepsy are not synonymous, and an understanding of the epileptic process and its treatment goes far beyond control of seizures. Tellenbach referred to the writings of Landolt (1963) when he suggested that:

> "Today, however, it seems to us more and more that the treatment of epilepsy on the whole has its limits in so far as the efficiency or impetuosity of the anticonvulsant action of some new drugs places us in certain cases more and more before the alternative: mental illness or epilepsy, seizures or madness. And, of course, it is still better to have seizures than to be mentally ill".

SECTION 3:

INTERICTAL PSYCHOSES

INTERICTAL PSYCHOSES

In section 1 the development of the concept that behavioural disturbances of epilepsy could be manifest outside the ictal period was traced. Many of the early authors (see below) discussed the development of psychotic states, case histories being provided which would be recognisable and classifiable in today's terminology. In section 2 it was noted how, in the early part of this century, the concept of an antagonism between psychotic states and epileptic seizures arose, and how an increased association between epilepsy and psychosis was compatible with an antagonistic relationship between the symptoms of psychosis and seizures.

The issue of interictal psychosis however still occasions considerable controversy. In order to fully understand the development of concepts related to these arguments, and to explore further the relationship between psychotic symptoms and epilepsy it is necessary to briefly review an even more controversial area, namely the association between epilepsy and personality disorder.

Personality Disorder

The history of the relationship between epilepsy and personality was summarised by Guerrant et al (1962). The "period of epileptic deterioration", typifying views in the last half of the last century, implied that personality

deterioration was a consequence of the disease itself, or possibly as a sequel to prolonged use of bromide therapy. Around the turn of the century, the term epileptic character, introduced originally by Morel, acquired a specific meaning and concepts regarding its development became intertwined with Freudian psychodynamics. Turner (1907) provided an early example of the change:

> "In early days the convulsion, or fit, was regarded as the sole element of importance in the clinical study of epilepsy; but in more recent years the psychical factor has come to be looked upon as of almost equal importance, and both are regarded as manifestations of a predisposition associated with inheritance ... it is rare to find epileptics who do not present some form of mental obliquity ... the possession of which is a feature of their hereditarily degenerative disposition ... the mental condition is not solely a consequence of seizures but is an expression of the same nervous constitution which gives rise to the convulsion.

The belief was that epilepsy was a constitutional disorder in which the seizures were but one manifestation of more diverse symptomatology. The psychoanalytic expression of this was most forcefully put by Clark (1923) who recognised pre-epileptic constitutions, suggesting that the seizure itself was simply a psychological regressive and protective mechanism employed by an over-stressed ego.

At the time such theories were being put forward, there were many writers who acknowledged that some patients with epilepsy may show psychiatric difficulties, but by and large reported that their patients were, from the

psychological point of view, normal. Lennox forcefully made the point in a review of personality in epilepsy, suggesting that the majority of patients with epilepsy were entirely normal and that difficulties which arose were related to complex interactions between the complications of having epilepsy. These included for example, anoxia or cerebral damage with repeated seizures, the prolonged administration of anticonvulsant drugs, and disabling psychological reactions to social stigmatisation which was so common in epilepsy (Lennox & Lennox 1960).

The introduction of the EEG into clinical practice, and the clear delineation of a type of epilepsy deriving from the temporal lobes, led to what Guerrant et al (1962) have referred to as the "period of psychomotor peculiarity". The two groups most influential in developing these ideas were those of Gibbs and colleagues from the United States and Gastaut and collaborators in France.

The views of the former school may be best summarised by the quotation of Gibbs and Stamps (1953) that:

> "The patient's emotional reactions to his seizures, his family and to his social situation are less important determinants of psychiatric disorder than the site and type of the epileptic discharge".

Gibbs (1951) noted that anterior temporal foci were common in epileptic patients, and further that the highest instance of psychiatric disorder occurred

in cases with a spike focus in this region. Figure 1, taken from Gibbs (1951) shows the percentage of severe personality disorder and psychosis associated with various sites of epileptic focus.

Gibbs made the important statement that the psychiatric symptoms accompanying psychomotor epilepsy were indistinguishable from those encountered in "purely psychiatric disorders", and suggested that pathological and physiological involvement of temporal lobe structures were related to their presentation.

Gastaut and his group clearly documented the underlying neuropathological changes of psychomotor seizures, re-emphasizing the importance of Ammon's horn sclerosis. They also identified an association between behaviour disorders and seizures which arise from medial temporal structures. In one of the earliest controlled studies of personality in epilepsy, Gastaut et al (1953) compared forty-three patients with psychomotor epilepsy with twenty-one suffering from generalised-functional epilepsy and a smaller group with symptomatic epilepsy with neocortical surface lesions. Only patients with lesions involving limbic structures, the majority of whom had psychomotor seizures and temporal lobe EEG abnormalities, showed personality disorders.

FIGURE 1

Ictal and Non-Ictal Psychiatric Disorders in Temporal Lobe Epilepsy

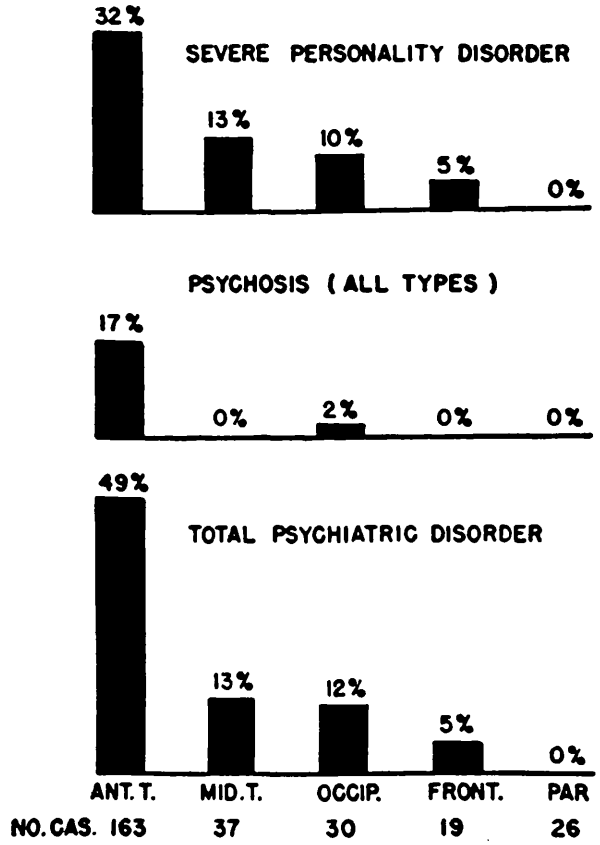


FIG. 2.—Incidence of (a) severe personality disorder, (b) psychoses and (c) total psychiatric disorder (either or both a and b) among patients with variously located epileptic foci. This column-diagram should be read in the following manner: Severe psychiatric disorder occurred in 49% of the 163 patients with a focus of seizure activity in one or both anterior temporal areas and without other focal abnormality.

Showing the incidence of psychopathology in patients with various sites of epileptic abnormality (from Gibbs 1951)

Much confusion in discussion of this area has arisen due to a misunderstanding of the history outlined above. In particular, two concepts have become confused, namely the ideas stemming from the era of psychosomatic medicine postulating susceptible personalties (period of the epileptic character) and the later ideas of "psychomotor peculiarity". The latter essentially emphasise that patients with chronic lesions in temporal, and in particular limbic system structures, could go on to develop secondary personality disorders. The precedence for this had been set by the clear delineation of frontal lobe personality changes and the discovery of behavioural changes in animals following bilateral lesions of the amygdala in the Klüver-Bucy syndrome.

Tizard (1962) critically reviewed the concept of the epileptic personality in studies which had been carried out up to 1962. She pointed out the major methodological difficulties including selection bias, assessment reliability and validity, and the large number of studies that had relied on Rorschach testing, notorious for the subjective nature of its interpretation. Since that review, a number of studies have been carried out, some of which have attempted to specifically answer these criticisms including that of Guerrant et al (1962). These are summarised in Tables 5 and 7.

TABLE 5

PERSONALITY AND EPILEPSY: ADULT STUDIES SINCE 1962*

Author	Number of Cases	Result
Guerrant et al, 1962	32 TLE 26 Primary GEN 26 Chronic medical illness	All groups similar: medical illness-more neurosis. GEN-more Pd; TLE-more psychosis.
Small et al, 1962	25 Psychomotor 25 Centrencephalic or extratemporal foci	No differences: high scores both groups.
Kløve and Doehring, 1962	20 Epilepsy, unknown aetiology 20 Symptomatic epilepsy 20 brain damage, no epilepsy 20 Affective disturbances 20 controls	Epilepsy of unknown aetiology highest scores.
Meier and French, 1965	53 TLE	Bilateral > unilateral esp validity, D, Pa, Sc, caudality. Independent > dependent.
Matthews and Kløve, 1968	51 Nonneurological controls 48 Brain damage, no epilepsy 65 Epilepsy, unknown aetiology (29 major motor, 22 psychomotor, 18 mixed).	No differences. D most frequently elevated in epileptic patients. Most abnormalities in nonneurological controls.

TABLE 5 (continued)

Mignone et al, 1970	98 Psychomotor 53 Nonpsychomotor	No differences between psychomotor and nonpsychomotor. Sc increased in those psychomotor with generalised seizures. Deviant responses: dominant > nondominant.
Stevens et al, 1972	29 Psychomotor 14 Generalised 6 Focal	No differences. Sc scale-high scores for psychomotor and generalised. TLE higher on D and Pa.
Rodin et al, 1976	78 TLE 78 Controls	TLE higher on D and Pa.
Lachar et al, 1979	37 TLE 28 Non-TLE	None.
Hermann et al, 1980	47 TLE	Adolescent onset associates with increased ppd, Pt, Sc, Pa compared with child and adult onset.
Hermann et al, 1982a	TLE Ictal fear 11 Other aura 14 Generalised 16	Ictal fear higher than other on psychopathic deviate, Pa, Pt, Sc, Social introversion. Goldbergs system generalised-normal TLE-other aura, abnormal neurotic TLE-fear, abnormal psychotic.

TABLE 5
(continued)

Hermann et al, 1982b	33 complex partial seizures 34 complex partial seizures with secondary GEN	complex partial seizures with 2 generalisation score higher.
Dikmen et al, 1983	37 complex partial seizures 25 secondary generalised 34 complex partial seizures with generalisation 48 Primary generalised.	complex partial seizures with 2 GEN higher D

---

*MMPI Scale; (Ca) Caudality, (CPS) complex partial seizures, (D) depression, (F) Validity, (GEN) generalised, (N) neurosis, (P) psychosis, (Pa) paranoia, (Pd) personality disturbance, (ppd) psychopathic deviate, (Pt) psychasthenia, (Sc) schizophrenia, (Si) Social introversion, (TLE) temporal lobe epilepsy.

In these tables, only adult studies that have used some form of rating scale have been included, and in the majority of studies some attempt has been made to compare patients with either temporal lobe or psychomotor epilepsy with epilepsy of some other form.

Minnesota Multiphasic Personality Inventory (MMPI)

Considering the MMPI studies, thirteen are quoted and several conclusions emerge. First, the earlier studies fail to show significant differences between temporal lobe epilepsy or its variants and other forms of seizures. However some of the studies are complicated in that non-epileptic control groups also score high on psychopathology (Guerrant et al 1962: Matthews and Klove 1968), or alternative psychological tests suggest that "centrencephalic" or generalised seizure patients have more cerebral damage than one would suspect from a primary generalised seizure disorder, for example patients doing worse on psychological tests than those in the psychomotor group (Small et al 1962, Stevens et al 1972)

Secondly, some differences do emerge especially in sub-categories of patients with temporal lobe disorder. Bilateral findings appears to provoke more disturbances of personality than unilateral lesions (Meier and French 1965) while those with multiple seizure types or secondary generalised seizures also score more deviant profiles (Mignone et al 1970, Rodin et al 1976; Hermann

et al 1982b).

Rodin et al (1976) explored this is most detail comparing patients with temporal lobe seizure and one seizure type with those with more than one seizure type, and then comparing control patients who had one seizure type to those who have more than one seizure type. The first analysis revealed higher elevation of MMPI scores in patients with more than one seizure, while the second evaluation did not. In other words, behavioral abnormalities did not increase solely as the result of having more than one seizure type, and was over represented in the temporal lobe population. A third analysis, comparing patients with temporal lobe epilepsy and more than one seizure type to controls with more than one seizure type, was also performed. The temporal lobe group showed more psychotic tendencies and higher elevation of paranoia on the MMPI. A problem in interpretation of such comparisons is that patients with temporal lobe epilepsy generally, as shown in the Rodin et al (1976) study, are prescribed more anticonvulsants, tend to have more clusters of seizures, and more frequently have a known aetiology for their attacks.

Thirdly, the scales which tend to be reported abnormal most frequently when differences are noted are the depression scale, (D), the paranoia scale (representing suspiciousness, over-sensitivity, ideas of references and delusions of persecution), the schizophrenia scale (representing behaviour

characterised by bizarre and unusual thoughts) and the psychaesthenia (PT) scale which is related to classifications of phobia or obsessive compulsive behaviour. The relevance of this for the understanding of psychosis is that several of these scales directly record psychotic symptomatology, and these are the ones which are most often noted to be abnormal.

Finally, some of the later studies have selected out sub-groups of patients who appear to be particularly susceptible to the development of these changes, particularly towards the psychotic dimension. For example, the association of adolescent age of onset with a higher frequency of scoring on these psychotic sub-scales (Hermann et al 1980), although this was not found in the study of Mignone et al (1970) when they viewed their overall sample of patients. The finding of Hermann et al (1982) that patients with an aura of ictal fear are more susceptible to record high scores on the MMPI profiles especially paranoia, psychaesthenia, schizophrenia and psychopathic deviancy (represented by absence of deep emotional responses and meaningful interpersonal relationships) is one of a series of studies (see table 6) in which the suggestion that not all patients with temporal lobe epilepsy will be susceptible to psychopathology, but only a sub-group with medial temporal or limbic seizures is explored (see below).

TABLE 6
STUDIES SHOWING MORE PSYCHOPATHOLOGY IN ASSOCIATION WITH MEDIAL TEMPORAL/LIMBIC SEIZURES

Author	Limbic Flag	Scale	Changes
Kristensen & Sindrup * 1978	Sphenoidal electrodes		Psychotic-epileptic patients more medio basal foci.
Nielsen and Kristensen, 1981	EEG site of focus	BFI	Hypergraphia, elation, guilt and paranoia.
Dana-Haeri et al, 1984	Neurohormones		Greater release of prolactin in patients with psycho-pathology.
Hermann et al, 1982a	Aura of fear	MMPI	Psychopathic deviate, paranoia, psychasthenia, schizophrenia, social introversion, abnormal psychotic.
Wieser, 1983	Implanted electrodes	BFI	Neocortical vs. limbic: limbic score higher on hypergraphia, sex, humourless-ness, sadness and philosophical interest.

TABLE 6 (CONTINUED)

Author	Limbic Flag	Scale	Changes
Stark-Adamec et al, 1985	Auras of: formed images humming jamais vu time changes	BFI	Seizure patients with psychopathology report more of these auras.

BFI = Bear-Fedio Inventory
*** Psychosis Study**

The MMPI studies have been subject to a meta-analysis by Whitman et al (1984). They used Goldberg's (1972) sequential diagnostic system which classifies from group MMPI profiles, normal or abnormal; if abnormal, sociopathic or psychiatric; if psychiatric, neurotic or psychotic. A total of 809 patients with epilepsy from ten MMPI studies were compared with 1107 patients from fifteen MMPI studies with non-neurological illnesses. Further there were 870 subjects from twenty-two MMPI studies with non-epileptic but neurological conditions. The latter included multiple sclerosis, cerebral palsy and localised or diffuse brain damage. Their data revealed that patients with epilepsy were, as a group, at higher risk for psychopathology than the general population, although there was no evidence that people with epilepsy were at higher risk than patients with other chronic disorders. However, when neurotic against psychotic categorization was studied, patients with epilepsy manifested more severe psychopathology than both the neurological or the illness control groups. Within the epilepsy group however there were no seizure differences noted when temporal lobe was compared with generalized epilepsy. Sub-groups of patients with temporal lobe abnormalities were not however examined.

There has been a criticism that many of the MMPI studies are negative simply because the MMPI was not designed to assess psychopathology in epilepsy,

and therefore would be an insensitive instrument. Dikman et al (1983) attempted to provide some evidence for the validity of the MMPI by comparing a group of patients with epilepsy who had a history of psychiatric difficulties and those with no such problems. The MMPI appeared sensitive to these changes, noting significant differences between the two groups on several scales. However, Dikman et al did criticise some of the earlier MMPI results, particularly the suggestion that the schizophrenia scale may be elevated more frequently in epileptic populations than would be expected. They pointed out that the seventy-eight items on the MMPI Sc scale appear to describe the cognitive and dissociative sensory experiences which patients with epilepsy might be expected to report. Indeed, when they gave these items to board certified neurologists thirty-seven percent of them were thought to be descriptive of seizure phenomena, anticonvulsant drug effects, or cognitive difficulties associated with brain damage.

In part to overcome some of the difficulties of interpretation of MMPI data, Bear and Fedio (1977) developed their own rating scale derived from prior reports of personality in epilepsy. They noted that many of the traits were not necessarily indicative of psychopathology, but were regularly referred to in the literature in relationship to interictal personality changes. Their data, and subsequent studies using this scale, in addition to the small number of other

reports of personality in epilepsy are shown in Table 7.

Non-MMPI Studies

As with the MMPI studies, the results of investigations using the Bear-Fedio Inventory (BFI) are somewhat mixed. In their original report, Bear and Fedio (1977) compared patients with unilateral temporal lobe epilepsy with normal subjects, and with a group who had neuromuscular disorders. They noted that epileptic patients reported a different profile of responses to non-epileptic controls, noting such personality features such as humourlessness, dependence, circumstantiality, increased sense of personal destiny and others as being distinctive. There were differences between self-reported behaviour profiles and independent rater profiles from a close family member or friend, and laterality differences were noted, patients with left temporal epilepsy describing more anger, paranoia and dependence, while those with right temporal foci reporting more elation. This group also examined MMPI profiles and noted no differences, emphasising the value of their new scale in temporal lobe epileptic patients.

Subsequently studies tended to either confirm or refute their findings, authors of the latter studies tending to imply that the scale did no more than assess non-specific psychopathology (Mungas 1982: Rodin and Schmaltz 1984: Master et al 1984). This was largely based on comparisons between patients

hospitalised for psychiatric illness, and patients with temporal lobe epilepsy, few or no differences being noted between these populations. While not supportive of a profile of psychopathology distinctive for temporal lobe epilepsy, these critics miss the point that there is a cerebral basis to psychopathology in the absence of epilepsy, and that patients with conditions other than epilepsy may have disturbed function within their temporal lobes.

Of more interest are the positive findings, and for the relationship to psychosis a persistent reporting of high paranoia scores in temporal lobe groups by four different studies is worthy of comment (Bear and Fedio 1977, Hermann and Riel 1981, Nielsen and Kristensen 1981, Brandt et al 1985). The studies hint at left temporal medio-basal abnormalities being the most relevant for this form of psychopathology.

Another trait which is distinguishing in several studies in that of hypergraphia (Bear and Fedio 1977: Nielson and Kristensen 1981; Rodin and Schmaltz 1984) which itself has become the subject of independent research studies (see Trimble 1986). There is some evidence that this phenomenon may appear as an all or nothing state or trait in certain patients, and is related to temporal lobe abnormalities, possibly of the non-dominant hemisphere. Of more interest however, is that the only other clinical group where hypergraphia

is a recognised clinical sign is in the major psychoses, namely schizophrenia and mania.

A criticism of the BFI studies is that they have failed to confirm that all patients with temporal lobe epilepsy suffer from a distinctive personality profile which can be detected by the scale. While Bear and Fedio (1977) do refer to a consistent profile of changes noted in patients, it is not claimed that they would be seen in all patients at all times, clearly an unrealistic expectation.

The view that there is an inter-ictal behaviour syndrome associated with temporal lobe epilepsy was, from the clinical point of view, most strongly supported by the writings of Geschwind and colleagues (Waxman and Geschwind 1975). They highlighted changes in sexual behaviour, hypergraphia and religiosity and in their reports providing striking clinical examples. They also highlighted stickiness or viscosity, patients showing a striking preoccupation with detail and concerns over moral or ethical issues. Rodin et al (1984), expanding their epilepsy sample from the study quoted above, and removing subjects with high and low scores on certain MMPI derived items, noted, with cluster analysis, that a cluster corresponding to the epileptic personality was noted in association with temporal lobe seizure disorder in 7% of patients.

TABLE 7

STUDIES OF PERSONALITY AND EPILEPSY - NON-MMPI

Author	Scale	Number of cases	Result
Standage & Fenton, 1975	Present State Examination non-psychotic: Eysenck Personality Inventory.	27 Epilepsy 27 Medical controls	No difference - both groups high scores. TLE vs. non-TLE - no difference.
Bech et al, 1977	Marke-Nyman Inventory	30 Juvenile Myoclinic Epilepsy 29 Psycho-motor 30 Grand mal 22 Controls (Ménière's)	Low validity in Juvenile Myoclonic Epilepsy
Trimble and Perez, 1980	Middlesex Hosp Hospital Questionnaire	281 51% Generalised 36% TLE & generalised 8% TLE alone	No major difference.
Kogeorgos et al, 1982	General Health Questionnaire Crown-Crisp Experimental Index	66 Epilepsy 50 Neurological controls	No major difference.

TABLE 7
continued

Author	Scale	Number of Cases	Result
Sorensen, et al 1988	Eysenck Personality Inventory Bellack Interview	28 TLE 15 Psoriasis 15 Primary GE 15 Controls	Ego functioning poorer in those with more than one seizure type. No R/L differences.
Bear & Fedio, 1977	BFI MMPI	27 TLE 15 R 12 L 12 Normal 9 Neuro-muscular disorders	MMPI, no differences BFI, many differences between TLE and others. R vs L esp. paranoia, elation, dependence, anger.
Hermann and Riel, 1981	BFI	14 GE 14 CPS	TLE significanlty greater on personal destiny, dependence, paranoia, philosphical interest.

TABLE 7
continued

Author	Scale	Number of Cases	Result
Nielsen and Kristensen, 1981	BFI	Lateral focus 14-L 11-R Mediobasal focus 9-R 8-R	Mediobasal focus > lateral for guilt and paranoia. L/R differences noted.
Bear et al, 1982	BFI	10 TLE 10 other seizures 10 Affectives 10 Schizophrenia 10 Aggressiveness	TLE and other seizures; TLE greater on religiosity, philosphical interests, sadness, emotionally and total test mean.
Mungus, 1982	BFI	14 TLE 14 Neurological & behavioural disorders 14 Psychiatric	No differences.

TABLE 7
continued

Author	Scale	Number of cases	Result
	BFI		
Rodin & Schmaltz, 1984		14 Psychiatric 148 Epilepsy 16 RTLE 16 LTLE 18 Pain patients 15 Psychiatric 40 Controls	TLE scored higher in 13 categories, hypergraphia esp. No R/L differences. Relationship to anticonvulsant drugs.
Master et al, 1984	BFI	55 TLE 16 Primary GE 27 Psychiatric 40 Controls	No differences between patient groups. No R/L differences.
Brandt et al, 1985	BFI	28 LTLE 19 RTLE 10 Primary GE 14 Controls	LTLE and generalised patients most different from controls, esp circumstantiality, humourlessness, sadness, viscosity, dependence, obsessionality& paranoia.

TABLE 7
(continued)

Author	Scale	Number of Cases	Result
Stark-Adamec et al, 1985	BFI	70 Seizure patients: CPS, GE, CPS + GE 92 Psychiatric 28 Dialysis 447 Non-patients.	Seizure patients do not differ from each other. Links of psych-opathology in epilepsy to auras.

(BFI) Bear-Fedio Inventory, (CPS) complex partial seizures, (GE) generalised epilepsy, (L) left, (LTLE) left temporal lobe epilepsy, (MMPI) Minnesota Multiphasic Personality Inventory, (R) right, (RTLE) right temporal lobe epilepsy, (TLE) temporal lobe epilepsy.

Finally, the complexity of these studies has been commented on by Stark-Adamec (1985) and more recently by Adamec (1989) whose studies have been one of several identifying medial-limbic seizure disorder as being the form of temporal lobe epilepsy most likely to be associated with psychopathology (Table 6). They gave a modified BFI to 114 patients with epilepsy of varying diagnosis, to ninety-one psychiatry patients, to forty-three patients with chronic illness other than epilepsy and 100 normal controls. Three classifications of seizure patients emerged from an item cluster analysis followed by discriminant function analysis, namely correctly classified seizure patients, those classified as psychiatry patients and those classified as non patients. The twenty-five percent classified as psychiatric patients were distinguished from other seizure patients on depression, mood and metaphysical (religious) clusters and further had five of thirty-three aura experiences more intensely and frequently. These they refer to as limbic auras, namely formed images, humming or buzzing, irritability, jamais-vu and time changes.

As shown in Table 6, this is one of six studies, in which a limbic marker has been used to identify patients with medial-temporal limbic seizures, where an association with psychopathology has been demonstrated. These include the study of Wieser (1983), using depth electrode recording to verify the site of origin of the seizure in patients with temporal lobe epilepsy. He noted that

patients with a medial focus scored higher on a number of the BFI scales when compared with patients with either temporal neocortical involvement or extra temporal foci. Similar links to limbic pathology emerge from the hormonal studies of Dana-Haeri et al (1984).

Interictal Psychotic Disorders

Establishing the prevalence of psychosis in patients with epilepsy is hampered by a dearth of investigations, and those that are reported are usually from selected specialist centres. Most early studies do not discriminate different forms of psychopathology, and the meaning of the term schizophrenia has varied over time such that little reliance can be placed on its use until recent times when more clearly defined research criteria were introduced to classification (Table 8).

Echeverria (1873) gives a remarkable figure of 267 psychotic patients amongst 538 epileptics, and commented that in no case did he find epilepsy following insanity, the former always occurring first. The literature between 1925 and 1958 was reviewed by Davison and Bagley (I969), and, in contrast, an average figure from the collected patient sample was 0.7%. These studies do not reveal the prevalence to be significantly greater than that expected of schizophrenia in the general population. However, the authors point out that there are so many controlled variables, for example age structure, the

definition of schizophrenia, and the fact that in many instances the epileptic populations consist of mental hospital inpatients that little weight could be given to these figures.

Since their review, several other studies are available, again giving remarkably variable figures. The early study of Bartlet (l957) is often quoted in which he examined the case records of patients diagnosed as psychosis following epilepsy at the Bethlem Royal and Maudsley Hospitals from 1949 to 1953. Patients were required to suffer from delusions for at least a year, and he excluded any patients with schizophrenia complicated by epileptic seizures, and epileptic patients with acute psychosis not becoming chronic. He noted twelve psychotic patients, eight diagnosed as schizophrenia and three with affective psychosis given an estimate of 0.74%. However, his calculation of the overall number of patients suffering from epilepsy was an estimate based upon correction factors rather than actual cases.

More reliable information can only be derived from community epidemiological surveys where the bias of referral selection is largely removed. Even these studies are open to suspicion since patients who have epilepsy and psychosis may well be away from their community in a special setting, either a psychiatric hospital or a special institution dealing with problems of difficult

TABLE 8

PREVALENCE OF "INSANITY" PSYCHOSIS OR SCHIZOPHRENIA IN EPILEPSY

Author	No. of Cases	Prevalence	%
Echeverria (1873)	538	267	50.2
Davison and Bagley (1969) (1925-1958)	8572	59	0.7
Alstrom (l950) (Schizo-phrenia)	897	7	0.8
Gibbs & Gibbs (1952)	2484	219	8.8
Gastaut (1956)	1043	82	7.5
Bartlet (1957) Schizo-phrenia	1073	8	0.74
Bruens (1971)	720	17	2.4
Shukla et al (1979)	132	14	10.6
Onuma et al (1980)	708	40	5.7
Sengoku (1983)	879	39	4.4

TABLE 8
continued

Author	No. of Cases	Prevalence	%
Pond & Bidwell (1959)	-	-	7.0
Gudmund-sson (1966)	987	71	7.1
Zielinski (1974)	-	-	3.0
Standage & Fenton (1975)	37	-	8.0
Edeh & Toone (1987)	88	4	4.5
Schmitz & Wolf (1989)	697	28	4.0

epilepsy, and these figures are therefore an underestimate. Four studies provide information. Pond and Bidwell (1959) in a general practice survey reported that seven percent had been in a mental hospital before or during their survey year and estimated that approximately ten percent of the whole group would have a period of inpatient care at sometime in their lives. Although a precise figure for psychosis is not derived and no diagnostic categories given, Pond (1959) hints that seven percent psychosis in his figure.

Gudmundsson (1966) personally examined adult epileptic patients in a comprehensive study in Iceland and was able to compare the prevalence rates of psychiatric disturbances with a general psychiatric survey carried out in Iceland

previously by Helgason (1964). He gives a figure of 7.1 percent as psychotic. Zielinski (1974) provided data on non selected epileptic patients from Poland. Fifty-eight percent showed some "mental abnormality" and approximately three percent had psychotic symptoms.

In a recent epidemiological survey of general practice patients, Edeh and Toone (1987), identified 103 patients, of whom only 88 participated in the survey. Of these 31% had a history of psychiatric referral, 4 (4.5%) were categorised as currently psychotic.

These studies, reviewed in Table 8, particularly the epidemiological surveys, do reveal an increased prevalence of psychosis in epilepsy, although further, more extensive epidemiological investigations using standardized and validated criteria for diagnosis are urgently required. A summary figure of between 4.5 and 7 percent may be suggested. As noted, the EEG led to the identification of temporal lobe epilepsy in clinical practice, and the emphasis of the relationship of psychopathology in epilepsy moved from one which suggested no links, to the stance adopted by Gibbs (1951) in which psychopathology was associated with temporal lobe abnormalities, particularly anterior temporal discharges. This led to a succession of papers examining this association, information from which is given in Table 9. An over representation of patients with temporal lobe abnormalities with severe psychiatric illness was reported by Pond and Bidwell (1959), their temporal lobe epileptics having nearly a twenty percent hospitalization rate, compared with seven percent for the whole group. Likewise Gudmundsson reported an over representation of severe psychopathology in those with temporal lobe epilepsy (50%) as opposed to those without temporal lobe epilepsy (24%).

Specifically with regards to psychosis, Gudmundsson's figures were not based on all personally reviewed cases, and his diagnostic categories are somewhat idiosyncratic. Most of these cases were reported to have grand mal seizures (54%).

Table 9 is a summary of the studies that have examined the relationship between different types of epilepsy and psychosis, while Table 10 gives the distribution of type of epilepsy in series of psychotic epileptic patients.

These data should be seen in conjunction with some of the personality studies already discussed above. In particular the study of Guerrant et al (1962), who reported that the incidence of psychotic profiles in their temporal lobe group was twenty-three percent as opposed to four percent in their medical illness group. Other MMPI studies that suggested elevated psychoticism scores in patients with temporal lobe epilepsy or its variants include Mignone et al (1970), Rodin et al (1976), Hermann et al (1982) and the BFI studies were those of Bear and Fedio (1977), Hermann and Riel (1981) Nielsen and Kristensen (1981) and Brandt et al (1985).

Studies examining the differences between temporal lobe epilepsy and either focal epilepsies or generalised seizure disorders are again difficult to interpret, often because of selection bias. The large series reported by Gibbs (Gibbs and Gibbs 1952) derives largely from non-selective patients and the incidence of psychosis from their study is shown in Figure 1.

Gibbs noted the incidence of psychosis is high in temporal lobe epilepsy

TABLE 9

DIFFERENT TYPES OF EPILEPSY AND PSYCHOSIS: PREVALENCE OF PSYCHOSIS IN EPILEPSY SUB-GROUPS.

AUTHOR	TLE		OTHER FOCAL		GENERALISED		MIXED	
	N	%	N	%	N	%	N	%
Gibbs and Gibbs, 1952		17		2.0				
Ervin et al, 1955	25/31	81						
Bingley, 1958	5/74	7						
Pond & Bidwell, 1959*		20						7
Stevens, 1966	17/100	17					11/100	11
Small et al, 1966	5/50	12					6/50	12
Small & Small, 1967	0/46	0					1/43	2
Gudmundsson, 1966	5/71	7			38/71	54.0	21/71	30
Currie et al, 1971	12/616	2						
Taylor, 1972+	19/100	19						
Shukla et al, 1979	11/62	18			3/70	4.0		

T A B L E 9 (continued)	TLE		OTHER FOCAL		GENERALISED		MIXED	
Author	N	%	N	%	N	%	N	%
Jensen & Larsen, 1979b	20/74	27						
Pritchard et al, 1980	6/56	11						
Onuma et al, 1980		9		2.5		3.6		
Ounstead and Lindsay, 1981	9/87	10						
Sherwin, 1981+	7/61	11						
Sherwin et al, 1982+	7/80	9	0/42					
Sengoku et al, 1983	21/350	6	14/326	4.0				

*Psychiatric hospitalization
+Temporal lobectomy series

TABLE 10

PSYCHOSIS AND EPILEPSY: TLE AND OTHER EPILEPSY TYPES

	TLE	OTHER	TOTAL
Bartlet (1957)	7	1	8
Gastaut et al, (1956)	52	31	83
Guerrant et al, (1962)	7	1	8
Slater and Beard (l963a)	55	14	69
Bruens (l971)	15	1	16
Shukla et al (1979)	11	3	14
Boudin et al (1982)	19	8	27
Trimble and Perez (1982)	17	7	24
Parnas et al (l982)	25	4	29
Garryfallos et al (l988)	9	0	9
TOTAL	217	70	287

(seventeen percent) and this is distinct from other focal disorders (two percent). The main psychotic presentations relate to paranoid illness, while the incidence of schizophrenia as given is low. A problem of interpretation with many earlier studies is the definition of schizophrenia, particularly in North America where diagnostic criteria for schizophrenia have until relatively recently been markedly different from the criteria used by Europeans. Nonetheless, the difference in presentation of psychosis between the temporal lobe group and the other focal group is remarkable.

The studies which fail to distinguish between patients with a temporal lobe focus and others derive largely from one group. Patients were from a medical clinic meeting strict criteria for either temporal lobe epilepsy, or focal or generalised epilepsy. These studies (Small et al 1966: Small and Small 1967: Stevens 1966) compare patients with temporal lobe or psychomotor epilepsy with patients with other focal disorders or generalised seizures of various forms. Little difference is seen between groups, although the frequency of schizophrenia in patients with temporal lobe epilepsy is given as 17%, a figure consistent with other data already quoted. Stevens (1966) states:

"It would be correct to say that nearly two thirds of all the adult epileptics studied who were known to have had psychotic episodes which required hospitalization also had a diagnosis of psychomotor temporal epilepsy".

She tempered this with the acknowledgement that in her study the

psychomotor-temporal group comprised fifty-four percent of the total adult clinic population. In an analysis of individual symptoms she further noted:

"Diagnosis of schizophrenia, mood disturbance, anxiety and withdrawal are more common in the psychomotor temporal group".

Her data, in contrast, show mental slowing and apathy to be more frequent in a "grand mal diffuse EEG abnormality group".

Her interpretation of this increase in psychosis in her psychomotor group is that it is an age related phenomena, both epileptic patients and potential schizophrenia patients increasing the prevalence of mental disorder with increasing age. Quite why this should relate to schizophrenia, but not to mood disturbance, anxiety, mental slowing and apathy is not clear.

Several series show clear differences in the prevalence of psychosis in temporal lobe as against other epileptic groups, including those of Shukla (1979), Sengoku et al (1983), Pond and Bidwell (1959) and some studies shown in Table 11. Studies of patient with temporal lobe epilepsy only (Table 10) vary from the low frequency of psychosis given by Curry et al (1971) of 1.8% to the higher figures given by Ounsted and Lindsay (1981) of 10.3%. This latter series was a follow-up study of patients assessed in 1964 of "a large wholly unselective population" of children with epilepsy, from which a sub-group of children with temporal lobe epilepsy was drawn. Many variables were coded

in 1964, and the children were followed-up in 1977. Of the original hundred, eight-seven patients could be followed, and nine had developed a schizophreniform psychosis. Several additional patients revealed first rank symptoms of Schneider. The figure of 10.3% is therefore an underestimate of the number of patients showing psychotic symptoms.

These data compliment those of the frequency of psychosis reported in patients following temporal lobectomy studies, which averages 7.4% (Trimble 1992).

The clear bias towards the temporal lobe group with regards to psychosis is shown in Table 9 and 10. Although Bartlett (1957) had found only a small number of case histories of epilepsy and psychosis in his series, he commented on the high incidence of EEG and clinical evidence implicating temporal lobe abnormalities, supporting a view which was becoming popular then, that the psychosis was related to temporal lobe dysfunction. As can be seen, all of the series given show temporal lobe epilepsy to be more commonly associated with psychosis, irrespective of the classification of psychosis, an issue to be discussed below.

TABLE 11

SURVEYS OF EPILEPTIC PSYCHOSIS IN MENTAL HOSPITALS

	Number of cases with epilepsy	Number of psychoses	% psychosis
Liddell (1953)			4.3
Bartlet (l957)	1073	8	0.7
Standage (l973)	53	8	15.1
Betts (l981)	78	47	60.2
Mann and Cree (l976)			5.3
Stevens (l980)	21	2	9.0

There are several series of studies of epileptic patients in psychiatric hospitals, and these are given in Table 11. Naturally, the frequency is high, the predominant diagnoses being paranoid and schizophrenia-like psychosis. The latter was the specific subject of study of Standage (1973) and they formed forty percent of the cases of Betts (1981).

Summarising these data it would seem that there is substantial evidence that psychosis is over represented in epilepsy and further it is over represented in patients with temporal lobe epilepsy compared with other forms of epilepsy. Many of the comparison groups have been patients with generalised seizures, but it is recognised that such patients often show temporal lobe pathology and indeed using newer methods of investigation such as video-telemetry it has become appreciated that so called primary generalised epilepsy often reflects secondarily generalised seizures from a focus. Further, although extra temporal foci have been used in some studies, again it cannot be assumed that such foci do not generate discharges through the limbic structures, and hence cause complex partial seizures.

Phenomenology

A number of studies in the more recent era emphasise the schizophrenia-like nature of many of the chronic psychosis seen in patients with epilepsy. Earlier examples come from Clark and Lesko (1939), Mulder and Daly (1952) Rodin

et al (1957) and Ervin et al (1955). The latter group reported a diagnosis of schizophrenia in eighty-one percent of forty-two patients with temporal lobe epilepsy, reaching the conclusion that there was a high correlation between the two. These early authors made the point that the psychiatric symptomatology in the epileptic patients was remarkably similar to schizophrenia noted in non-epileptic patients. The statement of Gibbs (1951) on this point is clear:

"The psychiatric symptoms which accompany psychomotor epilepsy are clinically indistinguishable from those encountered in 'purely psychiatric' disorders" (p 526).

The most important literature stems from the writings of Hill (1953) and Pond (1957). They emphasised the development of chronic paranoid hallucinatory states which were seen especially with temporal lobe epilepsy with complex auras which occurred several years following the onset of seizures, usually in the late teens or twenties. Pond gave an early description of the clinical features:

"They include paranoid ideas which may become systematized, ideas of influence, auditory hallucinations often of a menacing quality, and occasional frank thought disorders with neologisms, condensed words and inconsequential sentences ... a religiose colouring of the paranoid ideas is common. The affect tends to remain warm and appropriate, which is sometimes in contrast to "true schizophrenia", nor is there typical 'schizophrenic' deterioration to the empty hebephrenic state". (p1444).

These features have essentially been confirmed by authors ever since. The most comprehensive series reported is that of Slater and Beard (1963). They

collected sixty-nine cases from the Maudsley Hospital and the National Hospital, Queen Square with a clinical diagnosis of epilepsy supported where possible by EEG evidence, and a diagnosis of schizophrenia. They clinically classified the psychosis into three groups; chronic psychoses with recurrent confusional episodes, chronic paranoid states and hebephrenic states. The usual onset was insidious, with gradual appearance of delusions, especially in the chronic paranoid sub-group. In seventeen cases the chronic psychosis appeared as a sequel to a series of epileptic convulsional episodes, in a further twenty, short lived psychotic episodes lasting from eleven to thirty-eight days occurred intermittently before the onset of the more chronic disorder. The schizophrenic symptomatology of their sub-groups is shown in Table 12.

Delusions were shown by all but two of their patients, and in many cases this was religious or mystical (see below). Passivity feelings were prominent, and many patients attributed feelings of special significance to common place events. A number of patients claimed special powers, for example of healing, being able to see through walls or read thoughts, and persecution of an extreme kind was noted in many.

Fifty-eight patients had hallucinations both visual and auditory, the latter being commonest. They were often of persecutory voices, but first rank Schniderian

TABLE 12

SCHIZOPHRENIC SYMPTOMATOLOGY FROM SELF-DESCRIPTION OR OBSERVED IN HOSPITAL

	GROUP A	GROUP B	GROUP C	TOTALS
Delusions in clear consciousness	11	46	10	67
HALLUCINATIONS IN CLEAR CONSCIOUSNESS				
auditory	6	31	9	46
gustatory	-	2	1	3
olfactory	-	4	1	5
somatic	-	5	2	7
visual	3	10	3	16
Total patients affected	7	35	10	52
CATATONIC DISORDERS OF BEHAVIOUR				
Impulsive & bizarre acts	3	6	4	13
loss of mobility & volition	1	12	6	19
manneristic behaviour	3	21	10	34
negativism	1	2	2	5
Total patients affected	4	26	10	40
Thought disorder, schizophrenic type	4	16	11	31
Loss of affective responsiveness	1	17	10	28

A = chronic psychoses, B = paranoid states, C = hebephrenic states

(Slater and Beard, I963a)

hallucinations were also frequent. Thought disorder was shown by half of the patients, reflected in an inability to handle abstract concepts, a tendency to ramble, and circumstantialities. Also there was typical schizophrenic thought disorder with thought blocking, neologisms, and evidence of disturbed syntax. Motoric disturbances, for example mannerisms were frequent, although catatonic phenomena were rare. Bruens (1971) divided the psychotic syndromes of his patients into four categories. These were paranoid syndromes with delusions, more or less systematised; psychosis with marked mental regression and transient paranoid symptoms; schizophrenia-like psychosis with thought disorders and affective disturbances, and relatively short lived confusional states. Hallucinations occurred in seventy-eight percent, and were mainly auditory, although visual hallucinations were not uncommon. Delusions were seen in eighty percent of patients, including delusions of reference, delusions of grandeur and guilt. The schizophrenia-like presentations in epileptic patients are not confined to Western cultures, and have also been described from countries such as Nigeria, (Asuni and Pillutla 1967), India (Kanaka 1966), and Japan (Sengoku et al 1983).

Religiosity

The association between epilepsy and religiosity has been noted. It has been suggested that a number of well known mystics and prophets may have suffered from epilepsy, but further examples come from recent times. The

case of Swedenborg is an example as is the case of Van Gogh, who not only was an extremely religious man, but may be said to have other features of the epileptic personality syndrome as described by Geschwind, including hyposexuality and hypergraphia. He was also subject to intermittent psychotic bouts (Gastaut 1956).

Examples of patients with epilepsy whose religious feelings appeared to have hypertrophied are discussed by a number of earlier writers including Eccheviria (1873), Clouston (1896), Kraepelin (1923) and Clark and Lesko (1939). The latter authors describe four patients with chronic schizophrenia-like illness and epilepsy, three of whom had religious delusions or hallucinations. Slater and Beard (1963) commented that mystical delusions were remarkably common in their series, occurring in thirty-eight percent. Bruens (1971) noted that "religious contents were fairly common" to the hallucinations of his patients.

There have been few systematic studies of this, but an extensive series was reported by Dewhurst and Beard (1970) who reviewed religious conversions. These had been described in association with epilepsy by Howden (1872-73), but with singular exceptions, cases in the literature were rare. Dewhurst & Beard described six cases, all of whom had temporal lobe epilepsy, and were

not notably religious prior to their conversion. Out of Slater's twenty-six cases, only eight had religious interests prior to the onset of their illness.

Hyper-religiosity was one of the eighteen personality traits selected by Bear and Fedio in their studies, and as noted above results are mixed. It was not associated with a laterality effect or to site of seizure focus in the studies of Nielsen and Kristensen (1981) and, in the other studies did not appear to distinguish temporal lobe epileptics from others where this comparison was made. The exception was the follow-up study of Bear et al (1982) who noted that religious preoccupations significantly differentiated patients with temporal lobe epilepsy from a mixed psychiatric sample.

Tucker et al (1987) examined seventy-six patients with partial complex seizures and gave them the Wiggins Religiosity Scale. The data were compared with those collected from thirty-one subjects with primary generalised seizures, and twenty-seven subjects with pseudo-seizures and no epilepsy. No significant differences were noted between groups, and neither was there a laterality effect for the temporal lobe epilepsy sample. Wilmore et al (1980) compared twenty patients with temporal lobe epilepsy with fourteen with generalised epilepsy on a specially designed 154 item questionnaire assessing various aspects of religiosity, and differences were noted between the groups on only

seventeen items, the generalised epilepsy groups scoring in the more religious direction.

The negative results from questionnaire studies, which stand in contrast to the long standing clinical observations require further investigation and explanation. It is most likely that, as with hypergraphia, religiosity in patients with epilepsy is either culturally appropriate, and therefore has been of less clinical interest, or pathological, in which case it is an all or non phenomenon, and is seen in only a minority of patients. It would not therefore necessarily emerge as a prominent factor in questionnaire studies unless a sufficiently large number of patients was evaluated.

EEG Studies

A comprehensive evaluation of the EEG manifestations of psychotic episodes occurring interictally was presented by Dongier (1959-60). The clinical presentations associated with 536 psychotic episodes occurring in 516 epileptic patients interictally were documented by a group of investigators following considerable briefing in order to verify the various concepts and terminologies employed by different investigators. Forty-four percent of psychotic episodes were associated with generalised discharges, sixteen percent with focal discharges, the majority (11.6%) being temporal. With regards to forced normalisation, disappearance of the EEG abnormalities

during the psychotic episode was seen in twenty-four percent of cases, mainly of a focal or bisynchronous discharge. Over half of the psychotic episodes were associated with alteration of the state of consciousness, and of the remainder, thirty percent showed predominantly affective disorders, the rest showing schizophrenia-like presentations or pure hallucinosis. Confusional symptoms were more frequent in patients with centrencephalic seizures, these presentations often being associated with diffuse delta waves or more or less continuous bisynchronous spike and wave discharges on the EEG.

Affective disorders were not closely associated with epilepsy type, but focal epilepsies tended to show more depression (45% of TLE cases compared with 24% of centrencephalics). Delusions were more frequent among focal epilepsies especially where a pre-existing focal discharge disappeared. In this group, the duration of the psychosis was often several days or weeks in contrast to the briefer psychotic episodes often seen with more generalised EEG disturbances. Finally, the schizophrenia-like presentations were more often associated with temporal lobe epilepsy (20% compared with 12% in centrencephalic cases). In summary, Dongier's data show differences in the presentation of psychosis between psychomotor epilepsy and generalised epilepsy, the former presenting more affective disorders and schizophrenia-like or paranoid presentations.

Bruens (1980) provided information on fifty-seven epileptic patients suffering from psychosis from the Hans Berger clinic and gives equivalent figures as fifty-eight percent and twenty-two percent. As can be seen from table 13, there is a considerable conformity of data on this point. Similar data, emphasising the association between focal seizures especially with complex symptomatology and prolonged psychosis with schizophrenia-like symptoms, in contrast to briefer episodes of dysphoric non-paranoid psychoses often associated with confusion derives from the figures of Door-Zegers and Rauh (1980) (83% schizophrenia-like illnesses in temporal lobe epilepsy against 23% in generalised disorders), in a retrospective series collected over twenty years from Heidleberg.

Affective States

As noted above, several authors comment on affective disorders in association with the psychoses of epilepsy, although discussion of affective psychosis per se is rare. It has been recognised for many years that epileptic patients may suffer from depressive symptoms (Griesinger 1857) and in the early descriptions of ictally related changes of the mental state, excitement, manic presentation and over activity were notable (Morel 1860). However, interictal affective psychosis, in particular classical manic or bipolar pictures are considered rare. Admittedly, in many early studies, operational criteria

TABLE 13

SCHIZOPHRENIC, PARANOID, CONFUSIONAL, AND DYSPHORIC PSYCHOSES IN GENERALISED AND TEMPORAL LOBE EPILEPSY

AUTHOR	TLE		GEN	
	S	C	S	C
Dongier (1959, 1960)	49	20	12	64
Shukla et al (1979)	92	18	43	57
Dorr-Zegers and Rauh (1980)	83	17	23	77
Bruens (1980)	58	42	22	77
Perez and Trimble (1980)	69	31	28	72
%	**70.2**	**25.6**	**25.6**	**70.0**

(S) schizophrenic and paranoid psychoses, (C) confusional and dysphoric psychoses, (TLE) temporal lobe epilepsy, (GEN) generalised epilepsy.

were not used to distinguish different forms of psychoses, and paranoid affective states may have been common.

The series that report affective psychoses are singularly few. Gibbs and Gibbs (1952) noted 4.2% of 678 cases of psychomotor epilepsy to have manic depressive illness or depression, and 2.8% had 'suicidal tendencies'.

Currie et al (1971) noted only 4 of 666 cases to have a severe depressive illness, a remarkably low figure.

Bartlet reported one depressive and two manic psychoses in his series of eleven, Bruens (1980) had three depressive psychoses out of fifty-seven (one generalised epilepsy), while Dorr-Zegers and Rauh (1980) had three cases, two bipolar illnesses, both with focal seizures.

Dongier (1959-60) reported forty-seven cases of depressive episodes and twenty of manic episodes, the distribution of centrencephalic and temporal forms of epilepsy being similar for the two groups. As noted, patients who showed normalisation, particularly of a pre-existing focus, frequently presented with affective disturbances as part of their psychotic episodes. However, it is not clear that any of her examples represented more classical manic

depressive psychoses.

Betts (1974) reported endogenous depression to be the principle psychiatric diagnosis of seventeen percent of seventy-two patients admitted to mental hospital, although it is not clear how many of these patients were psychotic.

The highest frequency of affective psychosis was reported by Fenton (1978) who noted six patients with an affective psychosis of a total of fourteen psychotic patients in a sample of eighty consecutive admissions of epileptic patients to the Maudsley Hospital. Five more had a schizo-affective disorder, thus making eleven of fourteen with an affective or schizo-affective psychoses (78%).

Robertson et al (1987) carried out a comprehensive survey of the phenomenology of interictal depressive states in sixty-six consecutively referred cases. Thirteen were psychotic (19.6%), although bipolar presentations were rare.

A number of authors have commented on the frequency of suicide in epilepsy (Marchand and Aguriaguerra 1948; Barraclough 1981) which seems especially high for patients with temporal lobe epilepsy. However, it cannot be assumed

that such patients are necessarily psychotic.

The most interesting study of affective psychoses in epilepsy is that of Flor-Henry (l969) referred to below. All his cases had temporal lobe epilepsy, and manic depressive states were characterised by euphoric or depressive alterations of mood, exhibiting periodicity, but leaving the personality intact between phases. Of fifty cases, eleven were schizo-affective, and nine manic depressive (40%).

Summarizing these data, it is clear that affective psychoses have been much less the subject of study than the schizophrenia-like illnesses, and, with the singular exception of Flor-Henry's highly selected series of patients with temporal lobe epilepsy, the majority report manic illness to be infrequent, and classical bipolar affective disorders to be rare. Depressive psychoses are commoner, figures varying from the two percent reported by Bruens to the seventy-eight percent reported by Fenton.

What is clear is that affective symptoms are often intermixed with psychotic symptoms in the classical schizophrenia-like psychoses. This emerged from the extensive study of Slater who noted the affective disturbance shown by all of his patients, usually in the form of periodic moods of depression or

TABLE 14
RISK FACTORS ASSOCIATED WITH PSYCHOSIS OF EPILEPSY

Age on Onset:	Early adolescence
Interval:	Onset of seizures to onset of psychosis: ~ 14 years
Sex:	Bias to females
Seizure type:	Complex partial: automatisms: more than one
Seizure frequency:	Diminished, especially temporal lobe
Seizure focus:	Temporal, especially left sided
Neurological findings:	Sinistrality. Pathology: gangliogliomas, hamartomas. Forced normalization in subgroup.
EEG:	Mediobasal focus

TABLE 15
AGE OF ONSET OF EPILEPSY AND INTERVAL TO ONSET OF PSYCHOSIS

Author	Age at Seizure Onset	Interval (years)
Gastaut (1956)	20	11
Slater and Beard (1963a)	15	14
Jus (1966)		13
Flor-Henry (1969)	13[a]	14
Davison and Bagley (1969)	15	15
Bruens (1971)	13	12
Standage (1973)		19
Kristensen and Sidrup (1978a,b)	10[b]	21
Jensen and Larsen (1979b)	14	14
Dorr-Zegers and Rauh (1980)		15
Trimble and Perez (1980)	11[c]	16[d]
Parnas et al (1982)		22
Sengoku et al (1983)	14[e]	14
Schmitz and Wolf (1989)		13
	MEAN	15

[a] Controls, 18
[b] Controls, 12
[c] Nuclear schizophrenia, 11, nonnuclear schizophrenia, 9
[d] Nuclear schizophrenia, 16, nonnuclear schizophrenia, 27
[e] Controls, 14

irritability. The mood swings were described as short lived and severe, and in nearly fifty percent of patients one more attempts of suicide were made during such a state. Ecstasy was reported by seventeen percent of his patients, most typically as a semi-mystical experience. Flatness of affect was reported in forty percent, but generally, particularly in relationship to classical schizophrenia, his patients retained affective warmth, and this was one of the characteristic distinguishing features between the schizophrenia-like psychoses of epilepsy and process schizophrenia.

RISK FACTORS FOR INTERICTAL PSYCHOSES

A number of risk factors which may be associated with the development of psychosis and epilepsy have been suggested and these are listed in Table 14. These are individually discussed.

Age of onset of seizures, and relationship to age of onset of psychosis

The significance of age of onset of seizures for the development of psychopathology was noted in the MMPI study of Hermann et al (1980) where a group of patients with temporal lobe epilepsy, in contrast to those with other forms of epilepsy were shown to have higher elevations of psychotic sub-scales with an adolescent onset of seizures (aged 13-18). The age of onset of seizures, in samples from which it can be determined, is shown in Table 15. It is clear that the mean age of onset is usually in early adolescence.

However, controlled series do not reveal differences between psychotic and non-psychotic groups. For example, Flor-Henry (1969) gives figures of thirteen years for his psychotic sample, and eighteen for a control group. The figures of Kristensen and Sindrup (1978a) are 10 and 12 years respectively, and Sengouku et al (1983) give 14.2 and 14.9 years. Ounsted and Lindsey were unable to relate age of onset to the later development of schizophrenia-like illness.

The interval between the age of onset epilepsy and the age of the onset of psychoses has been given more attention. This was first discussed in detail by Beard (1963). In Slater's series, the interval was significantly less for those patients developing hebephrenic states. The mean interval for the whole series was fourteen years, and they noted a correlation co-efficient of 0.48 between the ages of onset of epilepsy and the psychoses. They gave this as one reason for suggesting an aetiological relationship exists between epileptic seizures and the psychosis.

As shown in Table 16, with the exception of the Scandinavian series, there is a remarkable homogeneity of the interval, being in the region of eleven to fifteen years.

This mean interval has come in for considerable discussion. Slater's data were criticised because no case occurred in which the onset of psychosis was before and not after the onset of the epilepsy (Slater and Moran 1969). Re-examination of their data, taking these facts into account, testing statistically whether epilepsy had an influence on the distribution of the age of first admission for the schizophrenia-like illness, they noted that for both males and females the psychosis occurred earlier than would be expected, but this was only significant for females.

Male/female differences in relationship to age of onset were further examined by Taylor (1971). Using the data provided by Slater and Beard (1963), he pointed out there was a large excess of females who had both onset of epilepsy and psychosis before they were twenty. In general, those patients who developed psychosis had onset of epilepsy around puberty, which was significantly later than that of a control group who had been referred for temporal lobectomy who did not have psychosis. This led Taylor to suggest that a different aetiology was related to the seizure disorder in the two groups, and that cerebral maturation differed between the sexes. He summarized this by suggesting that females have more of a risk for the development of psychosis, but this is passed by their twenty-fifth year.

Sex

The various series reported show a relatively even distribution of gender, some with more males (Slater and Beard 1963) others with more females (Kristensen and Sidrup 1978a). However, Taylor (1971) noted that the sex ratio in epilepsy generally shows a bias towards males, giving figures of 135 males to 100 females from department of Health and Social Security data. His own analysis of Slater's cases suggests an increased risk in females, and he has provided further confirmation from the temporal lobectomy cases of Falconer (Taylor 1975). Of 88 cases, psychosis was commoner in females (24%) than in males (9%).

Seizure Variables

The association between temporal lobe epilepsy and psychosis has already been emphasised, and the specific relationship between certain forms of psychosis, particularly presenting with paranoid or schizophrenia-like symptoms and temporal lobe lesions has been suggested. It is not surprising therefore that most studies report that patients with psychoses have complex partial seizures, sometimes associated with secondary generalization. In Slater's series these were commoner in those with chronic psychoses of a paranoid or recurrent nature, as opposed to the hebephrenic group.

There are two controlled series available. Flor-Henry (1969) reported more infrequent psychomotor attacks in his psychotic sample. Kristensen and Sindrup (1978) noted a higher frequency of automatisms, or automatisms with epigastric or déjà vu aura in their psychotic group. There was no difference in the incidence of generalised seizures.

Schmitz and Wolf (1989) in a survey of 28 psychotic patients who attended a neurological out-patient clinic, noted that psychoses were significantly more frequent in patients with complex as opposed to simple partial seizures.

The relationship between seizure frequency and psychosis has been examined by several authors, noting the relationship of the onset of the psychosis to the seizures themselves. No clear relationship was observed by Hill et al (1957), Glazer (1964) or Small et al (1966). In contrast, Stevens noted ten out of thirteen psychomotor temporal lobe epileptic patients with psychosis who decompensated during a remission for seizures, often brought about by a change of seizure therapy. In contrast 4 out of 5 grand-mal patients appeared to have an exacerbation of their psychosis in association with increased seizures and worsening of the EEG.

Bruens (1971) had five out of nineteen patients (26%) who showed diminished epileptic activity during the psychosis, four of these having evidence of a temporal lobe focus. In Slater's series, only grand-mal attacks were taken into account, and no clear relationship emerged. Flor-Henry (1969) suggested that this negative result was because other forms of seizures were ignored, since his own study demonstrated that psychotic patients exhibited fewer seizures, in particular fewer psychomotor and what he referred to as minor temporal seizures when compared with a control group. When seizure frequency and type of psychosis was examined he noted that affective psychoses were correlated with major convulsive epilepsy infrequently manifested.

Kristensen and Sindrup (1978) did not note differences with regards to generalised seizures when psychotic patients were compared with controls, but did notice a diminished seizure frequency for complex partial seizures.

While acknowledging that assessment of seizure frequency is difficult, particularly retrospectively as is the case in the studies quoted, the controlled studies both suggest a diminished frequency of psychomotor temporal lobe seizures in patients developing psychosis, and there are several reports of individual patients who have some antithetical relationship between seizures and psychosis which would seem to be of importance. These data suggest

that there is a sub group of patients where such a relationship does hold, and this may be viewed as a form of antagonism between seizures and psychosis, a variant of the phenomena described by Landolt, as in some cases the EEG is shown to normalise.

Several authors have noted the association between psychosis and more than one seizure type (eg Bruens 1971: Parnas et al 1982, Schmitz and Wolf 1989) - usually with secondary generalisation from focal seizures.

EEG Studies

Bruens (1971) noted forced normalization in five cases, while the EEG investigations of Slater's series (Beard 1963) revealed the preponderance of temporal lobe abnormalities as already discussed. Kristensen and Sindrup (1978b) compared the EEG findings of ninety-six patients with partial epileptic seizures and complex automatisms with psychosis, and a control group with epilepsy and no psychosis. There was no difference between the groups with regards to the frequency of patients with focal spike activity during either the wake or sleep EEG, but highly significant differences were noted with regards to sphenoidal recordings. Thus, sphenoidal spikes were recorded in eighty-two percent of psychotics as opposed to forty-one percent of controls. No significant differences were noted in the location of temporal lobe spikes, in

relationship to whether they were anterior, mid or posterior temporal, but psychotic patients exhibited a significantly higher number of independent spikes, and their back ground activity more frequently showed a mixture of diffuse slow-wave activity. The medio-basal temporal lobe abnormalities, as located with sphenoidal electrodes in psychotic patients, represent another study showing links between medial-limbic disturbances an psychosis (see Table 8).

Ramani and Gumnit (l982) have reported the only study of intensive monitoring of interictal psychoses of epilepsy. In reality, their patients were largely ictally related phenomena in the sense that they had been admitted to hospital for control of intractable seizures, and they experienced a psychotic episode while in hospital the duration of which varied from one to three weeks. It is not clarified whether the episode recorded was of the same character as the chronic psychosis from which a number suffered, the duration of the psychotic illness varying from one to thirty years. Nine had a schizophrenia-like psychosis, the majority having paranoid presentations. Six patients had interictal temporal lobe spikes, two had primary generalised epilepsy and two patients had generalised bursts of synchronous fronto-centrally predominant slow spike - and polyspike - wave discharges. One patient showed a striking reduction of seizures and EEG normalization. No unequivocal changes in the

EEGs were recorded in the other patients. Two patients, in addition to the one showing normalization, showed alternating psychosis, their seizures coming under control being related to the emergence of the psychosis.

Neurological Features

Findings at neurological examination, or following psychometric testing are omitted from many series. Jensen and Larsen (1979) comment that their psychotic patients "appeared to be intellectually brighter" than non-psychotics, while the average I.Q. of the sample of Toone et al (1982) was 96.

Beard (1963) reported lack of spontaneity, slowness and retardation in thirty-four cases, impaired memory in twenty-nine cases, and viscosity in twenty-two. Only thirteen of his patients (19%) were free of any indication of organic personality change. However, these findings were subjective.

Flor-Henry (1969) noted more abnormal neurological examinations and brain damage in schizophrenic as opposed to manic depressive epileptic patients, the latter having higher IQ (92 verses 105). Kristensen and Sidrup (1978) noted that the clinical neurological examination showed positive signs of organic damage in only a small proportion of their patients, but this was significantly greater in the psychotic sample compared with controls (13%

verses 5%). In addition they reported that their psychotic sample had a significant increase in left handers or ambidextrals (16 out of 92) compared with controls (5 out of 95). Such an increase in sinestrality had been earlier commented on by Taylor (1975), in whose series seven out of thirteen psychotic patients were left handed compared to 11 out of 75 non-psychotic patients. Further, more patients with an alien tissue lesion were left handed. When considering the latter group only, two three way interactions were noted by Taylor between sex, psychosis and handedness; and sex, psychosis and side of operation. These highlighted the excess of psychotic females, the absence of psychosis in right handed males and the excess of left sided surgical operations. Taylor felt that left handedness represented "unusual organization of cerebral function", and stressed that it did not necessarily mean a shift of dominance to the alternative hemisphere.

Radiological Studies

Air encephalography (PEG) was carried out in fifty-six of the sixty-nine cases of Slater and Beard (1963) and was reported normal in seventeen. The main abnormality was atrophy (36), in nineteen cases there being dilatation of one or both temporal horns either as part of generalised ventricular dilatation or by itself. Temporal horn abnormalities were exclusively defined in the groups with chronic psychoses and recurrent confusional episodes or the chronic paranoid

states and not noted in the hebephrenics.

Sherwin (1977) noted abnormal PEG in 18 of 23 patients with psychosis and epilepsy, and in 14 there was temporal horn dilatation.

Flor-Henry (1969) reported that fifty-two percent of his schizophrenia-like psychoses had air encephalographic abnormalities, but this was not significantly different from fifty-eight percent found in non-psychotic controls. Kristensen and Sidrup (1978) also failed to note differences between their psychotics and controls.

CT studies have been carried out by Toone et al (1982). They compared 57 patients with epilepsy and psychosis with 78 controls with a diagnosis of epilepsy and a psychiatric illness other than psychosis. Abnormalities were reported in forty-four percent of the index and fifty percent of the control subjects. No differences were noted when diagnostic sub groups were examined comparing schizophrenic, affective and paranoid patients. Laterality differences were noted which are discussed further below.

There is one study of CT attenuation densities of patients with epilepsy and psychiatric disorder in which twelve patients with a schizophrenia-like psychosis of epilepsy were evaluated (White et al - unpublished manuscript).

No significant relationships were found between regional CT and any clinical parameter, although the frontal densities and left temporal densities were non-significantly lower in the schizophrenia-like psychoses compared with non-psychotic patients.

These radiological studies suggest that patients with epilepsy and psychosis probably do not differ from controls in relationship to the gross amount of ventricular dilatation seen.

Family History

A number of authors have commented on the family history of psychosis or epilepsy in their samples, the most intensive investigation being that of Slater and Glithero (l963). In this study, accessible relatives were interviewed and reliance was not placed therefore only on hospital records or the patients own knowledge. The third party information was available on 88% of patients. They noted in the relatives eight epileptics, two schizophrenics and twelve patients with psychopathic personalities. By using mathematical calculations of the expected risk, they concluded that the instances of schizophrenia amongst the relatives was that which was expected from a sample of the general population. They noted that this was remarkably different from the expectation had their subjects been schizophrenics, where the heritability has

been established. Similarly no excess of schizophrenia was found in the relatives in the study of Flor-Henry (1969). Kristensen and Sindrup (1978) noted a positive family history of epilepsy to be more frequent in their control patients.

The only study to suggest a significant hereditary component to the psychopathology of epilepsy was that of Jensen and Larsen (1979). They noted major psychiatric disorders in sixty-five percent of the relatives of their psychotic patients compared with thirty-nine percent in relatives of non-psychotics. These were patients being evaluated for temporal lobectomy. The study of Slater and colleagues is the only one which evaluated genetic aspects comprehensively, and was carried out by authors well versed in genetic methodology.

Metabolic Aspects

The relationship of abnormal folate metabolism to psychiatric disorders in general, and to those of epilepsy in particular has been of interest since the early publications of Reynolds (1967). He postulated that a deficiency of folate, brought about by anticonvulsive treatment, may lead to psychopathology, particularly dementia and schizophrenia-like illnesses in epilepsy. He

described a series of cases with schizophrenia-like psychoses with anticonvulsant drug induced megaloblastic anaemia or non-anaemic folate deficiency. In one case a clear inverse relationship between seizures and psychosis was noted, leading Reynolds to suggest a significant role of folate deficiency, folate being a significant CNS methyl donor, in the development of psychosis.

Bruens (1971) noted diminished folate levels in five cases where it was measured, while Ramani and Gumnit (1982) noted that most of their patients had low serum folate levels, but these were no different from non-psychotic epileptic patients in their unit.

The role of folate is inextricably bound with that of anticonvulsants, and several authors have examined prescriptions in relationship to psychosis. The results do not suggest an association between the interictal psychoses and prescribed drugs (Slater and Beard 1963, Flor-Henry 1969, Bruens 1971), although it is recognised that individual patients may develop a psychosis associated with anticonvulsant drugs. This may be an intoxication which produces an organic psychosyndrome, or an example of forced normalisation.

There is one CSF report, that of Peters (1979) who compared CSF monoamine metabolites in a group of psychotic and non-psychotic patients with temporal lobe epilepsy using the probenecid technique. The psychosis was determined by the use of the MMPI, and CSF homovanillic acid (HVA) was found to be lower in the psychotic sample. This intriguing finding requires replication, but is consistent with abnormalities of dopamine metabolism in association with psychosis, especially upregulation of post synaptic receptors leading to decreased synaptic dopamine release and breakdown.

Laterality

Flor-Henry (1969) was the first to discuss the issue of laterality in relationship to psychosis and epilepsy. In his study, 18% of all cases of psychosis lateralised to the right hemisphere in contrast to fifty percent of the controls. Further, when bilateral cases were taken into account, he found that with respect to psychosis, bilateral and unilateral left foci were equivalent. When left sided foci and bilateral were compared with right sided lesions, a highly significant excess of psychotics was noted in the former. With regards to the type of psychosis, Flor-Henry reported the highest incidence of right-sided unilateral (non-dominant) foci in manic depressives, while in schizophrenic patients, the dominant lobe was mainly involved. This issue has been taken up by a number of other authors, the combined data from surveys where it is

TABLE 16
LATERALITY AND EPILEPTIC PSYCHOSIS

AUTHOR	LEFT	RIGHT	BILATERAL	TOTAL
Slater & Beard (1963a,b)	16	12	20	48
Flor-Henry (1969)	19	9	22	50
Taylor (1975)	9	4	0	13
Kristensen & Sindrup (1978a,b)	22	26	31	79
Hara et al, (1980)	6	4	0	10
Pritchard et al (80)	4	1	1	6
Ounsted & Lindsay (1981)	7	0	2	9
Sherwin (1977)	11	3	3	17
Sherwin (1981)	5	2	0	7
Sherwin et al (1982)	5	2	0	7
Toone et al (1982a)	4	0	8	12
Pamas et al (1982)	12	6	7	25
Trimble & Perez (1982)	9	4	4	17
Onuma et al (1987)	17	5	19	41
TOTAL	**146**	**78**	**117**	**341**
% OF TOTAL	**42.8**	**22.9**	**34.3**	**100**
% OF N	**65.2**	**34.8**		

(N) Left + Right (224)

possible to establish the laterality of the focus being shown in Table 16.

Slater and Beard (1963) looked for a laterality effect but did not find it. Flor-Henry suggested that if laterality effects are important they may have been obscured by the high proportion of bilateral foci in their study. In general, with the exception of the Scandinavian findings (Kristensen and Sindrup 1978), there is a clear bias towards a left sided abnormality, coming from different samples collected in different ways. The follow-up study of Ounstead and Lindsay (1981) required that the laterality of the focus was established thirteen years prior to the follow-up, minimising any bias that could be crept in. Nine of their patients had developed schizophrenia-like psychoses with first rank symptoms of Schneider, and seven had a left-sided focus.

Sherwin (1977; 1981: 1982) provided evidence from a series of studies carried out in different centres using EEG criteria for the assessment of laterality. In the first report (Sherwin 1977) of thirty-four patients with "psychotic-like reactions and aggressivity", fifty percent had EEGs with localising features, of which eleven were left sided, three were right sided and three were bilaterally abnormal. In fourteen showing temporal horn dilatation, thirteen were abnormal on the left side, and one was bilaterally abnormal. These findings are in keeping with earlier studies such as Larsby and Lindgren (1940), who

reported that more than three quarters of "psychiatrically deteriorated" epileptic patients with ventricular abnormalities revealed left sided changes.

Seeking better confirmation of laterality, Sherwin (I981: I982) examined patients who had undergone investigation for temporal lobectomy either at UCLA, in California, or at INSERM in Paris. From the UCLA group, seven cases were identified having a paranoid or schizophrenic type psychosis, five of which had a left temporal lobectomy. In the second sample, seven patients with undifferentiated schizophrenia, paranoid schizophrenia or hebephrenia were found among eighty cases. When the relative frequencies of the left and right sided lesions in non-psychotic and psychotic patients were compared, a significant excess of left sided lesions was found in the psychotic group (five out of seven). In this sample, forty-six patients were noted who, for a variety of reasons, did not come to operation. More than half (nineteen out of thirty-seven) of the left-sided non-surgical cases demonstrated major psychiatric problems including two cases diagnosed as schizophrenia. In contrast, less than a quarter of the right side of cases demonstrated such difficulties, and there were no psychotics. Finally, forty-two patients were examined who had surgery for other focal epilepsies (frontal, parietal or occipital lesions) and in these, none had a history of psychosis.

The importance of these surgical studies is that laterality was confirmed by the techniques used for pre-surgical work up, and in those operated on by improvement in seizures following the operation.

Toone et al (1982), in a CT study, noted no laterality findings although in their psychotic group four schizophrenic and one paranoid patient had left sided abnormalities, and two affective patients had right sided abnormalities. They further noted that when left sided and predominantly left sided abnormalities were compared with right and predominantly right sided abnormalities, there was an excess of left abnormalities in the psychotic samples (sixteen verses seven). For the schizophrenic sub-group the figures were six left and two right. Patients with hallucinations, where a laterality effect was noted, showed a complete absence of right sided lesions.

The issue of laterality has been examined further by several authors. For Flor-Henry the issue was involvement of the dominant temporal lobe, although Taylor (1975) examines the issue in relationship to sinestrality. Thus, several groups note an excess of sinestrality in relationship to psychosis and temporal lobe epilepsy (Taylor 1975: Kristensen and Sindrup 1978: Toone et al 1982: Sherwin et al 1982) ranging from seventeen to over seventy percent. Sherwin et al specifically examined the relationship to dominance as well as

handedness, and noted that it was handedness which was the important issue. Taylor (1975) suggested that sinestrality implied abnormal organization of cerebral function, and did not necessarily specify that there was a right hemisphere location for speech in the affected patients. Further, Taylor (1975) and Sherwin et al (1982) emphasised an interaction between sex, psychosis and handedness, with an over-representation of psychosis in left handed females.

Conclusions

The various risk factors associated with the development of the psychoses of epilepsy are shown in Table 14, taken from the literature and reviewed in this section. Certain associations seem relatively clear. For example, the psychoses are over represented in patients with epilepsy compared with the general population (Table 8), especially in temporal lobe epilepsy (Tables 9 & 10). Further patients with a mediobasal/limbic focus would seem more susceptible (Table 6). When the psychoses are broken down with regards to clinical type, the association between temporal lobe epilepsy and a schizophrenia or paranoid like psychosis becomes stronger (Table 13), especially when the left temporal lobe is predominantly affected by the focus (Table 16). In the majority of patients reported in the literature the psychosis precedes the epilepsy, the latter beginning in early adolescence (Table 15)

with an interval of approximately eleven to fifteen years intervening before the onset of psychosis.

There are clear associations between a diminished seizure frequency in some patients, and the onset of an acute psychosis (as seen in forced normalization), or more insidiously with a psychosis emerging as the frequency of seizures diminishes. Psychotic patients are more likely to be left handed, usually present with complex partial seizures and automatisms, and often but not always will show evidence of structural pathology.

SECTION 4:

RATIONALE OF STUDIES

RATIONALE OF STUDIES

The introductory sections have emphasised how a psychosis can be associated with epilepsy, and that this is more likely to occur than by chance. There is also a suggestion from the literature, although it is a point of controversy that the psychoses are commoner with temporal lobe epilepsy. The phenomenological character of the psychoses have been poorly documented, although, the works of Slater et al (1963) suggest they have a schizophreniform nature.

In order to clarify these issues the first investigation was an examination of the presenting clinical features of the psychoses of epilepsy in a clinical population referred to the investigator at the National Hospital for Nervous Diseases, Queen Square. An attempt was made to objectify, as far as possible, the phenomenology using the Present State Examination of Wing (Wing et al 1974) and comparison was made with a schizophrenia control group. It was hoped that this would lead to a clarification of the kind of psychoses seen in an epilepsy clinic, and their relationship to schizophrenia in the absence of epilepsy.

With regards to the pathogenesis of these psychoses, two predominant view points have been put forward. First that they represent an organic psychosis,

(Slater et al 1963), secondary to underlying structural brain disease, and second that they are epileptic psychoses and more related to disturbance of function (Flor-Henry 1969). The most appropriate way to test these hypotheses, which are discussed more fully in section 6, was through using neuro-imaging studies. Three investigations are therefore described. The first two emphasise structural imaging. A population of patients with a psychoses of epilepsy were examined using two available methods of structural imaging, namely CT scans and MRI scans. It was anticipated that findings from these studies would allow clarification of the organic underpinning of these conditions. The third investigation was a study using Positron Emission Tomography (PET), specifically to examine the issue of changes of brain function in relationship to the psychoses of epilepsy. It was anticipated that by using varying techniques of structural and functioning imaging that a further understanding of the pathogenesis of these psychoses would emerge.

SECTION 5:

THE INVESTIGATIONS

STUDY 1:

AN INVESTIGATION OF THE CHRONIC PSYCHOSES OF EPILEPSY USING THE PSE.

PHENOMENOLOGY OF THE CHRONIC PSYCHOSES OF EPILEPSY

Introduction

In the introductory section to this thesis the history of the relationship between epilepsy and psychosis was presented and some early descriptions of the symptomatology of the inter-ictal states was reviewed. Prior to carrying out any radiological studies of the inter-ictal psychoses, it seemed of importance to describe as accurately as possible the phenomenology of these patients. In the literature, the majority of investigators have relied on clinical impressions to define patient symptoms and no attempt had been made to systematically evaluate phenomenology.

In psychiatry over the past 20 years more definitive methods have been adopted for quantification of psychopathology, mainly using rating scales in an attempt to increase reliability of clinical observations. These have been of two sorts, either self-assessment questionnaires filled in by patients, or interview rated scales which provide working definitions of psychopathology to compare patterns of symptoms in different populations. A more recent development in this field has been the use of structured standardized interviews, in which the manner in which symptoms are elicited as well as the way in which they are recorded is laid down. Questions are asked in a specific order, and ratings of patients answers are made based on standardized definitions. At the time this

investigation was carried out, two of the most widely used were Spitzer's Psychiatric Status Schedule (Spitzer 1978) and the Wing Present State Examination (Wing, Cooper and Sartorius 1974). The latter was the more commonly used in Great Britain, and over the years had undergone a number of developments and refinements. The interview technique is based on the examination of the patient, and the clinician decides whether a particular symptom is present or not after all the questions laid down and appropriate probes have been asked. The questions relate to the patients' experiences during the month prior to the interview and this process of necessity excludes most of the psychiatric history, which becomes the subject of a separate enquiry.

In this investigation the ninth edition of the PSE was used. This consists of a check-list of 140 items which has been condensed from over 400 in earlier versions of the test. It is important to note that the interview is still basically clinical, the schedule not being like a questionnaire. It has reliability and has been shown to give good agreement, particularly for the diagnosis of schizophrenia in many countries of the world, as far separate as America, Taiwan, Czechoslovakia and Nigeria (WHO 1973). Prior to using the schedule, the investigator attended a special course to learn the appropriate techniques for the application of the PSE, and to understand the method of

standardization.

The results from the PSE schedule are analysed by a computer programme known as the CATEGO, in which the original items are passed through a progressive series of condensations, and decisions about the actual diagnosis are postponed until the final change. The item content is thus reduced to a number of "symptoms", which are then further refined to 38 basic "syndromes". These range from those measuring general and non-specific anxiety to neurosis, depression, delusions and hallucinations, and include measures of general attitude and behaviour, observed mood disturbances and motor symptoms. Mean syndrome profiles can be derived from the PSE to compare groups or to monitor change with time. The CATEGO programme prints out the syndromes with a three-point ranking, indicating the degree of certainty with which it may be said to be present.

The final output of the programme is an allocation to one of 50 sub-classes which are collapsed into broader classes. Descriptions of these are given by Wing, Cooper and Sartorius (I974). In general, each PSE syndrome profile is allotted to one class, which is basically descriptive and represents a summary of the PSE ratings. The method also indicates when more than one diagnosis can be made on the basis of signs and symptoms analysed. The technique

is largely used for identifying and classifying psychiatric symptomatology, in particular, for comparing international differences and similarities of diagnosis. Although it is not recommended for the classification of patients with organic brain pathology, since the interest of the study was in clarifying the phenomenology of epileptic psychosis arising in clear consciousness, rather than as part of an organic brain syndrome and since the descriptions of Slater et al (1963) emphasized the resemblance of the psychotic states to schizophrenia, it seemed the appropriate technique for attempting to clarify the phenomenology of these psychoses in detail.

Methods

Twenty-three patients consecutively referred to the investigator suffering from unequivocal epilepsy and active psychosis, the latter in the setting of clear consciousness and present for at least one month were examined using the PSE. Their data were compared with that of a group of schizophrenic patients, previously assessed by two psychiatrists, (the investigator and a colleague), both of whom agreed on the diagnosis of schizophrenia. All patients were interviewed while actively psychotic.

In addition patients received a full neurological examination, and a number of investigations including routine haematology, assessment of serum anticonvulsant levels, formal psychometry (carried out by the department of

psychology at the National Hospitals, Queen Square), and electro-encephalography (EEG).

The EEG was read independently by a member of the department of neurophysiology and information from the present EEG was evaluated with previous EEG's the patient may have had. In addition, sphenoidal recordings were carried out on 6 patients who had complex partial seizures, and one patient had prolonged video-telemetry. The EEG was used to clarify the diagnosis of epilepsy which was initially made on clinical grounds, and to assess seizure classification and laterality.

During the investigation, information was gathered from as many sources as possible, including from an independent relative, on the date of origin of epilepsy, the date of onset of the psychiatric illness, and the length and temporal pattern of the psychiatric illness.

The psychological tests results reported are the full scale WAIS. In 16 patients there were records of previous psychometry with which the current status of the patient could be compared.

Statistics

In the analysis of these results, Fisher's Exact Probability Test (Siegel 1956) or Student's T-test were used.

Results

Clinical Profiles

For the phenomenology study 10 patients with schizophrenia were compared with 23 patients with schizophrenia-like psychosis using the PSE. An additional patient with schizophrenia-like psychosis of epilepsy was included for further analysis of the EEG and seizure types in relationship to the phenomenology of the psychosis, and the assessment of the relationship of epidemiological variables to the psychosis.

The age range of the schizophrenia patients was 18 to 56 years (mean 34.7), and there were 6 males and 4 females. The age range of the epileptic group was 19 to 58 years (mean 37.5) and there were 15 males and 8 females.

The results of the CATEGO sub-classes and classes is shown in Table 17. The schizophrenia group, as expected from the clinical examination, were largely classified as nuclear schizophrenia (CATEGO sub-classes) and schizophrenic psychosis (CATEGO class). There were two exceptions. One was a depressive psychosis, and the other was a paranoid psychosis.

TABLE 17: CATEGO SUBCLASSES AND CLASSES - DIAGNOSTIC COMPARISON BETWEEN EPILEPTIC PSYCHOTIC AND SCHIZOPHRENIC PATIENTS

SUBCLASSES DIAGNOSES	EPILEPTIC N = 23		SCHIZOPHRENICS N = 10	
	C	U	C	U
Nuclear schizophrenia	10	1	8	-
Schizophrenia without first rank symptoms	-	1	-	-
Residual schizophrenia/mania	1	-	-	-
Mania	3	-	-	-
Psychotic depression	3	-	1	-
Paranoid psychosis/retarded depression	-	2	-	-
Paranoid psychosis/affective psychosis	-	1	-	-
Paranoid psychosis	-	1	1	-
TOTAL	17	6	10	-

CLASSES DIAGNOSES	EPILEPTICS N = 23		SCHIZOPHRENICS N = 10	
	C	U	C	U
Schizophrenic psychosis	11	1	8	-
Manic psychosis	3	-	-	-
Depressive psychosis	3	-	1	-
Paranoid psychosis, retarded depression	-	2	-	-
Paranoid psychosis	-	2	1	-
Borderline psychosis	1	-	-	-
TOTAL	18	5	10	-

C = Diagnosis certain U = Diagnosis uncertain

The sample from patients with epilepsy showed a variety of psychiatric syndromes and diagnosis. Table 17 also shows the degree of certainty of the diagnosis and when more than one diagnosis was plausible on the basis of PSE data. There was more certainty in the diagnosis of the schizophrenic sample than in the epileptic psychotic sample.

A preliminary diagnosis of affective psychosis was present in 10 out of the 23 epileptic patients (CATEGO sub-classes), and in 8 a final diagnosis of affective psychosis was made (CATEGO classes). Manic psychosis was present in 4 patients, and 3 received a final diagnosis of manic psychosis. Paranoid states or paranoid psychoses were present in 4 of the epileptic patients and in 3 these were associated with a diagnosis of affective psychosis. Only two patients had a class diagnosis of paranoid psychosis and in both cases this was uncertain. The diagnosis of nuclear schizophrenic syndrome, similar to that found in the schizophrenic group and a final diagnosis of schizophrenic psychosis was made in approximately half the epileptic patients.

Type of Epilepsy and Type of Psychosis

From the sample of patients with epilepsy, 16 had a clinical diagnosis of temporal lobe epilepsy and seven of generalized epilepsy. The former was recognised by seizure pattern, including auras, and EEG data. The latter was ascribed in patients where the seizure pattern was generalised from the

outset, and no evidence of a focus could be obtained by the methods available to the investigator. Table 18 compares the type of psychosis in patients with temporal lobe epilepsy and in those with generalized epilepsy as rated with the PSE. Affective psychoses including manic psychosis, psychotic and retarded depression were present in both types of epilepsy. There was a tendency for affective psychosis to be found more in relation with generalized than with temporal lobe epilepsy (4 out of 7, as compared with 4 out of 16 in the temporal lobe group), but this did not reach statistical significance.

Schizophrenic psychosis on the other hand was present in 12 patients, of whom 11 had temporal lobe epilepsy, and in the only exception in which the diagnosis of schizophrenia was made in a patient with generalized epilepsy, the diagnosis of schizophrenia was doubtful. Furthermore, this patient was not classified as nuclear schizophrenia in the CATEGO subclass, unlike all the other patients with certain diagnosis of schizophrenia (CATEGO sub-classes, Table 17). The occurrence of schizophrenic psychosis was significantly higher among temporal lobe epileptic patients than amongst those with generalized seizures ($p < 0.02$). Five of the 16 patients with temporal lobe epilepsy presented with other types of psychosis including psychotic depression and paranoid psychosis. Figure 2 summarizes these data showing the PSE syndrome profiles, comparing a group with temporal lobe epilepsy not

diagnosed as schizophrenia with a group with generalized epilepsy, not diagnosed as schizophrenia. Affective disorders were noted in both groups. All temporal lobe patients had either a primary or a combined disturbance of affect, and in 3 out of the 5, the combination was with a paranoid psychosis. Generalized epilepsy was less clearly related to paranoid psychoses, which were rare in this group (one out of 7). From Figure 2 it can be seen that the temporal lobe group have more delusions of persecution (PE), delusions of reference (RE) and special features of depression (ED) than the generalized group. The latter show more tension, sexual fantasies, over-activity, depersonalization and hypomania. In view of the small numbers no statistical analysis of these data were attempted.

The close phenomenological similarity between the patients diagnosed as schizophrenia and the temporal lobe epilepsy patients who also received a PSE sub-class diagnosis of nuclear schizophrenia is shown in Figure 3, which is a comparison of the syndrome profiles of these two groups. The two groups were compatible, not only in terms of symptoms of nuclear schizophrenia (NS), but also share similarity of other symptoms rendering both profiles almost identical. The two exceptions were delusions of grandeur, and visual hallucinations, both significantly more common in the non-epileptic group ($p < 0.05$).

TABLE 18: CATEGO SUBCLASSES AND CLASSES: DIAGNOSTIC COMPARISON BETWEEN PSYCHOTIC PATIENTS WITH TEMPORAL LOBE (TLE) AND WITH GENERALIZED (GEN) EPILEPSY

CATEGO SUBCLASSES	TLE N = 16	GEN N = 7
Nuclear schizophrenia	11	-
Schizophrenia without first rank symptoms	-	1
Residual schizophrenia/mania	-	1
Manic psychosis	1	2
Psychotic depression	1	2
Paranoid psychosis / retarded depression	2	-
Paranoid psychosis / affective psychosis	1	-
Paranoid psychosis	-	1

CATEGO CLASSES	TLE N = 16	GEN N = 7
Schizophrenic psychosis*	11	1
Manic psychosis	1	2
Depressive psychosis	1	2
Paranoid psychosis / retarded depression	2	-
Paranoid psychosis	1	1
Borderline psychosis	-	1

*Association between schizophrenic psychosis and temporal lobe epilepsy ($P < 0.02$)

Epidemiological Data and Psychological Data

As noted, there were no significant differences between the age and sex distribution of the schizophrenic patients compared with those with epilepsy and psychosis. This also applied when patients with schizophrenia rated on the CATEGO as NS were compared with the similar sub-group with epilepsy (Table 19). Although the numbers were too small to subject to statistical analysis, it is of interest that the proportion of patients married was greater in the epileptic sample, and there was little difference in the family history data.

Psychometry was carried out on the epileptic sample (N = 24). The results are shown in Table 20. Patients with TLE and a CATEGO classification of nuclear schizophrenia fall within the normal range, but a statistically significant difference exists between this group and the other two groups combined, mainly reflected in the lower performance scale of the latter. The type of impairments are shown in Table 20. Generalized impairments are commoner in patients with non-schizophrenic diagnoses. For those in whom a previous IQ was available, deterioration could be estimated by a fall in IQ greater than 10 points. As shown in Table 20 the percent deteriorated is considerably greater in those patients with non-NS CATEGO classifications.

Data showing length of epilepsy and length of psychosis are shown in Table 21.

TABLE 19A

DEMOGRAPHIC FEATURES OF NUCLEAR SCHIZOPHRENIC EPILEPTIC TLE AND NON EPILEPTIC PATIENTS

	AGE	SEX	STATUS	EMPLOY-MENT	PSY. FH	F H O F SCHIZ
Schizo-phrenic epileptics (11)	X 37.1 Range (23-58)	Males 7 Females 4	Married 3 Single 8	Yes 7 No 4	Positive 3 Negative 8	Yes 0 No 11
Schizo-phrenic Non-epileptic (9)	X 32.2 Range (18-47)	Males 5 Females 4	Married 0 Single 9	Yes 5 No 4	Positive 3 Negative 6	Yes 0 No 9

TABLE 19B

TYPE OF PSYCHOLOGICAL IMPAIRMENTS

	N	None	Generalised	Focal
TLE - schizophrenia	11	7	2	2
TLE - non-schizophrenia	6	0	4	2
Generalised - non - schizophrenia	7	5	2	0

TABLE 20 A

INTELLECTUAL ASSESSMENT OF EPILEPTIC PATIENTS WITH NUCLEAR SCHIZOPHRENIA (NS) AND OTHER FORMS OF PSYCHOSES. (STANDARD DEVIATIONS IN BRACKETS).

IQ	PERFORM-ANCE	VERBAL	FULL SCALE	% DETERIOR-ATED
Category				
TLE/NS	100 (14)*	98 (13)	100 (13)	18
TLE/other	85 (4)	89 (29)	87 (25)	66
Gen/other	80 (14)	88 (15)	85 (10)	28

*P < 0.02 TLE/NS v others

TABLE 20 B

TYPE OF PSYCHOLOGICAL IMPAIRMENTS

	N	NONE	GENERAL-ISED	FOCAL
TLE - Schizophrenia	11	7	2	2
TLE - Non-schizophrenia	6	0	4	2
Generalised - Non-schizophrenia	7	5	2	0

TABLE 21

COMPARISONS BETWEEN LENGTH OF EPILEPSY, LENGTH OF PSYCHOSIS AND THE INTERVAL IN PATIENTS WITH TLE AND A CATEGORY OF NUCLEAR SCHIZOPHRENIA MEANS COMPARED WITH OTHERS (STANDARD DEVIATION).

PSE/EPIL-EPSY	AGE	LENGTH EPILEPSY	LENGTH PYSCHOSIS	INTERVAL
TLE/nuclear schizophrenia N = 11	(Years) 37.2	(Years) 26.2 (11.0)	(Years) 10.0 (8.2)*	(Years) 16.2 (8.0)*
TLE/nuclear schizophrenia N = 6	37.3	28.2 (11.0)	2.1 (3.0)	26.7 (9.0)
Gen/Non-nuclear schizophrenia N = 7	36.7	29.9 (10.0)	4.7 (5.0)	25.1 (12.0)

*P < 0.05 TLE/nuclear schizophrenia and rest

A shorter interval is noted between the onset of epilepsy and the onset of psychosis in the NS group when compared with a combined temporal lobe and generalized group with non-NS.

EEG Data

Within those patients with epilepsy and psychosis (N = 24), 17 had complex partial seizures and the history of an EEG abnormality compatible with a diagnosis of temporal lobe epilepsy. Significantly, spikes or a slow-wave focus in one or both temporal regions were present. In the temporal lobe group the laterality of the focus as determined by the EEG was as follows: In 11 patients classified by the CATEGO programme as NS, 7 had exclusively left-sided EEG abnormalities, 2 had a right sided focus (one was left handed), 1 had bilateral foci with left sided predominance (who had exclusively left-sided findings on previous EEGs) and 1 had bilaterally independent foci.

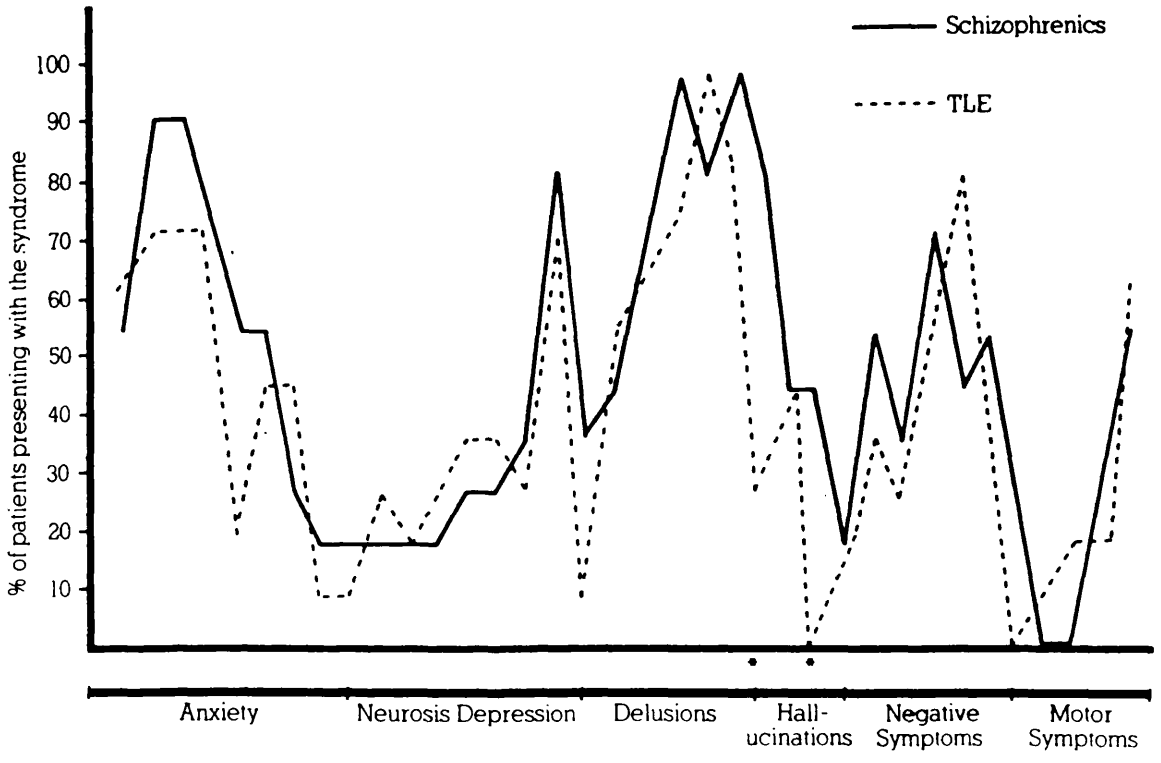
In six temporal lobe patients with CATEGO sub-classes other than nuclear schizophrenia 1 had a left temporal focus, 2 had unilateral right foci, 2 had bilateral foci, 1 with generalized involvement and 1 had no definite focus on the EEG. These data demonstrate a significant associated between a left sided focus and a classification of NS ($P < 0.05$). There was no clear relationship between a right sided focus and type of psychosis.

Figure 4 shows the syndrome profiles of those patients with a left sided or predominantly left sided lesion, compared with those with right sided lesions as derived from the CATEGO classification. Two significant differences are noted. Patients with left sided lesions show significantly more ideas of reference and nuclear syndrome (NS) than right sided patients. It should be noted that the patients who had nuclear syndrome and right sided lesions were left handed, and their dominance can not be accurately stated. Although non-significant, it is also noted that in the left temporal patients there were increased delusions of persecution (PE), delusions of reference (RE), fantastic delusions (SF), and auditory hallucinations (AH), and an absence of visual hallucinations (VH).

Summary

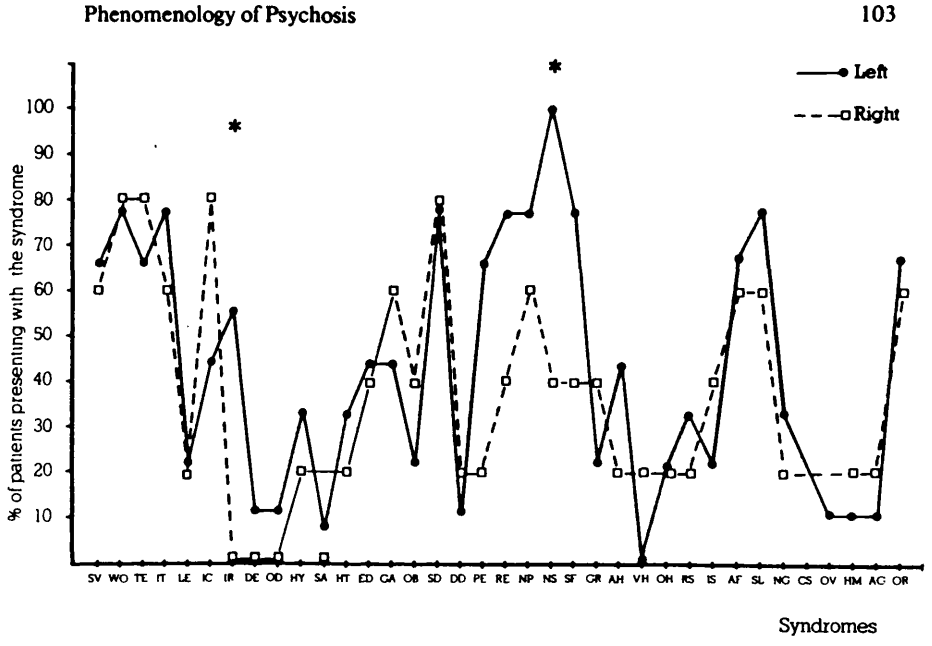
In this investigation the phenomenology of the inter-ictal psychoses of epilepsy was examined. Approximately half of the patients have a pattern of presenting symptoms which is recognized by the CATEGO programme as NS, comparable with patients with schizophrenia who do not have epilepsy. When this sub-group is examined the profile of their syndromes is virtually identical to the group with schizophrenia and while they do not differ with regards to family history, or employment status, more are married. Within the epileptic sample the group with temporal lobe epilepsy and NS appear less deteriorated

FIGURE 3



Showing the profile of PSE syndromes of patients with schizophrenia and those with temporal lobe epilepsy and a schizophrenia-like psychosis. Note the similarity of the profiles.

FIGURE 4



Showing the PSE syndrome profiles. Comparing patients with schizophrenia-like psychoses of epilepsy having a right or left temporal lobe focus. Note the significant association between left temporal lobe epilepsy and nuclei syndrome.

NS = Nuclear schizophrenia
IR = Ideas of reference

with relatively normal IQs and less generalized impairment. Further, the interval between the age of onset of their epilepsy and the age of onset of their psychosis is significantly less than other groups. When EEG data are examined they reveal an association between complex partial seizures of temporal lobe origin, particularly having a left sided focus and the presentation with nuclear schizophrenia (NS). Some other symptoms may also be more common in patients with a left sided focus, including delusions of persecution and ideas of reference and auditory hallucinations.

STUDY 2:

A CT INVESTIGATION OF THE INTER-ICTAL PSYCHOSES OF EPILEPSY

INTRODUCTION

CT scanning, introduced into the clinical neurosciences in the late I960's dramatically altered neuropsychiatry. Although the detection of structural changes associated with psychopathology, for example atrophy, cerebral tumours or meningiomas, has been of great importance, quantitative techniques have also been used to analyse scan data. As part of the neurological investigation of patients with inter-ictal psychoses of epilepsy, CT scans were performed and the results of both subjective assessments and quantitative analysis were compared with scans from patients with non-epileptic schizophrenia. In this study, phenomenology was also considered, patients with nuclear schizophrenia (NS) and epilepsy being compared with a group who had non-nuclear schizophrenia, and epilepsy.

Materials and Methods

CT scans were performed on EMI 5005, using 13 mm cuts of normal resolution: They were imaged at window width 40 and centred at a level of 18 EMI units. Pictures were obtained using an EMI multi-format imager, the magnification factor being 4.54.

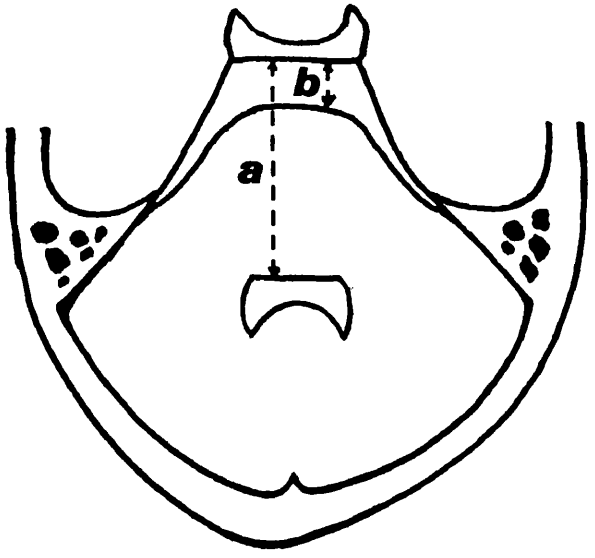
Radiological assessments included visual inspection of the scan, as well as linear measurements, the latter being performed with a transparent ruler to the nearest 0.5 mm. Subjective assessments of the sub-arachnoid spaces were

rated on a scale of 0-3, inter-observer reliability of the method having previously been established in consultation with three experienced radiologists.

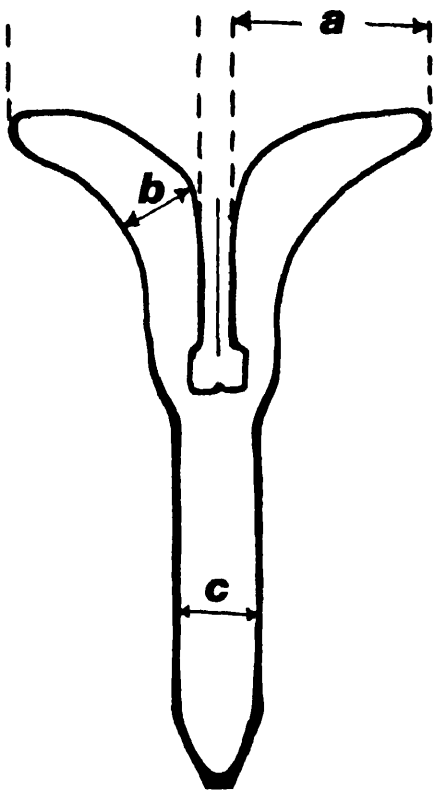
The width of the anterior horns, septum-caudate distance, cella-media distance, and the third ventricular size were performed as described by Gyldensted and Kosteljanetz (1975) and Gyldensted (1977) (see figure 5 and Table 22). The Evans Ratio was measured according to the original descriptions of Evans (1942), and assessment of the posterior fossa structures, including the fourth ventricle and cistern-brain stem ratios, were performed according to the method of Koella et al (1982) (see Figure 5 and Table 22). Finally, normal values, provided from the literature are given for comparison (Gyldensted and Kosteljanetz 1975, 1977: Koller et al 1981).

Statistical Analysis

The Fisher Exact Probability Test or Student's T-Test were used in these statistical analysis. Statistical evaluation against the normal values was not attempted.



CISTERN BRAINSTEM RATIO (KOLLER, 1981) = $\frac{b}{a}$ = $\frac{\text{width of prepontine cistern}}{\text{distance from posterior clinoid to floor of fourth ventricle}}$



a = anterior horn width

b = caudate-septum distance

c = width of third ventricle

FIGURE 5:
Showing measurements obtained on CT scans for the anterior horn width, caudate-septum distance, third ventricle width and the cistern brain-stem ratio.

TABLE 22

INDICES FOR CT STUDIES

Evans Index (CM + 4)	=	Distance between anterior horns, divided by Distance between inner tables in the parietal region.
Cella Medial Index (OM + 6)	=	Distance between outer tables, divided by Combined minimal cella medial width.
Fourth ventricle ratio (OM + 2)	=	Width of fourth ventricle, divided by Bimastoid diameter (outer tables).
Superior cerebellar cistern ratio (OM + 3)	=	Width of superior cerebellar cistern, divided by Distance between two inner tables at the same level.

Results

CT scans were available for examination in twenty of the epileptic sample, visual inspection revealing gross focal abnormalities in 7, and 4 were rated as showing mild atrophy. In the NS sample, focal lesions were seen on 3 scans: one had bilateral low density temporal lobe lesions, with greater changes on the left, one had similar lesions with greater changes on the right (the patient had previously undergone a right temporal lobectomy) and one had a left sided lesion compatible with an earlier resection of an angioma. In the temporal lobe and generalized epilepsy groups, 4 focal abnormalities were noted: One left sided lesion occurred in the parietal cortex, 2 patients had bilateral abnormalities and another had a right frontal lesion. In the non-epileptic schizophrenic sample, no focal lesions were noted, but two were reported as having mild atrophy.

Data from the measurement of scans are shown in Table 23 and 24. In the statistical analysis patients from the NS group were compared with those in the combined temporal lobe and generalized epilepsy group non-epileptic schizophrenia group. Of all of these statistical analyses only one significant difference was noted, namely the small combined cella-media size in the combined group of temporal lobe and generalized epilepsy. From Table 23 it can be noted that the NS sample more frequently had enlargement of the

cerebellar sulci, and from Table 24 that the psychotic groups generally show larger values for all measurements except the combined cella media size and the Evans Ratio. From the normative data provided, the most interesting discrepancies are the septum-caudate distance, the third ventricle size, and the fourth ventricle ratio.

Summary

Evaluation of CT scan data in these samples reveal few significant differences between the groups, although data from psychotic groups suggest some changes in comparison to normal values given in the literature. In particular these effect sub-cortical structures in the regions of the third and fourth ventricular systems. The only significant difference noted was the smaller cella-media size in the epileptic non-nuclear schizophrenia group which may have been a chance finding in view of the number of statistical comparisons.

TABLE 23

RADIOLOGICAL DATA (± SD)

DIAGNOSIS	A EPILEPTIC/ NUCLEAR SCHIZOPHRENIA n = 10	B EPILEPTIC/ NON-NUCLEAR SCHIZOPHRENIA n = 10	C NON-EPILEPTIC SCHIZOPHRENIA n = 10	D NORMAL VALUES (5 TO 95% IN BRACKETS)
Enlarged cerebral sulci (left)	1	1	1	
Enlarged cerebral sulci (right)	1	1	1	
Enlarged cerebellar sulci (left)	3	1	0	
Enlarged cerebellar sulci (right)	3	1	0	
Enlarged cerebellar Vermis	4	4	2	

*P < 0.05 (A v B)

TABLE 24
RADIOLOGICAL DATA (±SD)

DIAGNOSIS	A EPILEPTIC/ NUCLEAR SCHIZOPHRENIA	B EPILEPTIC/ NON-NUCLEAR SCHIZOPHRENIA	C NON-EPILEPTIC SCHIZOPHRENIA	D NORMAL VALUES (5 TO 95% IN BRACKETS0
	n = 10	n = 10	n = 10	
Maximum distance between anterior horns, mm	34.1 (5.9)	35.9 (4.9)	33.8 (4.6)	33.0 (26.4 - 39.6)
Bilateral septum caudate distance, mm	17.1 (3.7)	15.5 (7.8)	16.6 (3.1)	14.9 (100 -24.8)
Combined cella media size, mm	28.1 (5.6)	20.9 (8.7)*	27.5 (3.5)	29.7 (19.8 -36.3)
Evans ratio	0.26 (0.05)	0.27 (0.03)	0.26 (0.04)	0.26 (0.20 - 0.30)
Third ventricle size mm	4.08 (1.44)	5.08 (2.75)	3.7 (1.17)	3.3 (1.7 ± 6.6)

.. continued ..

TABLE 24 continued

DIAGNOSIS	A EPILEPTIC/ NUCLEAR SCHIZOPHRENIA	B EPILEPTIC/ NON-NUCLEAR SCHIZOPHRENIA	C NON-EPILEPTIC SCHIZOPHRENIA	D NORMAL VALUES (5 TO 95% IN BRACKETS0
	n = 10	n = 10	n = 10	
Cistern brainstem ratio	0.13 (0.02)	0.17 (0.09)	0.13 (0.05)	0.11 (± 0.01)
Fourth ventricle ratio	0.12 (0.03)	0.11 (0.02)	0.10 (0.01)	0.007 (±0.003)

*P < 0.05 (A V B)

STUDY 3:

MAGNETIC RESONANCE IMAGING (MRI) INVESTIGATION OF THE INTER-ICTAL PSYCHOSES OF EPILEPSY

INTRODUCTION

Although brain structure can be well demonstrated by CT scans, more recently, this technique has been superseded by the MRI. Although not widely available, their superiority over CT in providing visual images of cerebral structure suggest that they may provide information beyond that given in CT studies in patients with schizophrenia-like psychoses of epilepsy.

The principle of MRI involves examination of the physico-chemical environment of proton nuclei in tissue, based on the inherent electromagnetic forces that exist in such electrically charged particles.

Briefly, any object that has a charge and velocity produces a magnetic field perpendicular to it. A charged nuclear particle spinning in the body's tissues, thus produces a magnetic field, although in this case the field is referred to as the angular magnetic moment with a vector perpendicular to the axis of rotation. A charged nuclear particle spinning about its axis, acts like a tiny bar magnet, and, before the application of an external magnetic field, the sum total magnetisation of many of them spinning in tissues is zero, since their direction of movement is random. On application of an external magnetic force, the tiny magnets are aligned just as an ordinary compass needle will align in the earths magnetic field. The alignment is parallel (or anti-parallel) to the external

field. The protons in such a setting actually spin, like a spinning top, around the alignment of the applied field, a process referred to as precession. Protons, which possess their own inherent specific precession, once aligned can now be excited by the momentary application of a radio signal broadcast at their own specific frequency (the Larmour frequency) from a radio frequency transmitter.

The procedure of imaging makes use of the fact that waves emitted from the nuclei differ in both frequency and amplitude, the former locating the position of the particular nucleus in the body and the latter reflecting the number of nuclei present at that position. Thus, within the static externally applied magnetic field, energy is imparted to the parallel protons, exciting them to a higher energy level by radio-frequency waves of exactly the right frequency, and after the signal is finished electromagnetic energy of the same frequency will be given off, detected by a receiver coil (see Figure 6). After the application of the radio frequency pulse, the magnetization returns exponentially to its pre-excitement level, a process referred to as relaxation. This may be defined by two-timed constants referred to as T1 and T2, of which T1 is always greater than T2.

The T1, or spin-lattice, relaxation time, representing relaxation along the

longitudinal axis, is the time taken for the protons to recover their previously aligned position in the static field after excitation in this axis by a 180 degree pulse. In practice, due to the configuration of most scanners a so called inversion recovery image is used to give a T1 weighted image.

The T2 relaxation time, representing relaxation in the transverse plain, hence transverse relaxation time, is the exponential time constant which results from decay of coherence, due to the interaction of the spinning nuclei. It relates to energy exchange between protons and is also referred to as the spin-spin relaxation time. T2 is thus a measure of the length of time the tissue maintains its temporary transverse magnetisation, perpendicular to the external magnetic field, following a 90 degree pulse. The spin echo is proportional to the proton density and T2 and is frequently used for T2 measurement.

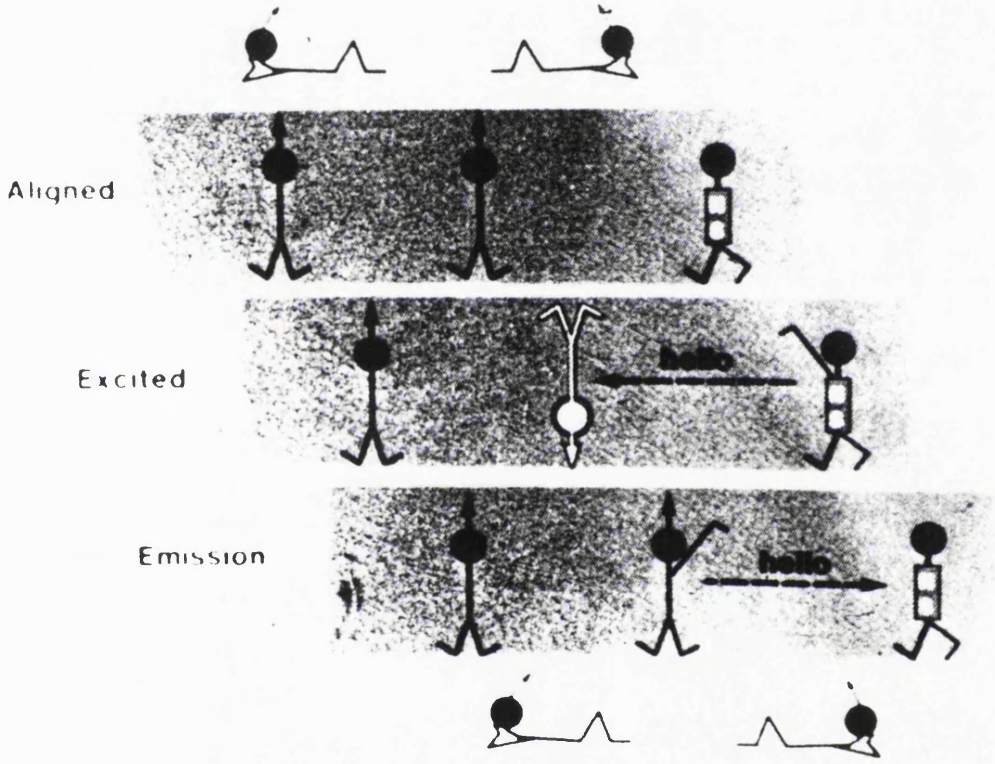
Thus, each tissue in the body, has a specific T1 and T2 value, and they essentially reflect the physico-chemical environment of the proton nuclei. The T1 relates to interactions of protons with surrounding nuclei, the T2 depending on interactions of protons with each other. In the brain, the proton behaviour measured relates to the hydrogen nucleus, most commonly of CNS water. Thus the spinning atomic nucleus will behave like a spinning top only if it has an odd atomic mass or number, an atom with an even number being non-

magnetic. While MRI spectroscopy can image ^{1}H, ^{13}C, ^{15}N, ^{19}F, ^{23}Na and ^{31}P, imaging at the present time is largely confined to hydrogen nuclei.

It should be noted then, that information derived from MRI depends on four factors (proton density, spin-lattice, spin-spin, and the motion of protons), while CT depends on two (number of atoms in a given volume of tissue and the atomic number of those atoms). Thus the potential information from MRI is between one and two orders of magnitude greater than in a CT image (Armstrong and Keevil 1991).

In practice, the stronger the magnetic field that the body part is placed in the greater the proportion of nuclei that will line up in the direction of the field and the stronger will be the signal that will eventually be received. Most magnets use magnetic fields of between 0.2 and 1.5 tesla, in comparison to the earths magnetic field of approximately 0.00005 tesla.

FIGURE 6



A Cartoon showing the principles of MRI.

In practice, the actual imaging technique involves a series of choices for sequencing related to the direction and timing of the radio-frequency pulses delivered, the data being spatially encoded to provide information on proton density, T1 and T2 times. Every magnetic resonance image contains both T1 and T2 information, but by appropriate choice of time and length of the radio-frequency pulses the image can be weighted to depend mainly on one or other of these relaxation times, or to represent mainly proton density.

Since it is an electronic process, reconstruction of images can be done in any direction, and is usually slice encoding. Inversion recovery and spin-echo techniques are the most widely employed. By exploiting differences between relaxation times of different tissues, heightened contrast between them is achieved, and hence better images. The use of contrast media such as Gadolinium DTPA is a method of further enhancing tissue differentiation.

The derived images on MRI have low spatial resolution, being 0.8 mm^2 in some machines. Most pathological conditions increase the length of T1 and T2, free water having even higher values. Since on T1 images increasing the time darkens the images, and on T2 images it lightens the image, on T1 images CSF and pathological areas are relatively darkened and viceversa on T2 images. Both T1 and T2 are shorter in white matter than in grey, but the

signal from bone is weak, and not well imaged. This has great advantage for imaging in neuropsychiatry, since the bony structures of the cranial vault, which on CT scanning so often obscure the structures of interest such as the temporal lobes, are not present. Table 25 presents the advantages and disadvantages of MRI.

In addition to purely visual inspection of scans to detect anomalous tissue, there is potential to use quantitive information from the scans, especially actual T1 and T2 measurements. In view of this, an MRI study of epilepsy was carried out, which included patients with schizophrenia-like psychosis of epilepsy. A dedicated T1 scanner was used, and quantitive assessments of T1 times was taken as the main measurement of interest.

Materials and Methods

In this study, the image analysis was conducted using an MD 800 scanner. This has a field strength of 0.08 tesla, with a resonance frequency of 3.4 Mhz. The standard pulse sequence for this scanner was used which employs an alternating saturation recovery and inversion recovery sequence with a repetition time (TR) of one second and an inversion time (T1) of two hundred milliseconds. This was used for all patients and controls. The slice thickness was 12 mm and the display matrix was 256 x 256. The spatial resolution was 2 mm x 2 mm. A calculated T1 image was generated using a computed

algorithm.

Ten slices in three planes were taken for all patients including one coronal (through the external auditory meatus), one saggital (in the mid-line) and eight trans-axial slices (from the level of the cerebellum cranially to above the lateral ventricles).

T1 values were measured in multiple regions of interest (ROI) which corresponded on transaxial slices to frontal grey (medial and lateral), frontal white, occipital grey (medial and lateral), occipital white, globus pallidus-putamen, thalamus, temporal grey, (medial, anterior and lateral), temporal white, and cerebellum (medial and lateral). On coronal section the temporal grey (medial and lateral) and temporal white areas were measured bilaterally.

Between 10 and 20 pixels were counted for each area. In order to ensure homogenous tissue measurements of ROIs, the T1 value taken for each one had a standard deviation of less than 5%. Only occasional measurements were unobtainable due to poor image quality.

The daily reproducibility of T1 measures, using standard phantoms of copper

TABLE 25

ADVANTAGES AND DISADVANTAGES OF MRI

ADVANTAGES	DISADVANTAGES
No radiation	Noise discomfort
Minimal risk [a]	Claustrophobic
Good grey/white discrimination	Limited discrimination between pathologies
Less degradation of image with movement	Length of scan time
No bone artifacts	Artifacts from ferromagnetic material (eg tooth filling).
Clear structural images	
Ability to visualize several planes	
Potential for functional imaging	

[a]Only patients with cardiac pacemakers, intracranial magnetic clips or in the first trimester of pregnancy should not be scanned.

sulphate in the relevant T1 range had a standard deviation of less than 5% of the means.

All measurements taken were blind to either the classification of the epilepsy of the patient or the classification of any psychopathology.

In order to analyse regional differences, individual ROIs were combined for similar anatomical areas and a group mean calculated. For example, combined temporal-medial grey included ROIs on the trans-axial slice - temporal grey medial, plus temporal grey anterior, in addition to the temporal grey medial on the coronal slice.

For the analysis of the size of the corpus callosum the saggital slice taken in the mid-line was used. This was visualised using the inversion recovery pulse sequence giving the best grey-white matter differentiation. The mid-line of the corpus callosum was identified as accurately as possible using surrounding anatomical markers, such as the pituitary gland and the roof of the fourth ventricle. Measurements were taken from the visual display unit, using computerized cursors which gave the calculated distance between points in millimetres. Measurements of the corpus callosum were done twice, and the average of the two used. Test-re-test reliability of this method was good,

(Pearson's r>0.8).

The middle, anterior and posterior thickness of the corpus callosum were therefore measured. The mid-point of the corpus callosum was taken for the middle measurement, the junction of the genu and the body was used for the anterior measurement, (estimated at a point midway between the mid-point and the anterior end of the corpus callosum), and the junction of the splenium and body for the posterior measurement (estimated at a point midway between mid-point and posterior end of the corpus callosum). The maximum length of the corpus callosum visualised was used for the length measurement. Cerebral height was taken from the mid-point of the corpus callosum (including corpus callosum) superiorly to the maximum height of the brain. Cerebral length was taken as the maximum anterior-posterior measurement of brain tissue visualised.

Statistical Analysis

The tests used included two tailed T test and one way ANOVA with the least significant difference (LSD) of means. Non parametric data were analysed using the Mann-Whitney U Test and the Kruskal-Wallace analysis of variance.

The sample were 50 patients with epilepsy, the diagnosis of epilepsy being based on clinical grounds according to the criteria of Hopkins and Scambler

(1977). CT scans were obtained on all patients. In addition to neurological examination all patients were examined psychiatrically, and a sub group of psychotic patients (17) were further evaluated (see below) and compared with 17 matched patients from within the epileptic sample to form controls for them.

In the first part of the study, patients with epilepsy were compared with non-epileptic controls, the latter consisting of 14 healthy volunteers with no history of any neurological or psychiatric illness, who were all abstainers from alcohol. They were obtained through the co-operation of the Salvation Army.

Results

In the first analysis, 50 patients with epilepsy were compared with the 14 healthy controls, with gross inspection of scans, and quantitative analysis of T1 times. The 50 patients were 28 males and 22 females with a mean age of 34.7, range 17-65. The controls were 10 males and 4 females with a mean age of 35.5 and a range of 20-57. There were no significant differences between these groups.

In the epilepsy sample, (N=50), the mean duration of epilepsy was 20.3 years (SD +/- 11.6), and 48 patients were on anti-epileptic medications (13 on monotherapy and 35 on polytherapy).

Routine neurological examination was normal in 38, and CT scans were normal in 33. Gross reporting of MRI images revealed lesions compatible with cerebral atrophy in 4, cerebral infarcts in 3, tuberous sclerosis in 2, and single cases of chronic subdural haematoma, porencephalic cyst, A-V malformation, and an occipital tumour. The latter was not seen on CT scan. Four cases of marginal cerebral atrophy and ventricular dilation reported on CT scan were not specifically noted to have atrophy on MRI scan.

Table 26, shows seizure type and EEG focus of all patients, 36 having a clinical diagnosis of temporal lobe epilepsy. When the total sample of epileptic patients and controls were compared the patient group had higher T1 values in all ROIs, (see Figure 7 and Table 27). The differences were most marked in the temporal lobes, particularly the grey matter. Specifically on the left side, temporal grey medial, coronal ($p < 0.01$), temporal grey lateral coronal ($p < 0.05$) and temporal grey anterior ($p < 0.05$) all showed statistically significant differences between patients and controls.

The second analysis carried out was an attempt to control for gross structural lesions, using the CT scan as a discriminator. Thirty-three patients from the sample had no CT abnormalities, and they were compared with controls (Figure 8 and Table 28). T1 values still remain generally higher in the epileptic

TABLE 26

SEIZURE TYPE AND FOCUS OF EPILEPTIC PATIENTS (N = 50)

Generalised	
Primary	3 (6%)
Secondary	8 (16%)
Partial (simple and complex)	22 (44%)
Partial complex with secondary generalization	14 (28%)
Other	3 (6%)
Right focal	12 (24%)
Left focal	16 (32%)

population with a more pronounced increase in tissue relaxation times in the temporal lobes compared with controls. Temporal grey left anterior ($p < 0.01$), temporal grey left medial coronal, temporal grey right anterior, temporal grey left lateral coronal and occipital grey right (all $p < 0.05$) reached statistical significance.

When patients with a diagnosis of temporal lobe epilepsy (N = 36), generalized epilepsy (primary and secondarily generalized N = 11), and controls were examined a significant difference between the groups was seen in the right thalamus for the generalized group (mean 384 +/- 26), showing higher relaxation times than the temporal lobe epilepsy patients (mean 369 +/- 17) or controls (mean 364 +/- 14) ($p < 0.02$).

Analysis of laterality differences in T1 values in patients with a negative CT scan and a unilateral seizure focus on EEG is shown in Figures 9 and 10, the comparative data being given in Tables 29 and 30. Patients with left sided foci (N=10) had higher T1 values on the left although this was not true for all regions of interest. Only in the thalamus did this reach statistical significance. Patients with a right sided focus (N=9) showed higher T1 values on the right with a statistically significant difference being noted in frontal white, temporal grey anterior and temporal grey lateral (coronal). In the temporal grey anterior

region 15 out of 19 patients with a lateralized seizure focus had higher T1 values on the side that corresponded to the side of the EEG abnormality.

Images of the corpus callosum were available on 48 patients. The basic data and comparative data on the controls is given in Table 31. No gross pathological changes were noted in the corpus callosum in any patients or controls.

Table 32 shows comparison between controls and all epileptic patients on the measured parameters. Significant differences were seen in the mid-collosal thickness ($p < 0.01$) and also the ratio of the corpus callosum to cerebral height ($p < 0.01$). To examine the relationship of seizure discharge to collosal thickness those with generalized seizures (mean age 31.3 years, range 19-37) were compared with those having only partial seizures without generalization (mean age 37.4, range 19-65).

Where analysis of variance of corpus callosal thickness by seizure type was performed there was a significantly larger width in epileptic patients with generalized seizures versus controls (Table 33). Epileptic patients with partial seizures tended to have smaller mid-callosal thickness than patients with generalized seizures, but larger than controls, although these differences were

TABLE 27

MRI T_1 DATA - ALL EPILEPTIC PATIENTS VS CONTROLS

FWL	MEAN	SD	
Controls	278	14	
Patients	281	16	
FWL	**MEAN**	**SD**	
Controls	280	10	
Patients	287	23	
FGL	**MEAN**	**SD**	
Controls	393	11	
Patients	397	14	
FGR	**MEAN**	**SD**	
Controls	400	10	
Patients	402	14	
TGL A	**MEAN**	**SD**	
Controls	398	9	$p < .05$
Patients	410	26	
TGR A	**MEAN**	**SD**	
Controls	403	12	
Patients	411	22	
TWL	**MEAN**	**SD**	
Controls	317	13	
Patients	321	17	
TWR	**MEAN**	**SD**	
Controls	323	12	.. continued ..
Patients	325	17	

TABLE 27 (CONTINUED)

TGL MED. COR.	MEAN	SD	
Controls	394	11	$p < .01$
Patients	406	19	
TGR MED. COR.	**MEAN**	**SD**	
Controls	398	10	
Patients	403	17	
TGL LAT. COR.	**MEAN**	**SD**	
Controls	383	10	$p < .05$
Patients	393	18	
TGR LAT. COR.	**MEAN**	**SD**	
Controls	395	9	
Patients	400	18	

F = Frontal
T = Temporal
W = White matter
G = Grey matter
L = Left
R = Right
MED = Medial
COR = Coronal

TABLE 28

M R I T_1 VALUES, EPILEPTIC PATIENTS VERSUS CONTROLS (CT NEGATIAVE)

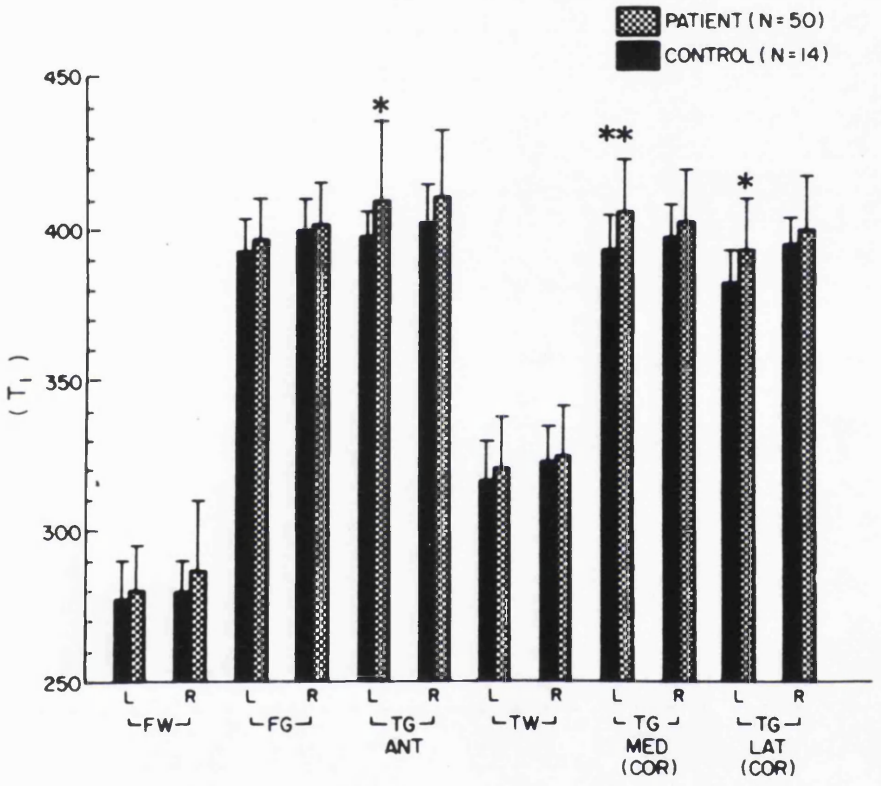
		Mean	5.0	
FWL N = 14 N = 33	CONT	278	14	
	PT	277	15	
FWR	CONT	280	10	
	PT	281	14	
FGL	CONT	393	11	
	PT	397	15	
FGR	CONT	400	16	
	PT	403	14	
TGL(A)	CONT	398	9	P < .01
	PT	417	18	
TGR(A)	CONT	403	12	P < .05
	PT	416	23	
TWL	CONT	316	13	
	PT	319	17	
TWR	CONT	323	12	
	PT	324	17	
TGL (MED COR)	CONT	394	11	P < .05
	PT	406	19	
TGR (M E D COR)	CONT	398	10	
	PT	404	19	
TGL (LAT COR)	CONT	383	10	P < .05
	PT	394	19	

TABLE 28 (continued)

T G R (LAT COR)	CONT	395	9	
	PT	402	16	
OC G L	CONT	388	8	
	PT	389	10	
OC G R	CONT	381	9	P < .05
	PT	390	13	

F = Frontal
T = Temporal
W = White matter
G = Grey matter
L = Left
R = Right
OC = Occipital

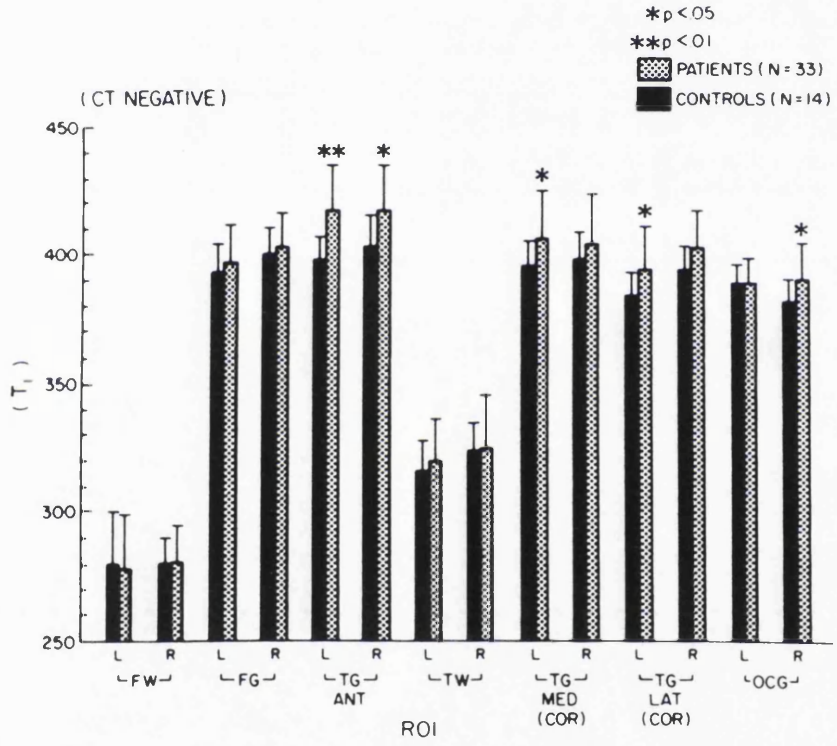
FIGURE 7



Showing T_1 values for various regions of interest comparing patients with epilepsy (n=50) and controls (n=14).

FW	=	Frontal white
FG	=	Frontal grey
TG ANT	=	Temporal grey anterior
TG MED	=	Temporal grey medial
TW	=	Temporal white
COR	=	Coronal

FIGURE 8



Showing T_1 values for various regions of interest showing data from patients with normal CT scans.

FW	=	Frontal white
FG	=	Frontal grey
TG ANT	=	Temporal grey anterior
TG MED	=	Temporal grey medial
TW	=	Temporal white
COR	=	Coronal

not statistically significant. Similar results were obtained for the ratio of corpus callosum to brain height analysis. No other callosal dimensions showed significant differences. The relationship of handedness to the callosal morphology was assessed by comparing right handed to left handed patients matched for sex and seizure type, but no significant differences were noted. Similarly analysis of the corpus callosum thickness by sex and seizure type co-varied with length of epilepsy did not show any significant differences.

Psychiatric Diagnosis

From the total sample of 50 patients, 17 were psychotic clinically. The actual diagnosis was initially made on clinical grounds, and then a PSE was carried out as close as possible in time to the scannings. The CATEGO sub-class was obtained and various clinical groups were compared with other patients with epilepsy and no psychopathology matched as far as possible for certain variables.

Of the 17 patients, 12 were categorised as having nucleur schizophrenia (NS). Seven had a psychosis with Schneiderian auditory hallucinations. From within the total sample of 50 patients another 17 patients were found who had no evidence of past psychiatric history or any present psychiatric disturbance.

Of the 12 psychotic patients with a CATEGO classification of NS, 7 had a t29

TABLE 29

MRI T_1 VALUES IN PATIENTS WITH A RIGHT SIDED EEG FOCUS (N = 9)

FW	MEAN	SD	
Left	277	10	P < .05
Right	286	13	
FG	**MEAN**	**SD**	
Left	405	19	
Right	401	20	
THAL	**MEAN**	**SD**	
Left	388	19	
Right	376	16	
TG (MED)	**MEAN**	**SD**	
Left	399	11	
Right	403	15	
TG (LAT)	**MEAN**	**SD**	
Left	394	8	
Right	401	14	
TG (ANT)	**MEAN**	**SD**	
Left	410	24	P < .05
Right	421	28	
TW	**MEAN**	**SD**	
Left	326	11	
Right	333	12	
OCG	**MEAN**	**SD**	
Left	388	15	
Right	394	13	

T A B L E 29 (continued)

TGM	MEAN	SD	
Left	407	10	
Right	412	17	
TW (COR)	**MEAN**	**SD**	
Left	306	20	
Right	301	16	
TGL (COR)	**MEAN**	**SD**	
Left	394	12	P < .05
Right	406	15	

OC	=	Occipital
F	=	Frontal
T	=	Temporal
W	=	White matter
G	=	Grey matter
L	=	Left
R	=	Right

TABLE 30

MRI T^1 FOR PATIENTS WITH A LEFT SIDED EEG FOCUS (N = 10)

FW	MEAN	SD	
Left	285	15	
Right	282	15	
FG	**MEAN**	**SD**	
Left	402	27	
Right	397	14	
THAL	**MEAN**	**SD**	
Left	383	22	$P < .05$
Right	366	11	
TG (MED)	**MEAN**	**SD**	
Left	395	22	
Right	391	18	
TG (LAT)	**MEAN**	**SD**	
Left	390	10	
Right	389	12	
TG (ANT)	**MEAN**	**SD**	
Left	419	12	
Right	408	12	
TW	**MEAN**	**SD**	
Left	319	16	
Right	324	22	
OCG	**MEAN**	**SD**	
Left	380	16	
Right	383	14	

TABLE 30 (continued)

TGM (COR)	MEAN	SD
Left	402	21
Right	402	18
TW (COR)	**MEAN**	**SD**
Left	303	25
Right	295	8
TGL (COR)	**MEAN**	**SD**
Left	395	18
Right	401	14

OC	=	Occipital
F	=	Frontal
T	=	Temporal
W	=	White matter
G	=	Grey matter
L	=	Left
R	=	Right

TABLE 31

EPILEPTIC PATIENTS AND CONTROLS - CORPUS CALLOSUM DATA

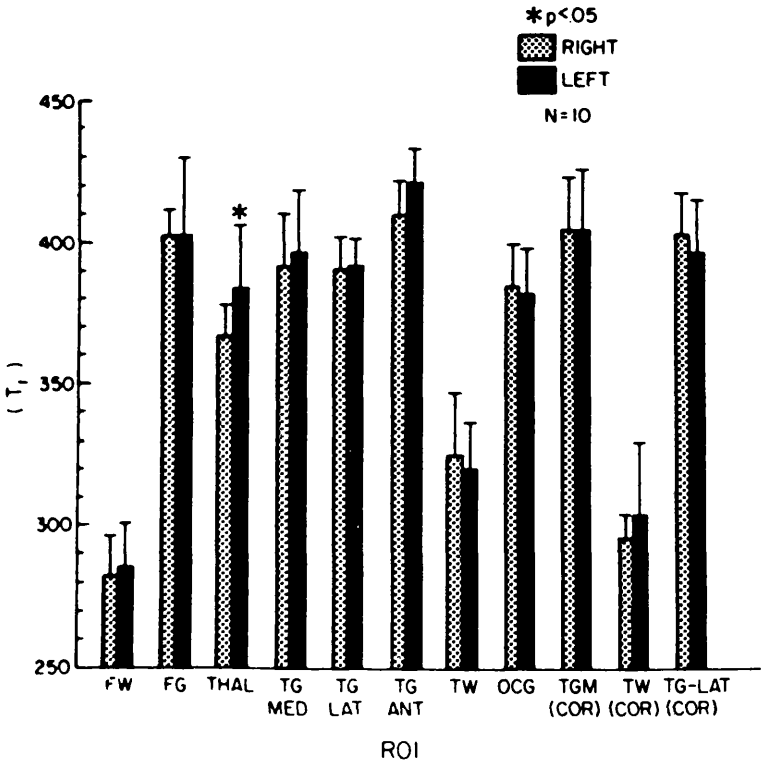
	CONTROLS (N = 14)	EPILEPTICS (N = 48)
Age	35.5 (20-57)	34.7 (17-65)
Sex		
M	10	27
F	4	21
Handedness		
R	12	38
L	2	10
Seizure type		
Generalised (1° + 2°)	-	10
Partial (simple and complex)	-	21
Partial with occasional 2° generalisation	-	14
Other	-	3

TABLE 32

COMPARISON OF EPILEPTIC PATIENTS VS CONTROLS IN CORPUS CALLOSUM MEASUREMENTS

MEASUREMENTS IN MILLIMETRES EPILEPSY N = 48)	MEAN ± SD	CONTROLS (N = 14) MEAN ± SD	T VALUE	2 - T A I L E D PROBABILITY
Callosal length	76.1 ± 5.8	74.8 ± 4.9	0.84	NS
Callosal width (ant)	7.8 ± 1.5	7.4 ± 1.2	0.82	NS
Callosal width (mid)	6.6 ± 1.2	5.8 ± 0.7	3.09	P < 0.01
Callosal width (post)	7.2 ± 1.5	6.7 ± 1.0	1.43	NS
Cerebral height	51.0 ± 4.5	52.8 ± 2.1	-1.40	NS
Cerebral length	162.8 ± 9.9	166.1 ± 7.1	-2.05	NS
Callosal to cerebral height ratio %	0.13 ± 0.03	0.10 ± 0.01	3.88	P < 0.01

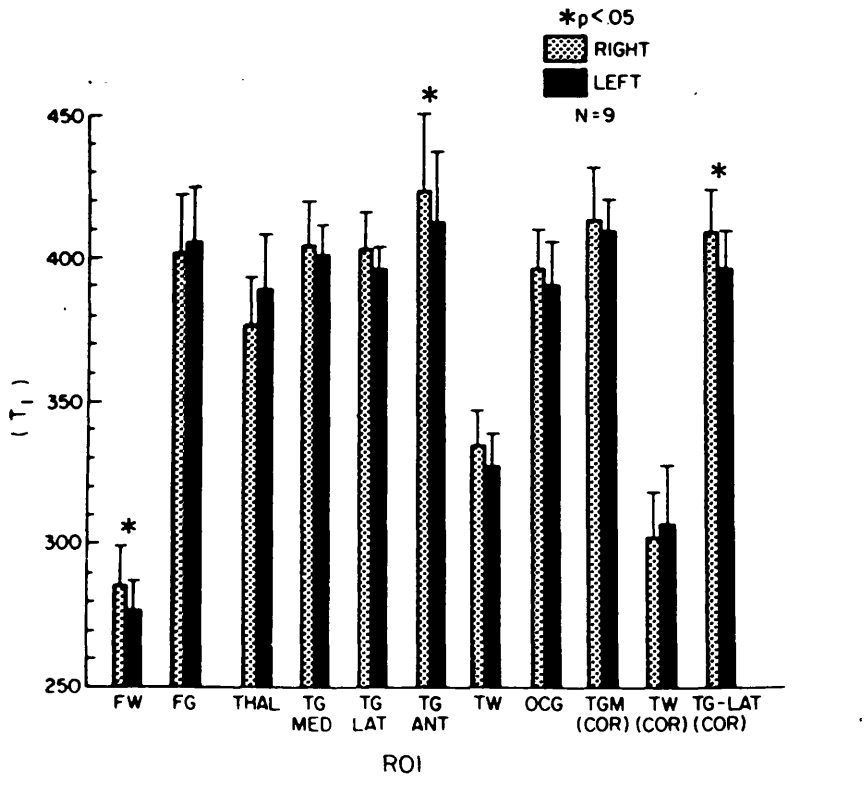
FIGURE 9



Showing T_1 values in relationship to the laterality of the focus on the EEG in patients with normal CT scans. Left side focus.

FW	=	Frontal white
FG	=	Frontal grey
TG ANT	=	Temporal grey anterior
TG MED	=	Temporal grey medial
TW	=	Temporal white
COR	=	Coronal
Thal	=	Thalamus
OCG	=	Occipital grey

FIGURE 10



Showing T_1 values in relationship to the laterality of the focus on the EEG in patients with normal CT scans. Right side focus.

FW	=	Frontal white
FG	=	Frontal grey
TG ANT	=	Temporal grey anterior
TG MED	=	Temporal grey medial
TW	=	Temporal white
COR	=	Coronal
Thal	=	Thalamus
OCG	=	Occipital grey

normal CT scan, 5 an abnormal scan (one right sided angioma, one occipital infarct, and three generalized atrophy or ventricular enlargement). In the control group of 17, 14 of the scans were reported as normal, one had a probable basal ganglia infarct, one had a right occipital lobe lesion, and one a left hemisphere porencephalic cyst.

All patients categorized as NS had a clinical diagnosis of temporal lobe epilepsy. On the EEG, six had a right sided focus, three a left sided focus, and three bilateral foci. In the control group, 12 had a diagnosis of temporal lobe epilepsy, 4 generalized epilepsy and 1 frontal lobe epilepsy.

Three separate analyses were carried out. In the first, patients with epilepsy and no psychiatric history were compared with those patients who had NS. The analysis of the mean T1 relaxation times showed no significant differences between the groups (Table 34). In order to control for the effect of any gross structural lesions in the interpretation of the data, re-analysis was carried out only on a sub-group of patients with normal CT scans, but again no significant differences for any area were reported.

In the second analysis, patients with hallucinations (N=7) were compared to the psychotic group without hallucinations (N=10). Higher T1 values were

found, predominantly in the white and grey matter of the frontal and temporal regions in those hallucinating, a significant difference being noted in the left temporal white areas (Table 35).

In the third analysis, patients rated as having an affective psychosis (N=9) were compared with a group with NS without affective symptoms (N=8), the results being shown in Table 36. The only significant difference was in the left thalamus, and comparison with normative data taken from healthy controls, (thalamus left = 374 +/- 14) reveals that the group with NS have the significantly higher thalamic values.

In a separate analysis, the corpus callosum was examined in twelve patients with a CATEGO classification of NS and 16 patients with no present or past psychiatric history. The control values were 14 healthy volunteers who had no history of neurological or psychiatric illness. The results are shown in Table 37. The regional measurement by group analysis of variance only demonstrated a significant difference in mid-collosal thickness ($F = 7.23$, $P = 0.002$), a subsequent post-hoc analysis indicating that the patients with no psychiatric history showed a significantly thicker corpus callosum than either the control group or the epileptic patients ($P < 0.05$).

TABLE 33

ONE-WAY ANALYSIS OF VARIANCE OF CORPUS CALLOSUM WIDTH (MIDDLE) BY SEIZURE TYPE

MEASUREMENTS IN MILLIMETRES
BETWEEN GROUPS F RATIO 6.3, P 0.004

SEIZURE TYPE	N	CALLOSAL WIDTH MEANS ± SD	
Control	14	5.8 ± 0.7}	P < 0.01
Generalized	10	7.2 ± 0.8}	
Partial	21	6.5 ± 1.1	

TABLE 34

MEAN T_1 VALUES (±SD) FOR PATIENTS WITH EPILEPSY AND NO PSYCHIATRIC ILLNESS FOR THOSE WITH NUCLEAR SCHIZOPHRENIA (NS)

	LEFT		RIGHT	
	Epileptic control (n = 17)	NS (n = 12)	Epileptic control (n = 19)	NS (n = 12)
Frontal grey, medial	400 ± 19	401 ± 27	398 ± 16	392 ± 20
Frontal white	281 ± 20	282 ± 13	293 ± 23	286 ± 12
Occipital grey	394 ± 12	390 ± 11	391 ± 12	389 ± 9
Temporal grey, medial	405 ± 15	402 ± 12	404 ± 11	398 ± 13
Temporal grey, anterior	414 ± 27	406 ± 13	418 ± 24	408 ± 14
Temporal white	330 ± 15	322 ± 13	327 ± 12	327 ± 18

TABLE 35

MEAN T[1] VALUES (+SD) FOR PATIENTS WITH HALLUCINATIONS COMPARED WITH THOSE WITHOUT

	LEFT HEMISPHERE		RIGHT HEMISPHERE	
	No hallucinations (n = 10)	Hallucinations (n = 7)	No hallucinations (n = 10)	Hallucinations (n = 7)
Frontal grey, medial	393 ± 12	406 ± 35	385 ± 14	396 ± 24
Frontal white	277 ± 11	282 ± 15	280 ± 13	288 ± 14
Occipital grey	389 ± 11	387 ± 10	385 ± 12	391 ± 9
Temporal grey, medial	399 ± 10	402 ± 14	395 ± 12	400 ± 21
Temporal grey, lateral	392 ± 14	389 ± 10	390 ± 16	395 ± 14
Temporal white	311 ± 18	329 ± 9*	319 ± 18	332 ± 21

*P < 0.05

TABLE 36

MRI T_1 VALUES COMPARING PATIENTS WITH AFFECTIVE AND SCHIZOPHRENIC-LIKE PSYCHOSES

FWL	MEAN	SD
Affective	275	9
Nuclear schizophrenia	284	16
FWR	**MEAN**	**SD**
Affective	281	16
Nuclear schizophrenia	286	12
FGL	**MEAN**	**SD**
Affective	395	15
Nuclear schizophrenia	401	12
FGR	**MEAN**	**SD**
Affective	395	17
Nuclear schizophrenia	403	19

T A B L E 36
(CONTINUED)

THAL L	MEAN	SD	
Affective	369	21	$p < .05$
Nuclear schizophrenia	396	24	

THAL R	MEAN	SD
Affective	368	21
Nuclear schizophrenia	376	24

G L MED	MEAN	SD
Affective	397	10
Nuclear schizophrenia	405	13

G R MED	MEAN	SD
Affective	396	17
Nuclear schizophrenia	398	16

T A B L E 3 6
(CONTINUED)

G L LAT	MEAN	SD
Affective	388	12
Nuclear schizophrenia	395	13

G R LAT	MEAN	SD
Affective	390	17
Nuclear schizophrenia	395	12

F = frontal T = Temporal W = White matter G = Grey matter L = Left R = Right Thal = Thalamus

TABLE 37

CORPUS CALLOSUM (CC) MORPHOLOGY IN CONTROLS AND EPILEPTICS WITH AND WITHOUT NS

	NORMAL CONTROLS	EPILEPTICS (NS)	EPILEPTICS WITH NO PSYCHIATRIC HISTORY
	(n = 14)	(n = 12)	(n = 16)
CC length	74.8 ± 4.9	76.4 ± 3.3	76.6 ± 5.5
CC anterior thickness	7.4 ± 1.2	7.3 ± 1.8	7.8 ± 1.0
CC middle thickness	5.8 ± 0.7	5.8 ± 1.0	7.0 ± 1.1[a]
CC posterior thickness	6.7 ± 1.0	7.0 ± 1.8	7.4 ± 1.6

Measurements in millimetres
[a]Turkey HSD, $p < 0.05$

Summary

In these investigations patients with epilepsy have been compared with controls and increased T1 values are noted in many cerebral areas, especially in the temporal areas which reflects the high percentage of patients with temporal lobe epilepsy in this sample. These data are replicated when patients who had negative CT scans are analysed separately. When patients with generalized seizures are compared with a temporal lobe group, the area of the thalamus appears to be involved in the former. When patients with a lateralised temporal focus are examined, increased T1 values appear to be maximum in the temporal regions on the side which coincides with the electrical abnormality on the EEG focus. In patients with seizures that generalise, the corpus callosum appears to be enlarged.

With regards to psychotic patients, no obvious differences are noted between them and controls with epilepsy an no psychosis. Within the psychotic group, patients with hallucinations appear to have an increased signal from the left temporal, white matter. Further, no differences are noted in the size of the corpus callosum. The only difference that emerges when affective psychotics are compared with those with NS is in the thalamus.

STUDY 4

A POSITRON EMISSION TOMOGRAPHY (PET) INVESTIGATION OF THE INTER-ICTAL PSYCHOSES OF EPILEPSY

INTRODUCTION

The main source of cerebral energy is glucose, but provided there is coupling between oxygen consumption and ATP production, energy metabolism can be deduced from measuring oxygen use. Although under normal conditions there is a coupling between cerebral blood flow (CBF), and the cerebral metabolic rate of oxygen use ($CMRO_2$), and thus assessment of CBF may provide information regarding metabolism, in pathological states this relationship may be lost.

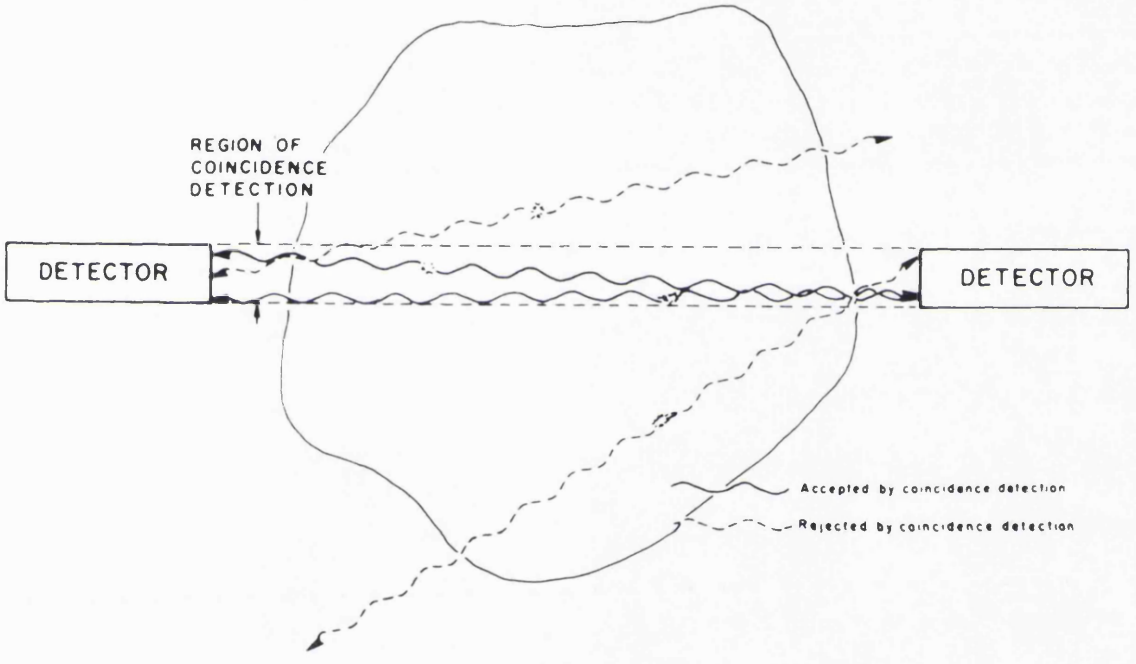
In PET, radioactive isotopes of biological substances are created by a cyclotron, which fires protons at a nucleus of, for example carbon. The latter gains protons and becomes unstable, being an 'antiparticle' to a negatively charged electron. When in tissue it combines immediately with an electron, the two particles converting their mass into radiation energy. They subsequently annihilate. The latter gives rise to the release of two coincident gamma rays of equal energy which travel at 180 degrees to each other (see Figure 11). The presence of these rays is picked up by the detectors of the scanner, positioned such that they only record coincident events, these being separated from other non-simultaneously released gamma rays. Thus, the decay event is known to have taken place on a line connecting the two detectors. Cameras are placed in a ring around the patients head, the exact

structure being dependent on the system used. Computerized reconstruction of the image is performed using technology similar to that of CT scanning. However, it is essential to recognize a fundamental difference between the two techniques, namely that in the CT scan, rays from an external source are passed through the patients brain. In PET, rays are emitted from the brain, detected and quantified. Thus, the image of PET is indeed an image and one of tissue tracer distributions. It is not an anatomical map as is provided by CT or by MRI.

The importance of PET studies in the inter-ictal of psychosis of epilepsy, and comparing data with studies with CT and MRI is related to the fact that it is possible to study brain function with this technique as opposed to looking for alterations of structure.

The spatial resolutions of machines vary, but typically are between 7 and 15 mm. For technical reasons, related to the finite range of the decay of positrons, the maximum resolution of the method is in the region of 2 to 3 mms. In order to obtain accurate readings from a cerebral structure it should have a size approximately twice that of the resolution of the machine.

FIGURE 11



Showing the coincidence detection of gamma rays used in PET.

The main biologically important positron emitters created include carbon-11, nitrogen-13, fluorine-18 and oxygen-15. In practice, since all but fluorine-18 have short half lives the patient has to be in close proximity to the cyclotron for the investigation to be carried out.

At the present time there are two main systems for imaging metabolism based either on oxygen or on glucose or deoxyglucose. Since the studies to be reported here used oxygen this will be described in more detail.

Oxygen-15 labelled carbon dioxide (CO_2) and oxygen are continuously inhaled. The CO_2 is rapidly converted in the lungs to $H_2{}^{15}O$ and is distributed throughout the arterial tree, about 20% reaching the brain, where it equilibrates rapidly with tissue water. Since this is removed by the venous system at a steady state the concentration of radioactivity measured will reflect both the delivery to and the decay from the tissue. Thus, at the steady state it is possible, using mathematically derived formulae with various corrections, to calculate blood flow.

Similarly, ^{15}O is delivered to the brain, but this becomes attached to haemoglobin. In the brain it is used to fuel the Krebs cycle for the production of ATP, the radioactive oxygen appearing in water as the result of the

metabolism. Again, with sophisticated mathematics and correction for sources of error (Lammertsma et al 1981) it is possible to define the oxygen extraction fraction (OEF), namely the fraction of available oxygen extracted from the blood, and from this and the CBF to calculate the $CMRO_2$.

PET provides information on several parameters including CBF, cerebral metabolism, oxygen extraction ratio (OER), and, if more recently developed transmitter ligands are used, neuro-receptor occupancy and activity can be examined.

In this investigation the cyclotron and PET scanner at the Hammersmith Hospital was used (ORTEC-ECATIIR). The technology allowed for assessment of regional cerebral blood flow (rCBF), regional oxygen metabolism ($rCMRO_2$) and the regional oxygen extraction ratio (rOER).

Materials and Methods

The scan procedure was as follows. Oxygen-15 with a half life of 2.1 minutes was produced by a cyclotron. During continuous sequential inhalation of $C^{15}0_2$ and oxygen by the patient, a series of transaxial emission tomograms was taken at levels of two, four, six and eight centimetres above the orbital meatal line. All emission data were corrected for attenuation by corresponding transmission scans. Tracer equations which relate steady state

measurements to tissue blood flow and oxygen extraction ratios were used to calculate absolute quantitative values of rCBF, $rCMRO_2$, and rOER. (Frackowiak et al 1980).

A computer print out of the quantitative data was available and ROI's of 2.5 cms^2 were chosen for analysis corresponding to various anatomical brain areas. These were frontal, temporal, posterior temporal and occipital cortical regions (see Figure 12). In addition, three areas were measured from temporal cortex of 1.5 cms^2 in a continuous strip on slice OM+4 (see Figure 13).

Additional areas investigated included a 'fronto-temporal bridge' (FTCB) which represented and island of cortical tissue between the frontal and temporal areas on slice OM+4; a limbic strip, representing the combined values of temporal and frontal regions of interest, and the basal ganglia, the latter being assessed directly from a visual display unit, using a 2.6^2 cm ROI.

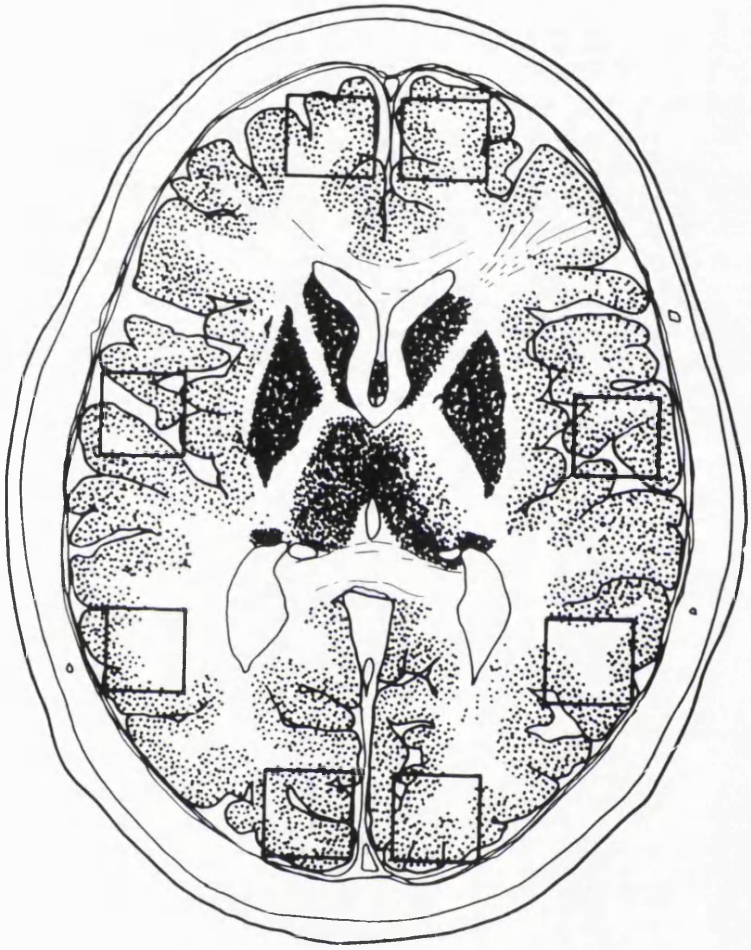
Statistical Analysis

Statistical analysis of the data was by one way ANOVA following log transformation and the post-hoc means test.

Four groups of patients were examined, two of which were psychotic. The first of the latter comprised of six patients who were free from neuroleptic medication at the time of performing the scan. One had been drug free for nine days, the second for twenty-four days, two others had received no neuroleptic medication for over seven months, and two had never received neuroleptic treatment. The second group (N=6) were receiving anti-psychotic medication at the time of the scan. The two other groups included an age matched, non-psychotic epileptic sample (N=5), and an age matched non-epileptic volunteer sample (N=5). All of the epileptic patients were receiving anticonvulsant medication at the time of the scans and all had partial seizures.

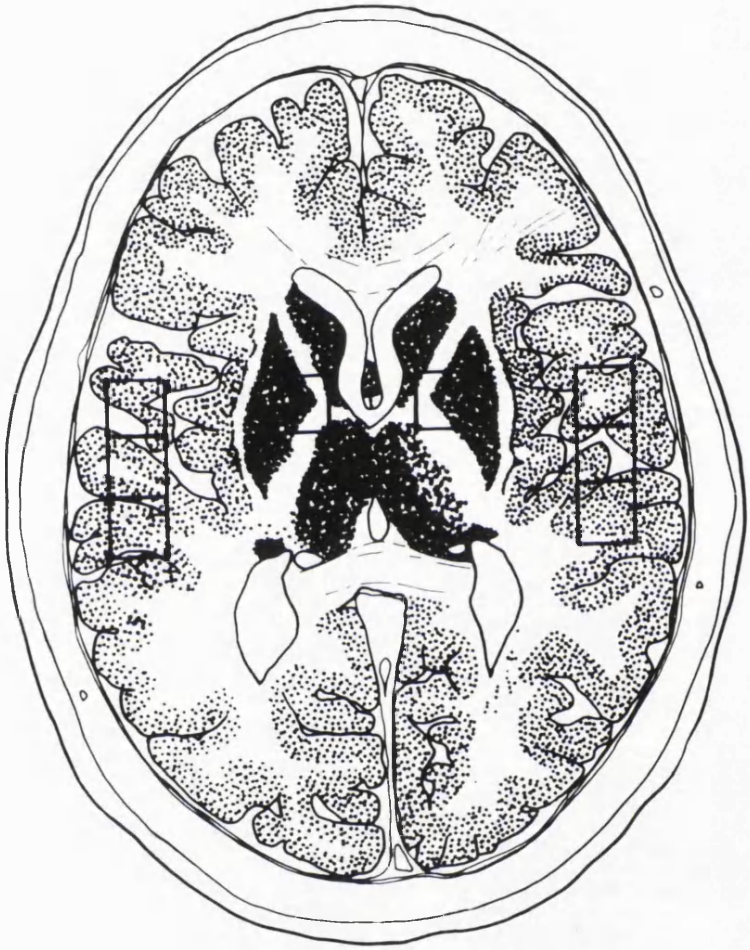
The psychoses of the patients was rated using the PSE, the examination occurring as close as possible to the time of the scan.

FIGURE 12



Showing the proposed area of analysis of PET data. Frontal, temporal and occipital sites.

FIGURE 13



Showing proposed additional temporal location for PET analysis.

Results

The basic epidemiological information of the four groups is given in Table 38. There were no significant differences between the groups for age, IQ or seizure frequency in the month prior to the scan. The PSE rating for the two psychotic groups were as follows: In the untreated group, four had NS, one had psychotic depression (PD) and one patient who did not have a PSE had clinical symptoms of schizophrenia and a past history of first rank nuclear symptoms. In the treated group two had NS, two depressive psychosis (PD), one paranoid psychosis (DP) and one patient was improved and not rated as being psychotic.

The absolute values for the $CMRO_2$, rCBF, rOER, for the left and right sides of the brain in the ROIs are shown in Table 39. Analysis of variance of all four groups revealed statistical differences in the following areas: The $rCMRO_2$ was significantly greater in the non-epileptic sample, compared with one of the epileptic groups in the left temporal regions, the left basal ganglia and the right anterior temporal regions. The rCBF was significantly greater in the non-epileptic sample, in the left anterior temporal and posterior temporal regions, and the right mid and posterior temporal regions, the right FTCB, the right basal ganglia and the right limbic strip. The non-epileptic sample, had a significantly lower rOER compared with the non-psychotic epileptics in the left

FTCB, the right temporal anterior region, the right FTCB and the right limbic strip.

Analysis of the three epileptic groups revealed significant differences between the epileptic non-psychotic and the epileptic psychotic group, but in addition differences between the epileptic psychotic untreated, and the epileptic psychotic treated groups. These significant differences are shown in Table 39. With regard to the former, the rOER, was significantly lower in the epileptic psychotic sample in all areas examined, with the exception of the left and right occipital areas, and the right temporal medial area.

With regards to differences between psychotic non-treated and the neuroleptic treated group, the latter showed significantly higher values for the rOER in the following regions: The left posterior temporal region, the left limbic strip, and both the left and right FTCB and the basal ganglia.

Analysis of laterality differences was carried out by subtracting the values for the right hemisphere from those of the left hemisphere and comparing the resultant differences between the epileptic psychotic and the non-psychotic epileptic control group. The absolute values for the differences are shown in Table 40, for the two epileptic samples. Significant differences are noted for

several values. In the frontal area, the epileptic psychotic group have significantly higher values for the rCBF than the non-psychotic group. In the temporal areas, the $CMRO_2$ difference is significantly lower medially and posteriorly ($P < 0.06$), and the CBF posteriorly ($P < 0.06$) in the psychotic sample and the OER significantly higher in the temporal anterior zone. In addition, the $CMOR_2$ in the limbic strip is significantly lower in the psychotic group. No significant laterality differences emerge in the basal ganglia or occipital areas.

In addition to analysis of the absolute values, the pattern of the data is also noted. Thus, for the $rCMRO_2$ and the rCBF, the non-epileptic volunteers have the highest values of all groups for all regions examined. For the $rCMRO_2$, the pattern of: controls > epilepsy, > epilepsy psychotic, > epilepsy psychotic treated occurs in ten of the sixteen areas examined, the main exceptions being in the left basal ganglia where the treated group have a higher $CMRO_2$ than the non-treated group. With regards to the rCBF the pattern of control > epileptic psychotic, > epileptic non-psychotic, > epileptic treated groups is seen in fourteen of the sixteen areas examined. The exceptions were in the left occipital and the right posterior temporal areas. For the rOER, the pattern epileptic non-psychotic > epileptic psychotic treated, > controls, > epileptic psychotic non-treated is seen in ten out of sixteen areas examined, the main

TABLE 38

GROUPS UNDER INVESTIGATION

	MEAN AGE (YR)	MEAN IQ	MEAN SEIZURES PER MONTH
Control, non epileptic	37.8	-	-
Epileptic, non psychotic	34.0	98	9.2*
Epileptic, psychotic	38.2	97	3.9
Epileptic, psychotic on neuroleptics	42.3	96	1.4

(*1 PATIENT HAD 30)

TABLE 39

SHOWING VALUES FOR $rCMRO_2$ AND rOER IN THE REGIONS ASSESSED IN THIS STUDY. SIGNIFICANCE VALUES ARE FROM POST-HOC MEANS TESTS ON DATA ANALYSED FROM THE THREE EPILEPTIC SAMPLES ONLY. SIGNIFICANCE DIFFERENCES BETWEEN NON-EPILEPTIC VOLUNTEERS AND EPILPTIC SAMPLES NOT GIVEN IN THE TABLE

		Psychotic treated & untreated					
		Left			Right		
		$rCMRO_2$	rCBF	rOER	$rCMRO_2$	rCBF	rOER
Frontal	C	3.6 ± 0.2	47.2 ± 10.5	0.43 ± 0.10	3.6 ± 0.4	46.5 ± 10.2	0.44 ± 0.11
	E	3.3 ± 0.8	36.1 ± 9.7	0.52 ± 0.05}	3.2 ± 0.8	34.8 ± 10.7	0.52 ± 0.04}
	EP	3.2 ± 0.6	42.3 ± 4.3	0.41 ± 0.04}+	2.8 ± 0.4	36.9 ± 5.9	0.42 ± 0.05}*
	EPT	2.9 ± 0.6	32.7 ± 7.1	0.46 ± 0.06	2.7 ± 0.51	31.5 ± 8.8	0.46 ± 0.07
Temporal (A)	C	4.9 ± 0.9	64.7 ± 19.0	0.45 ± 0.12	4.5 ± 0.5	52.4 ± 20.3	0.43 ± 0.10
	E	3.6 ± 1.4	42.8 ± 19.0	0.50 ± 0.05}+	3.9 ± 1.3	40.8 ± 15.2	0.56 ± 0.03}
	EP	3.2 ± 0.5	43.9 ± 6.4	0.40 ± 0.04}	3.6 ± 0.3	49.1 ± 5.8	0.41 ± 0.05}#
	EPT	3.0 ± 0.7	35.8 ± 8.0	0.44 ± 0.05	3.1 ± 0.6	36.4 ± 7.7	0.43 ± 0.05
Temporal (M)	C	5.2 ± 0.5	56.4 ± 20.3	0.44 ± 0.13	4.5 ± 1.0	58.9 ± 18.2	0.46 ± 0.13
	E	3.7 ± 1.2	41.7 ± 15.2	0.52 ± 0.06}	3.7 ± 0.8	40.5 ± 9.3	0.54 ± 0.06
	EP	3.2 ± 0.5	44.2 ± 3.7	0.40 ± 0.05}*	3.8 ± 0.5	*{49.9 ± 5.3	0.41 ± 0.05
	EPT	3.2 ± 0.8	37.0 ± 9.8	0.45 ± 0.05	3.4 ± 0.8	{38.4 ± 7.5	0.42 ± 0.11
Temporal (P)	C	4.5 ± 0.5	56.3 ± 13.7	0.46 ± 0.11	4.3 ± 0.10	53.9 ± 7.4	0.43 ± 0.12
	E	3.4 ± 0.8	37.1 ± 12.1	0.52 ± 0.04}	3.3 ± 0.5	34.5 ± 7.7	0.56 ± 0.08}
	EP	2.9 ± 0.5	38.5 ± 4.2	*{0.41 ± 0.06}	3.5 ± 0.3	45.7 ± 7.1	0.42 ± 0.06}*

TABLE 39
(continued)

	EPT	2.9 ± 0.5	34.3 ± 8.7	{0.48 ± 0.05	3.4 ± 0.9	37.8 ± 11.1	0.48 ± 0.06
Occipital	C	4.2 ± 0.6	48.0 ± 16.7	0.53 ± 0.15	4.4 ± 0.4	47.5 ± 14.1	0.54 ± 0.13
	E	3.6 ± 1.0	39.0 ± 14.7	0.59 ± 0.06	4.0 ± 1.1	42.1 ± 14.4	0.55 ± 0.03
	EP	3.4 ± 0.5	38.7 ± 8.1	0.49 ± 0.03	3.7 ± 0.4	43.4 ± 6.7	0.49 ± 0.03
	EPT	3.1 ± 0.5	29.2 ± 6.0	0.59 ± 0.13	3.4 ± 0.6	33.6 ± 7.9	0.59 ± 0.13
FTCB	C	3.4 ± 0.3	42.9 ± 8.4	0.43 ± 0.01	3.4 ± 0.3	44.1 ± 8.0	0.44 ± 0.10
	E	3.1 ± 0.7	34.2 ± 8.7	0.53 ± 0.04}	3.1 ± 0.8	31.7 ± 7.4	0.55 ± 0.06}
	EP	2.5 ± 0.4	35.3 ± 1.9	+{0.39 ± 0.05}+	2.8 ± 0.3	*{38.9 ± 3.6	#{0.40 ± 0.04}#
	EPT	2.5 ± 0.5	28.2 ± 6.2	+{0.47 ± 0.06	2.5 ± 0.3	{29.0 ± 5.0	{0.46 ± 0.05
Limbic Strip	C	3.5 ± 1.1	52.6 ± 11.4	0.44 ± 0.10	3.9 ± 0.3	50.7 ± 9.9	0.44 ± 0.11
	E	3.3 ± 0.8	37.1 ± 11.9	0.52 ± 0.04}#	3.3 ± 0.8	35.9 ± 9.4	0.54 ± 0.04}
	EP	2.9 ± 0.5	45.5 ± 1.2	+{0.38 ± 0.05}	3.3 ± 0.4	42.4 ± 4.4	0.41 ± 0.04}+
	EPT	2.8 ± 0.6	32.9 ± 6.9	+{0.47 ± 0.05	2.9 ± 0.6	33.9 ± 7.3	0.46 ± 0.06
Basal Ganglia	C	4.9 ± 0.7	61.0 ± 12.5	0.46 ± 0.13	4.6 ± 0.8	62.6 ± 13.1	0.45 ± 0.14
	E	3.7 ± 1.5	45.4 ± 21.0	0.47 ± 0.04}	3.7 ± 1.1	44.1 ± 14.1	0.48 ± 0.05}*
	EP	3.2 ± 0.6	49.3 ± 5.1	*{0.38 ± 0.06}*	3.5 ± 0.5	51.7 ± 5.2	*{0.40 ± 0.04}
	EPT	3.5 ± 0.7	40.3 ± 8.7	{ 0.49 ± 0.09	3.5 ± 0.9	38.3 ± 7.2	{0.49 ± 0.07

C=Control; E=Epllepsy, non-psychotic; EP=Epileptic Psychotic on no neuroleptics; EPT=Epileptic psychotic on neuroleptics. *p , 0.05; +p < 0.01; #p < 0.001

TABLE 40

SHOWING VALUES OF LEFT-RIGHT SIDE COMPARING THE EPILEPTIC NON-PSYCHOTIC TO THE EPILEPTIC PSYCHOTIC GROUP

		EP	CONTROL	SIGNIFICANCE
Frontal	$CMRO_2$	+0.4	+0.1	0.10
	CBF	+5.4	+0.3	0.04
	OER	0	0	
Temporal (A)	$CMRO_2$	-0.4	-0.3	
	CBF	-5.2	-1.9	
	OER	-0.01	-0.05	0.02
Temporal (M)	$CMRO_2$	-0.6	0	0.05
	CBF	-5.7	-1.1	
	OER	-0.01	-0.03	
Temporal (P)	$CMRO_2$	-0.6	0	0.06
	CBF	-7.2	+2.6	0.06
	OER	-0.01	-0.04	
FTCB	$CMRO_2$	-0.3	0	
	CBF	-3.5	+2.4	0.10
	OER	-0.01	0.02	

TABLE 40 (CONTINUED)

		EP	CONTROL	SIGNIFICANCE
Occipital	$CMRO_2$	-0.3	-0.4	
	CBF	-4.7	-3.0	
	OER	0	0	
Basal Ganglia	$CMRO_2$	-0.2	-0.0	
	CBF	-2.5	+1.3	
	OER	-0.02	-0.01	
Limbic Strip	$CMRO_2$	-0.4	0	0.006
	CBF	-0.9	+1.2	
	OER	-0.02	+0.01	

exceptions being in the occipital lobes and the basal ganglia, in which the epilepsy psychotic treated have the highest values.

Summary

This study has examined rCBF, $rCMRO_2$, rOER, using PET in patients with epilepsy, both psychotic and non-psychotic, and in controls. Generally, the non-epileptic control group has higher values for rCMRO2 and rCBF than the epileptic samples, the most significant differences being seen in the temporal areas, particularly in the mid and posterior temporal zones. Again, this reflects the fact that many of these patients had temporal lobe epilepsy, and the results indicate hypometabolism with lower blood flow in the relevant anatomical areas.

Patients with psychosis compared with those that have no psychoses show lower rOER in the psychotic sample for several areas, reflecting the fact that the psychotic sample has lower $rCMRO_2$ and higher rCBF in many of the regions analysed. Significant differences emerge, mainly in the fronto-temporal regions, suggesting more involvement of the limbic system related cortex in the group with psychosis. This is supported by the highly significant differences for the limbic strip and basal ganglia. Laterality differences suggest more left sided disturbance in the psychotic group, most of whom have a schizophreniform psychosis. This applies particularly to the temporal

areas. Comparing patients on neuroleptic drugs with untreated patients, the neuroleptic group have lower rCBF, mainly in basal ganglia and limbic system related structures, with less of an effect on the rCMRO2, thus increasing the rOER in the sample leading to values comparable with control patients.

SECTION 6:

DISCUSSION

METHODOLOGICAL ISSUES

This thesis presents the results of radiological studies in patients with inter-ictal psychoses of epilepsy. However, first, an attempt was made to more precisely evaluate the phenomenology of these patients, and it was established that some 50% of them had a clinical profile equivalent to that of schizophrenia in the absence of epilepsy, with first rank symptoms, referred to by Slater as the schizophrenia-like psychoses of epilepsy. In the subsequent radiological studies, the psychiatric state of patients was monitored using the PSE, and an emphasis was placed upon examining the relationship of changes of structure and function to the presence or absence of a schizophrenia-like state, especially that of nuclear schizophrenia (NS). Three radiological studies have been described, two assessing structure (CT and MRI) and one assessing function (PET) in the inter-ictal state. Before discussing the findings in more detail, and then synthesizing these data with other studies on both the inter-ictal psychosis of epilepsy and schizophrenia in the absence of epilepsy, it is germane to consider a number of methodological issues that have to do with the techniques used.

In the clinical study, the PSE was used for patient evaluation. At the time the investigation was carried out several methods to measure and classify psychiatric symptoms using standardized or semi-structured techniques were

in use, and many rating scales which were either filled in by the patient or by the investigator being evaluated. The PSE went further than many comparative standardized procedures for evaluation by laying down precise criteria for the presence or absence of particular symptoms which are well described in the manual (Wing et al l974). The patients clinical condition could essentially be described in numerical form, and a series of condensations applied to the data such that syndromes, and ultimately a CATEGO class and if required an ICD rubric could be produced. In view of the earlier work on the schizophreniform psychosis of epilepsy which had suggested a high frequency of first rank symptoms (Slater et al 1963) and the similarity to the form of schizophrenia defined by Schneider with first rank symptoms, the PSE seemed ideal, since it is hierarchical in its condensations and lays heavy emphasis on the identification of first rank symptoms in the categorisation of schizophrenia.

Organic brain syndromes are dealt with poorly by the schedule, but it was not the purpose of the investigation to define such syndromes, but to assess patients who had overt psychopathology in clear consciousness at the time of the investigation. Since the PSE bases its evaluation only on the previous month, patients were taken who had been psychotic for at least a month, but no attempt was made to assess the longitudinal pattern of the illness beyond

that. The main issue was the phenomenology of the presenting symptoms and the relationship to schizophrenia in the absence of epilepsy.

It is further acknowledged that the PSE is less effective rating symptoms made on the basis of behaviour, affect and speech, as opposed to those symptoms that are subjectively described by the patient. Again, as the important symptoms from the point of view of defining this sample may have related to the first rank symptoms of Schneider, the PSE was an ideally suited instrument. The reliability is high (Wing et al 1974), especially if the examiner has undertaken a training programme which was the case with the investigator here.

Other schedules could have been considered, and if the investigation was to be repeated, particularly with the growing emphasis in schizophrenia research on positive and negative symptoms, alternative rating scales could be suggested. These would include the scale for Assessment of Negative Symptoms (SANS) and the scale for the Assessment of Positive Symptoms (SAPS) (Andreasen 1982:1984).

In general, the PSE, proved to be a satisfactory instrument for use in these studies, and the data obtained of relevance to the overall issue of the

phenomenology of the interictal psychosis of epilepsy (see below).

The diagnosis of epilepsy, and classification, was based on clinical grounds, with the additional help of EEG records. All patients had surface recordings, and only one patient had telemetry. At the time of the investigation telemetry was not widely available, and it was only used where the surface EEG did not clearly substantiate a diagnosis of temporal lobe epilepsy where this was suspected. The study would now be better performed using eight or sixteen channel telemetry to confirm the laterality of the EEG focus, although it is acknowledged that any surface recording technique may lead to false localization. In this study, the EEGs were blindly rated and it was fortunate that a high percentage had a unilateral focus. Since few of these patients went on to have further EEG and radiological investigations for surgery, and later temporal lobectomy, clarifying the laterality of the focus by cessation of seizures following surgery, as Sherwin (1981) was able to do, could not be achieved. Although carrying out these investigations on patients who are to have temporal lobectomy represents one ideal, most surgical centres do not operate on patients who are psychotic and such perfection with regards to assessment of laterality is unlikely to be achieved by EEG methods available for non surgical cases even up to the present time. In the future such techniques as BEAM, or magneto-electroencephalography may be useful in

studies of the inter-ictal psychoses of epilepsy to aid with issues of lateralization.

With regards to the imaging studies, the first investigation used CT scanning. This technique, when introduced, dramatically altered neurological practice and had a major impact in neuro-psychiatry. An attempt was made to assess structural lesions in relationship to psychopathology, and few gross abnormalities were found. The subjective assessment of subarachnoid spaces is a technique often used by radiological departments, and in this investigation intra-observer reliability had been established. The use of linear measurements, particularly using a transparent ruler, may be criticised on a number of grounds. There is often difficulty in discerning boundaries, the values are only given to the nearest 0.5 mm, and a two-dimensional measurement may have little to do with the overall volume of three dimensional structures such as the ventricles. Nonetheless, in radiological practice, measurement of, for example the Evans Ratio is well established and when the investigation was carried out more sophisticated computerised models for measurement of ventricular size were not available.

Although the data revealed some differences between the experimental groups, the investigation could be criticised for not providing further control

data and relying on CT scan measurements in normals reported by samples obtained by Gyldensted and Kosteljanetz (l975-1977) and by Koller et al (1981). These are widely used for comparative purposes and within the radiological data bank there were few control scans available which could be used to form a non-psychotic sample from known normal patients. In a small sample (N=5) of such patients who were also evaluated radiologically, data similar to the normal values quoted in Table 24 were found. This sample size however was not sufficient to include in these studies or in the statistical analysis. In retrospect it is unlikely that bringing more sophisticated assessments of ventricular size to CT scan studies would have revealed more than the straight forward linear measurement techniques used here. Certainly if the scanning were to be repeated, a more up to date scanner with more sophisticated analysis than the EMI 5005 would be used.

The CT scan data was complimented by the MRI scans. The imaging sequence was standardized and the machine variability of measured values was low as monitored by phantoms, thus some technical flaws in methodology were avoided. In measuring ROIs the images of patients with major structural abnormalities were technically more difficult as damage gave a more variable signal, probably as a result of tissue heterogeneity. However, in general the measurement of grey matter compared with white matter required smaller pixel

volumes, in keeping with other quantitative studies (Besson et al 1987). Partial volume effects were kept to a minimum by the rejection of ROIs with a standard deviation of less than 5% of the mean. In this study we were able to obtain a control group who were free from neurological and psychiatric illness and were abstainers from alcohol. The latter is relevant to the assessment of T1 relaxation times as this is influenced by alcohol (Smith et al 1985). Although the patient population was not restricted from alcohol intake, none of the patients to our investigators knowledge suffered from alcoholism.

There are several advantages to using MRI over CT scan for such investigations. MRI does not use x-rays and in most studies injected contrast medium is not required. Triplanar images, namely sagittal, coronal and transaxial can be obtained without having to move the patient in the scanner, leading to more precise localisation of abnormalities. Of most importance is the lack of bone attenuation of the signal, allowing visualisation of the posterior fossae and temporal lobes which are so important in studies of psychiatric patients and in particular in the inter-ictal psychoses of epilepsy.

Future investigations using MRI would be performed using a higher powered machine, and further information may be obtained by the assessment of other parameters, for example weighted T2 times. The MD800 scanner was

specifically developed for the quantitive assessment of T1 measurement and not for producing images of cerebral structure of high visual quality. As such it was thought ideal for the quantitative assessments of subtle cerebral pathology we were seeking, and significant differences have been recorded. In particular the finding of increased signal in association with the side of accompanying EEG change, suggests that the technique has good validity. In general, raised T1 values suggest underlying pathology although the precise nature of the pathology is unclear. T1 measurements are influenced by the ratio of free to bound water which depends on the water content of the tissue, the binding affinity of the molecules, and the chemical environment. Further, mobile hydrogen nuclei are found in lipids in the CNS. The changes in T1 values we have noted may merely be a non-specific indicator of underlying tissue change and further work with quantitative assessments of MRI scans in cerebral pathological states is continuing in order to establish their relevance.

The study of positron emission tomography in inter-ictal psychosis represented a follow-up on an earlier study carried out by the author using oxygen-15 and PET in partial epilepsy (Bernardi et al 1984). In that earlier study the technique was evaluated in epilepsy, and found to produce satisfactory images which corresponded to the findings of other authors using different tracers (Kuhl et

al l980). Further, the finding that the areas showing most change were in the temporal cortex, ipsilateral to the site of the focus as recorded on EEGs further validates the method as one for detection of underlying functional change in association with the inter-ictal state.

Analysis using the ROI method is hazardous, because it relies on subjective assessments, and often fails to take into account heterogeneity of values due to for example the partial volume effect. Indeed, the number of potential artifacts in the interpretation of PET data are large as outlined in Table 41 from Delisi and Buchbaum (1989).

Many assumptions are made with regards to the final image which have to be taken into account in interpretation of data. In particular, the kinetic constants used in the calculations are derived from animal studies, and from brains which are not subject to pathological processes.

The major criticism of the method relates to the lack of any anatomical placement technique when assessing the ROIs. Modern systems employ either stereotactic localisation methods with some kind of normalisation of images, or use accompanying CT or MRI scan data which can be transposed upon the PET images. Such techniques were not available when this

TABLE 41

POTENTIAL ARTIFACTS IN THE INTERPRETATION OF PET DATA (FROM DE LISI AND BUCHSBAUM, 1986)

Compound as tracer

1) Half-life and breakdown rate of label.
2) Purity of the compound.
3) Differences between oxygen and glucose.
4) Differences between labels, eg $^{18}F/^{11}C$.

Experimental conditions

1) Variation in anxiety and emotional state of subject.
2) Psychiatric state of patient.
3) Task performed during the uptake period.
4) Variation in sensory inputs, eg eyes open/closed.
5) Prolonged uptake period with inconstant physiologic changes.
6) Variation in blood sampling procedures.
7) Failure to control for age and sex.,

Instrumentation

1) Limited resolution.
2) Non-uniform resolution.
3) Scatter and partial volume effects.
4) Inadequate number of planes sampled.
5) Need to standardize adequately to phantoms.
6) Variation in head size and shape.
7) Head movement.
8) Change in distribution of tracer compound during the scan procedure first to last slice.

Data Analysis

1) Inaccuracy of models to describe biochemical kinetics.
2) No appropriate model for some substances.
3) Kinetic constants used derive from animals.
4) Differences in the kinetics between white and grey matter.
5) Difficulties in matching some slices among individuals.
6) Undersampling of anatomical structures.
7) Over interpretation of assumed anatomical details.
8) Computerized methods do not account for anatomical differences among individuals.
9) Accounting for cortical folding.
10) Lack of serial determinations of data in the same individual over time to know normal variation.

investigation was carried out, and clearly further work with scanners of higher resolution, narrower cuts, better standardization of head position with the scanner, and additional complimentary structural imaging would be of value.

In the investigations presented here the number of patients available for study was limited, and the conclusions reached are only tentative. Nonetheless, small sample sizes are often used in PET studies because of the limited availability of the technology. Collecting psychotic patients not on neuroleptic drugs was difficult, again limiting the final numbers. However, attempts were made to match the different patient groups as closely as possible, thus minimising the independent variables which may have influenced the data.

RELEVANCE OF FINDINGS FOR STUDIES OF THE INTER-ICTAL PSYCHOSIS OF EPILEPSY

The first study suggested that, in general, patients with epileptic psychoses are a heterogenous group in which disorders of affect are prominent. Diagnosis of paranoid psychosis was rare, mainly found in association with affective disorders. Psychosis resembling schizophrenia was significantly related to temporal lobe epilepsy but about one third of patients with temporal lobe epilepsy presented with psychoses other than schizophrenia-like.

The presence of affective psychosis in epilepsy has been the subject of controversy. Dongier (1959-1960), concluded that in epileptic psychosis, all types of affective disorders could be found associated with any type of epilepsy; however, a tendency was noted for generalized epileptic patients to develop psychosis characterised by normal affect, while those with temporal lobe epilepsy and psychosis showed a tendency towards depression. Affective symptoms were an almost universal finding in Slater's patients (Slater et al 1963), but he did not define any distinct diagnostic entities in his group . Flor-Henry (1969), in a retrospective study of selected populations of temporal lobe epileptic patients noted that manic depressive and schizo-affective psychoses were associated with epilepsy originating in the non-dominant temporal lobe. In contrast, Bruens (1971), noted manic depressive psychosis to be rare. In general, the latter appears to be the consensus. The diagnosis of manic, depressive and affective psychoses were found in the epileptic group, especially in the sub-classes of diagnosis. This suggests that affective symptoms were of importance and often present, even when a final diagnosis of an affective psychosis was not made. There was a tendency for affective psychoses to be found more frequently in generalized epileptic patients, but the data do not allow any conclusive associations to be made to any particular type of epilepsy.

The classification of epileptic psychosis associated with temporal lobe epilepsy has emphasised the schizophrenia-like nature of this condition, providing replication and confirmation of the studies of Slater et al (1963).

In this study, twelve out of twenty-three patients with epilepsy and psychosis fulfilled the PSE criteria to be classified as schizophrenia and eleven had a diagnosis of nuclear schizophrenia, a classification based on Schneider's first rank symptoms. This suggests that both patients with epilepsy, and non-epileptic patients classified as schizophrenics, are, from the diagnostic point of view, psychopathologically comparable (see Figure 3). The PSE is unreliable at assessment of some of the objective aspects of psychopathology, and it is not suggested from these studies that the clinical pictures are identical. The clinical impression is that these patients do retain a warmth of affect, unlike that seen in schizophrenia, and that motor symptoms are less prominant, features noted by Slater. The statistical analysis may have failed to detect some differences because of the small numbers in the sub-groupings.

The statistically significant association between a schizophrenic psychosis and temporal lobe epilepsy supports the suggestion that the psychosis is associated with a focus in the temporal lobe. The studies of structural images using MRI scans in those who had normal CT scans, where the influence of

gross structural lesions on T1 times was minimised, supported the data from CT scan studies that structural pathology per se was unlikely to be a significant link between the epilepsy and the ensuing psychosis. It should be noted that in all of our radiological studies patients were selected from the out-patient clinic, unlike some other studies, (for example Taylor 1975) where a high frequency of structural pathology was found in association with psychosis but patients were taken from a series who had received a temporal lobectomy and the finding of the lesion was relevant to their selection to the surgical series. The MRI data taken in conjunction with the CT data would suggest the alternative hypothesis, namely that the psychosis was associated more with change of function as opposed to change of structure. This was the view advocated by Flor-Henry (1969) was explored further in our PET study.

Of interest in the MRI study was the finding that patients with Schneiderian hallucinations had a significant increase in T1 times in the left temporal regions, although the finding of a single difference of this value should be interpreted with caution. However, it is not out of line with the laterality data already noted (see Table 16), and the CT study of Toone et al (1982), where patients with hallucinations were found not to have any right sided abnormalities and mainly left sided changes, suggesting a significant link with the left hemisphere. The T1 changes presumably reflect pathological or

physiological alterations in the brain, that may be interlinked with the clinical presentations. They do suggest some association between limbic pathology and hallucinations and in our analysis the area of the temporal lobe particularly affected was the white matter in the areas where pathological studies suggest changes occur in patients with temporal lobe lesions such as medial temporal sclerosis. This would suggest some link between Schneiderian hallucinatory experiences and limbic pathology.

The value of this interpretation is supported by the larger MRI study of patients with epilepsy. The regional changes identified in that study were relatively specific and lateralised to the area of abnormality noted on EEG changes. Thus, agreement was noted between the EEG focal side and T1 changes, even in patients without CT abnormalities, the focal epilepsies tending to show higher T1 values on the ipsilateral side. Also in this study it is noted that a significantly increased T1 relaxation time was found in the thalamus with patients with generalized seizures. This is of interest because the thalamus has been suggested to have a role in the generation of generalized seizures, thalamo-cortical projections being thought important for synchronization of electrical activity (Andersen and Andersson 1974). The other interesting finding in relationship to the epilepsy study related to the role of the corpus callosum in generalization of seizures. Thus, the largest measurements were

found in those patients with generalized seizures and no obvious focal onset, with presumed interhemispheric propagation of the seizure discharge. Patients with only partial seizures had smaller values, although these were higher than the mean values for the controls. The corpus callosum has been shown necessary for kindling generalized seizures in animal models (Jensen and Klinken 1976) and some recent theories of the pathogenesis of generalized epilepsy have highlighted the role of the corpus callosum (Harbaugh and Wilson 1982). The findings of this study lend support for a role of the corpus callosum in seizure generalisation.

With regards to the corpus callosum in patients with epileptic psychosis, the main finding was that patients with NS showed no significant association to the morphology of the corpus callosum. This is in contrast to reports of an increased corpus callosum size in schizophrenia by some authors (Nasrallah et al 1986). The presence of a thicker mid-callosal width in patients with epilepsy and no psychiatric illness may relate to the fact that this group contained patients with generalized seizure disorder which as noted is associated with an increased mid-callosal width. One interpretation of these data is that patients with NS have normal callosal morphology because this form of epileptic psychosis is related mainly to focal epilepsy, and does not rely on abnormal propagation of seizure discharges through inter-hemispheric

pathways for its pathogenesis. The study of the corpus callosum in this group therefore adds further weight to the suggestion that gross structural pathology is unlikely to be the most important link between epilepsy and a subsequent psychosis.

The use of PET in the inter-ictal psychoses of epilepsy was to examine functional as opposed to structural changes in this condition. In the study interesting differences between the groups emerge. First, with regards to differences between non-epileptic volunteers and the three epilepsy groups, data were similar to the earlier study on epileptic patients in the inter-ictal state (Bernardi et al 1983). Generally, the control groups have higher values for $CMRO_2$ and CBF than epileptic groups, the most significant differences being in the temporal lobes. Analysis of the epileptic groups revealed consistent patterns of change, although the results were not significant for all zones examined. When patients with epilepsy and no psychosis were compared with those with psychosis the psychotic sample had lower rOER values in many regions. This reflects the relationship between the $rCMRO_2$ and the rCBF, and the significant differences in these data are consistent with the epileptic psychotic sample showing lower $rCMRO_2$ and higher CBF in the regions analysed. Most of the differences are in fronto-temporal structures, and this suggests more involvement of the limbic system related cortex in the psychotic

group. This is supported by the highly significant differences for the limbic strip. There was also involvement of the basal ganglia.

The differences between the psychotic and non-psychotic groups do not reflect age differences, as they were well matched, and, in addition, changes of grey matter $rCMRO_2$ are minimal with aging (Frackowiak et al 1980). Neither is it likely to reflect partial volume effects since the latter, which may effect the rCMRO2 and rCBF will equalize out in the calculation of the rOER. All patients in the study had CT scans performed and no clear structural deficits were noted.

The finding of lower rOER in the psychotic sample must be seen in the light of other studies that examined patients with psychosis using similar techniques. The literature on cerebral blood flow and psychosis goes back to the original studies of Kety et al (1948), who, using the nitrous oxide technique found normal values in chronic schizophrenics. Using more sophisticated methods of regional analysis and inhalation with either 85-krypton or 133-xenon, Ingvar and colleagues (1974) noted deviations of rCBF distributions in schizophrenics, and highlighted the pattern of hypofrontality, a finding replicated in some other studies (for review see Trimble 1988). Several groups have examined patients with schizophrenia using PET, (see below) although

the published literature mainly reflects studies using fluorodeoxyglucose, rather than oxygen. The finding in this study of lowered $CMRO_2$ and lower extraction ratios in the psychotic patients when compared with non-psychotic controls are in keeping with the lower metabolic values found in some of these glucose studies of schizophrenia.

With regards to the laterality differences in the PET study, the findings are compatible with the emphasis on left sided abnormalities noted in the MRI study and the EEG phenomenology study. Five of the six untreated psychotic patients had a psychosis with first rank symptoms, emphasising the link of this clinical pattern to left sided temporal lobe disturbances.

It is important to note, when comparing the data from MRI and PET, that the latter show far more extensive areas of change. Thus, MRI changes in patients with temporal lobe epilepsy are confined to relatively discrete areas of the anterior temporal lobes, while functional changes seen with PET involve related frontal and posterior temporal cortex and some sub-cortical structures for example the basal ganglia, (Bernardi et al 1983). Similarly the functional changes noted in our psychotic group are quite extensive, and the laterality differences are detected particularly across temporal structures, the fronto-temporal cortical bridge and in the basal ganglia. These data lend support to

the concept that functional changes are more likely to underly the pathogenesis of the psychosis than gross structural changes.

In these studies, differences between patients on and off neuroleptic medications were also examined. The pattern of analysis suggests that cerebral blood flow is affected by such treatments, emphasising the importance of examining patients who are free from neuroleptic use for as long as possible. The rCBF was lowest in the epileptic psychotic treated group, significant in two analyses. In a separate analysis, not reported here, comparison of the treated and untreated psychotic groups for laterality differences revealed that the differences noted in the untreated group were not present in the treated group with the singular exception of the temporal anterior rOER. This suggests some regularization of abnormal patterns within the brain while on neuroleptic medication, reflected in the significant increase in the rOER in brain areas in the treated group. This leads to values for rOER similar and non-significantly different from the epileptic non-psychotic and the non-epileptic controls. Thus, in the treated group, the rOER is 'preserved', perhaps reflecting on some therapeutic action of the drugs.

Finally, the relationship between the prescription of anticonvulsant drugs and psychosis was examined in the first study. In all of our studies the patients

were on a variety of anticonvulsant drugs and accurate assessment of the total intake of medication over the years was not available. Those who have examined the issue of the relationship between drugs and psychosis are few. Slater and Beard (1963) found no relationship. Systematic studies of the effect of anticonvulsant drugs on both the mental state and behaviour reveal that they lead to alteration of cognitive function (Thompson and Trimble 1982), and possible mood (Robertson et al 1987) but apart from idiosyncratic reactions and the development of toxic psychosis there is little evidence in the literature to suggest any link between the persistent taking of anticonvulsant drugs and the development of psychosis. The singular exception is Vigabitrin, but none of our patients were receiving this newly introduced anticonvulsant (Sandier et al 1991).

SCHIZOPHRENIA AND THE TEMPORAL LOBES

One of the persistent themes of the studies reported in this thesis, has been that patients with temporal lobe epilepsy are more likely to develop psychopathology, especially if the abnormal electrical activity derives from medial temporal structures affecting the limbic system. The phenomenology of these psychoses often involves schizophrenia-like or paranoid states, and only specific differences, for example the relative maintenance of warm affect, and lack of motor symptoms, distinguishes schizophrenia from the schizophrenia-like psychoses of epilepsy. An important consequence of this is that the schizophrenia-like psychoses of epilepsy are a biological model for at least some forms of schizophrenia, notably those presenting with similar phenomenology. This would be patients with positive (Crow's type 1) symptom schizophrenia , and an emphasis in these studies has been placed on the presence of first rank symptoms. If the biological model has validity, and if the temporal lobes are involved in the pathogenesis of the schizophrenia-like psychosis of epilepsy, then it is in the temporal lobes in particular that one should seek changes in schizophrenia in the absence of epilepsy. The evidence that limbic system structures are involved in schizophrenia comes from several areas, but notably from neuropathological studies, neurophysiological investigations, and radiological data.

Neuropathological Data

Limbic system abnormalities in brains from schizophrenics were shown by Nieto and Escobar (1972). They detected gliosis in the periventricular and midbrain areas including the hypothalamus, thalamus, septal area and periaqueductal grey area. However, the hippocampus was also affected. Similar data, also using glial stains, were reported by Stevens (1982) on a series of patients hospitalized prior to use of neuroleptic medication. Gliosis was maximal in periventricular, periaqueductal and basal forebrain regions. Nuclei involved and included the thalamus, hypothalamus, septal, bed nucleus of the stria terminalis, substantia innominata, and nucleus accumbens. Changes were also noted in the amygdala. Neurone loss or infarction were seen in the globus pallidus, and several cases showed disruption of the fibre bundles traversing the periaqueductal region such as the fornix and stria terminalis. Stevens interpreted these data as compatible with evidence of third and lateral ventricular enlargement in schizophrenia, the pathology affecting predominantly limbic structures.

Bogerts and colleagues (Bogerts et al 1985: Falkai et al 1988), in a series of studies of schizophrenia on brains from the Vogt collection, from patients who never received ECT, insulin or neuroleptic treatment, reported reduced volume in five areas. The greatest was the parahippocampal gyrus, others being the

hippocampus, amygdala, globus pallidus and periventricular region. The inferior horn of the lateral ventricle also showed enlargement. In a more specific study of the entorhinal region they noted a significant volume reduction in schizophrenics verses controls with 37% reduction of neurones although no excess of gliosis. They believed their data suggested a developmental hypoplasia of medical temporal structures in schizophrenia, rather than an on-going pathological process which would have been associated with gliosis. In a comparison of their findings in schizophrenia with those of brains from patients with Huntington's chorea and Parkinson's disease, it was the hippocampal changes that were the most striking (Bogerts et al 1983).

Stevens (1986) reported on a clinico-pathological correlation of Bogerts' data, and noted that pallidum changes were more often associated with negativism and catalepsy while thought disorder was associated with pathology in the parahippocampal gyrus and enlargement of the inferior horn of the lateral ventricles. Hallucinations and paranoia were seen with amygdala and hippocampal pathology.

Further data in relation to hippocampal pathology in schizophrenia has been reported by Kovelman and Scheibel (1984). They reported pyramidal cell

disorganization in two separate groups of brains from schizophrenic patients, again suggestive of disruption at an early stage of CNS development. The pathology occurred throughout Ammon's horn but mainly involved interface zones; between proscubiculum and CA1, and between CA1 and CA2 and between CA2 and CA3.

Hippocampal pathology in schizophrenia has more recently been studied by Jeste and Lohr (1989); most patients had never received neuroleptics, the brains being taken from the Yakovlev collection. Using semi-automated image analysis they computed volume and pyramidal cell density in the hippocampus. They reported that sections from schizophrenic patients had consistently the lowest volume and pyramidal cell density in comparison with non-schizophrenic patients and normal controls. In their study, differences were greatest in the left CA3 and CA4 region. They attributed this to possible abnormal prenatal migration of neuroblasts into the hippocampal primordium. The relevance of CA4 abnormalities to the development of psychosis will be discussed later, but it is of note that some of the negative pathological studies have not studied this region, for example Christison et al (1989) who were unable to find abnormal array patterns in CA1 regions from the mid hippocampus of schizophrenic patients.

The question of the association of developmental abnormalities with these pathological changes has been followed further by Jakob and Beckmann (1989) and Crow and colleagues (Brown et al 1986: Crow et al 1989). Jakob and Beckmann examined the brains of 76 chronic schizophrenic patients matched with controls. Twenty brains were normal, but fifty-six showed macroscopic abnormalities with definite deviations of the sulco-gyral pattern of the lower temporal regions. In humans these appear between the seventh and eighth foetal month, while the parahippocampal gyrus and entorhinal region is formed at an earlier stage approximately the sixth foetal month. They discussed a genetically induced disturbed migration in the entorhinal region towards the end of the fifth month which may be responsible for these findings.

Many of the temporal lobe changes reported, for example by Bogerts et al and Scheibel et al were in the left hemisphere, but in their studies this was the only one examined. In the investigation of Jeste and Lohr (1989) maximum findings were in the left hemisphere, and this has been supported by other data. Brown et al (1986) compared the brains of patients meeting the strict criteria for affective disorder and schizophrenia, and noted that the latter had larger temporal horns of the lateral ventricle and thinner parahippocampal gyri. The greatest differences were noted in the left hemisphere. Crow and colleagues (1989) compared brains of patients with schizophrenia, with those suffering

from Alzheimer type dementia and controls. They noted ventricular enlargement, especially of the posterior and temporal horn of the lateral ventricle, in comparison with controls and patients with Alzheimer type dementia. The abnormality was highly selective for the left hemisphere. They speculated that one mechanism of the temporal horn enlargement could be arrest of cerebral growth since the size of the temporal horn decreases during development. This arrest could be related to exogenous or endogenous factors, although their own work favoured the interpretation that it is related to genetic mechanisms.

These pathological studies, are supported by the neurochemical data supplied by Reynolds (1983). Most neurochemical studies in schizophrenia relate to testing the dopamine hypothesis (for review see Trimble 1988), and several studies suggest increases in dopamine receptor density in limbic system or related areas. Reynolds (1983) assessed laterality in relationship to neurochemical findings. In a study which has now been replicated, he compared brains from patients with schizophrenia with controls and noted that dopamine was increased in the amygdala of the schizophrenic patients selectively on the left side.

EEG Studies

These neurochemical and neuropathological studies are supported by EEG and radiological data. Soon after the introduction of the EEG into clinical practice, reports of abnormalities in schizophrenia appeared (Hill 1950). These were largely of paroxysmal and non-paroxysmal dysrhythmias, sometimes with features similar to those seen in the EEG's of patients with epilepsy. Temporal lobe abnormalities in schizophrenia have been reported frequently, with a tendency to be greater on the left (Abrams and Taylor 1979).

Using intracerebral implanted electrodes, Heath (1982) investigated 63 patients with psychosis, 38 of whom were diagnosed as having schizophrenia. Spiking was seen in the septal region which included the septal nuclei, and nucleus accumbens, the olfactory tubercle and the diagonal band, as well as parts of the gyrus rectus.

Heath noted changes in the septal area when patients were actively psychotic, and in many cases the EEG abnormalities were not observed on surface recordings. Neither were similar findings seen in chronic pain control patients. Violence and aggression were associated with hippocampal and amygdala discharges. Similar findings, especially with regards to the septal region, have been reported by others (Rickles 1969: Sem-Jacobsen 1956).

Using telemetred EEG during psychotic behaviour in schizophrenic patients, Stevens and Livermore (1978) identified so called "ramp patterns", characterised by a monotonic decline in power from lowest to highest frequencies, which can also be seen in epileptic patients during sub-cortical spike activity. These were seen only in schizophrenic patients, and not in controls, and 50% of paranoid patients with auditory hallucinations had left sided ramps with increased slow activity. Psychotic events recorded clinically were associated with suppression of left temporal alpha frequencies.

Radiological Studies

Much of the CT literature in schizophrenia (for review see Trimble 1988), has to do with ventricular enlargement, especially of the lateral, third and fourth ventricles. These are well replicated findings in investigations on groups of patients with schizophrenia. A number of studies have specifically looked at temporal lobe structures, although these are poorly visualised by CT, and it is the more recent studies with MRI which have revealed most differences. McCarley et al (1989) compared the size of CSF spaces in schizophrenic patients and compared them with controls. Overall, ten of the eighteen CT measures were significantly enlarged in the schizophrenic group. These abnormalities were then correlated with electrophysiological findings and clinical measurements. Left Sylvian fissure enlargement was highly correlated with a left temporal scalp region feature of the auditory P300, that

differentiated schizophrenic patients from controls, and both the enlargement and the P300 were significantly correlated with positive symptoms.

Four investigations have specifically examined temporal lobe structure in schizophrenia with MRI. Besson et al (1987), noted no significant differences in T1 values between schizophrenic patients and controls, but reported that patients with high positive symptoms scores showed increased values in left medial temporal structures, compared with those with low scores. Suddath et al (1989) compared grey and white matter volumes in the temporal lobes of schizophrenia and controls and found that the volume of temporal lobe grey matter was 20% smaller in the patients. Anatomically the areas corresponded to those areas of the temporal lobe containing the amygdala and anterior hippocampus, and the right temporal lobe was significantly larger than the left, although this obtained for the controls as well.

Johnstone et al (1989) used MRI to assess temporal lobe structure in schizophrenics, patients with bipolar affective disorder and normal controls. Compared with the non-schizophrenic groups, the patients with schizophrenia had a significantly smaller left temporal areas.

Suddath et al (1990) examined 15 pairs of monozygotic twins discordant for

schizophrenia. Quantitative analysis at the level of the PSE hippocampi showed the hippocampus lobe smaller in the left in 14 affected patients compared with their control sib.

Another imaging technique that has been brought to this issue in schizophrenia is that of a positron emission tomography (PET). As with structural imaging techniques, virtually all studies that have been undertaken have showed differences between controls and schizophrenic patients, much emphasis having been placed in earlier studies on hypofrontality and changes of basal ganglia metabolism (for review see Trimble 1988). With regards to laterality and temporal lobe findings, Gur et al (1985), in unmedicated patients, showed higher resting left hemisphere cerebral blood flow, and when patients undertook a spatial task, decreases of anterior left hemisphere activity were noted compared with controls. De Lisi and colleagues (1989), using 2-Deoxy-Glucose, compared metabolic rate in the temporal lobes in twenty-one medication free patients and matched controls. The schizophrenics had significantly increased mean and maximum metabolic rates in both temporal lobes compared with controls but the schizophrenics had significantly higher glucose use in the left when compared with the right temporal lobe. Using region of interest analysis, this difference was present along all structures measured, being least marked for the superior temporal area, and increasing

inferiorly (superior hippocampus, mid-temporal, inferior hippocampus, inferior temporal). Significant correlations between a psychopathology rating scale, the BPRS, and the superior temporal gyrus left/right ratio was noted for suspiciousness, thought disorder, disorganised speech, hallucinations and emotional withdrawal.

Finally, Wiesel and colleagues (1987), using C_{11} glucose as a tracer, examined different brain regions in healthy male volunteers and twenty drug free schizophrenic patients. With regards to temporal lobe findings, left-right asymmetries were noted in the temporal lobe, in area 22, the metabolic rates of the schizophrenic patients being lower on the left compared with controls. Whether the different direction of this compared with other studies was related to tracer, or patient selection is unclear. In this study, analysis of amygdala findings revealed differences between hebephrenics and paranoid patients, the latter having higher metabolic rates in the left amygdala.

These studies of schizophrenic patients lead to the following conclusions. Schizophrenia is a neurological illness with pathology affecting limbic system structures (for review see Trimble 1988). The above review relates mainly to findings in temporal lobe structures, which have been noted abnormal using neuropathological, EEG and radiological techniques. There are several

studies showing hippocampal pathology in schizophrenia, and it is difficult not to conclude that this structure is intimately related to its pathogenesis. Associations with certain symptoms have been suggested by certain authors, in particular positive symptoms (Stevens 1986, Besson et al 1987), hallucinations, speech disturbance, suspiciousness, and hostility (De Lisi 1989: McCarley 1989). Although not universally found, a tendency to maximum dysfunction in the left hemisphere has been reported although there are some negative findings. This is remarkable in view of the data presented in the introduction to this thesis, and in the results. The conclusion that the schizophrenia-like psychoses of epilepsy and schizophrenia have in common underlying areas of anatomical dysfunction within the limbic system seems probable. It is difficult to avoid the conclusion that patients with schizophrenia, particularly those with positive symptoms are likely to show limbic system disturbances if looked for, and the hippocampus, amygdala, and parahippocampal gyrus, especially on the left side are most likely to be involved. Finally it is relevant to the issue of the links between epilepsy and psychopathology that the commonest form of epilepsy involved in the schizophrenia-like psychoses is that related to temporal lobe abnormalities, and that the lesions of this form of seizure disorder are often found in the hippocampus and amygdala. The limbic epilepsies, as emphasised in this thesis are a good biological model to help explore the pathogenesis of

psychotic states in non-epileptic populations.

THE SCHIZOPHRENIA-LIKE PSYCHOSIS OF EPILEPSY

There have been several explanations for the pathogenesis of these psychoses. The first issue related to whether or not they truly resemble schizophrenia in the absence of epilepsy. Early conclusions were reached by several authors. Gibbs et al (1938) believed that the relationship between epilepsy and schizophrenia was a positive one and that there were few differences between the presentation of psychiatric disorders in patients with and without epilepsy. Hoch (1943) thought in some patients it was "clinically impossible to differentiate epileptic psychosis from schizophrenia" while in others certain symptoms indicated an organic psychosis. Slater and Beard (1963b) used the term schizophrenia-like to emphasise the similarity of the phenomenology, but stressed differences, notably the way that epileptic patients with psychosis tended to remain friendlier, more co-operative, and retain affective warmth when compared with schizophrenics without epilepsy. They also noted the relative infrequency of catatonic symptoms.

Phenomenological comparisons and similarities are reported here in the PSE studies, and similar data have been reported by Toone et al (1982). The latter also emphasised the under-representation of catatonic features.

Bruens (1971) denied that the psychoses of epilepsy could be brought under the heading of any classic psychiatric syndrome, stating that none of his cases fulfilled strict criteria for the diagnosis for schizophrenia as laid out by some German authors. He noted there was "no praecox feeling".

The suggestion which emerges therefore is that these psychoses differ from process schizophrenia in certain fundamental ways from a phenomenological view point, in particular with the maintenance of affective warmth and lack of hebephrenic deterioration with personality dilapidation. It would seem appropriate therefore to refer to them as schizophrenia-like psychoses of epilepsy.

With regards to their pathogenesis, various theories have been suggested. A genetic relationship was ruled out by Hoch (1943) who noted no increase of schizophrenia in the consanguinity of epileptic patients and vice versa. Likewise, in the family studies of Slater, there was no specific predisposition to schizophrenia in the schizophrenia-like psychoses of epilepsy, and Slater regarded the latter as "non-endogenous but symptomatic", which could be regarded as "a phenocopy of a genetically determined condition" (p149). The only study to suggest a significant hereditary component was that of Jensen and Larsen (1979) in a highly selected group of patients who had temporal lobe

surgery. The relatives were not personally interviewed, and the psychiatric diagnosis of the relatives was not given.

Several early authors stressed psychological interpretations (Ziehen 1902). Pond (1957) felt that the continuing disruption created by recurrent ictal and post-ictal alterations of the mental state, especially as seen in temporal lobe epilepsy, may be influential for the later development of psychosis. This view receives only minimal support from the studies that have investigated the relationship between auras and psychosis, in the sense that the association with psychopathology relates to a limbic system origin of the aura rather than content, and the only study to specifically study content (Taylor and Lochery 1987) did not find a relationship.

Bruens (1971) emphasised both organic (temporal lobe) and psychodynamic factors noting with regards to the latter the disturbed overprotective environment in which epileptic patients live. He felt that organic and psychodynamic factors "potentiate" each other. Ramani and Gumnit (1981) felt that the psychoses were "the reaction of a constitutionally predisposed individual to the continual physiological or psychological impact of recurrent seizures".

Other authors who have emphasised sociological factors include Wolf (1988), patients in his investigations who became psychotic being vocationally and socially disintegrated with little or no professional training. Social integration was seen as a stabilising factor in a potentially psychotogenic situation. Likewise, social factors were considered important by Ferguson and Reyport (1965).

The problem with these theories is that they fail to explain the observed associations between psychoses of epilepsy and seizure expression, the link with limbic seizures and the laterality effects.

Several authors have drawn attention to common factors shared by epilepsy, the schizophrenia-like psychoses of epilepsy and schizophrenia. One of the earliest recorded abnormalities was that of temporal lobe pathology, initially outlined by Bouchet and Cazauvielh (1825). This issue was tackled again recently by Stevens (1986). She reported on the neuropathological and clinical findings of six cases of epilepsy followed by psychosis. Four demonstrated significant left hippocampal sclerosis, but for these cases the right hemisphere was not available for examination. Gliosis and mild degenerative changes were also noted in the pallidum, brain stem tegmentum, periaqueductal or periventricular regions of the basal forebrain and the thalamus. Stevens

described these changes as "similar to changes observed in our larger series of patients with schizophrenia" (p133). Stevens concluded that:

> "The association of the Mesial Temporal Sclerosis (MTS) and severe behaviour disturbances ... is related ... to a combination of MTS plus pathology in subcortical, limbic, pallidal, thalamic, hypothalamic and periventricular regions".

However, MTS was not seen as crucial in the sense that the interictal paranoid hallucinatory psychoses occurred in some patients without MTS. It should be noted that MTS is not exclusive to epilepsy, being reported in nine out of twenty-eight schizophrenic patients without epilepsy in the series of Stevens although unassociated with conspicuous pyramidal cell loss, which is seen in cases of epilepsy and psychosis. Stevens favoured scattered lesions in a number of sub-cortical areas which receive projections from medial temporal-limbic structures as responsible for interictal psychopathology.

EEG similarities have been noted since the earliest of the EEG investigations (Gibbs et al 1938; Jasper et al 1939). They noted how pathological dysrhythmias were seen in epilepsy, but also in schizophrenia. Gibbs et al (1938) wrote:

> "The disorders of behaviour encountered in individuals who display ... schizophrenic ... traits, when accompanied by the disorders of cortical rhythm present in epilepsy, suggest that all these might be considered various manifestations of epilepsy ..." (p266).

They criticised too rigid a terminology, and suggested that physicians should seek freedom of thought, making terminology secondary to underlying "vital processes". Jasper et al (1939) noted:

> "We could detect no single specific form of activity in the electroencephalograms from patients diagnosed schizophrenic which would distinguish them, as a group, from those classified as epileptic or as normal"

"Epileptiform activity" was noted in 21% of schizophrenics, and 6% of normals.

These cortical studies were complimented by the elegant studies of Heath (1962) with implanted electrodes. He drew distinctions between the depth recordings of seizure patients, and those with schizophrenia. However, the anatomical regions from which the abnormal recordings were obtained were the same in both groups, although seizure patients had more pronounced abnormalities in the hippocampus and amygdala, and less in the septal region while the schizophrenic and other psychotic patients had abnormalities predominantly in the septal region. Epileptic patients when they become psychotic showed septal abnormalities. For Heath it was the involvement of similar anatomical structures which lead to the development of psychotic behaviour.

The interictal EEG similarities in limbic areas in epilepsy and schizophrenia were underlined by the paper of Kendrick and Gibbs (1957). They studied

seventy-five patients who had been psychotic for a prolonged period of time, thirteen had psychomotor epilepsy, sixty-two had psychosis without epilepsy. Depth electrodes were implanted in a variety of areas, and waking and sleep recordings taken. Spiking was detected in medial temporal and frontal structures in the thirteen patients with psychomotor epilepsy and psychosis, and in the sixty-two patients with psychosis and no epilepsy. The authors commented that almost 50% of schizophrenic cases had a clearly defined spike-focus in the anterior temporal region and or in the frontal areas. The medial temporal lobe was thus frequently involved.

Other similarities between schizophrenia and the schizophrenia-like psychoses of epilepsy are revealed in the studies reported here, and include CT changes, notably ventricular size, MRI evidence of disturbed limbic system structure, and changes of function in studies using positron emission tomography. These do not abate with temporal lobectomy, attesting to their continuing presence and significance interictally (Radtke et al 1969).

Mechanisms

In view of these findings, most authors start their explanations of the association between epilepsy and psychosis with observations of links between psychoses and temporal lobe epilepsy, noting the extensive literature which emphasises the intimate association between the temporal lobes and

modulation of behaviour and emotion.

Berrios discussed the options prevailing a century ago, (see page 24) and Slater and Beard (l963) returned to some of these. Their arguments would reject 1a and 1b, and emphasise 2c, and variants of 2aii. Thus, either epilepsy was a precipitating factor for the schizophrenia-like illness, or the schizophrenia-like illness was epileptic in origin. They dismissed the first explanation on the grounds that epileptic psychotic patients lack pre-psychotic personalities of the schizoid type, and if anything note differing personality traits, including viscosity, aggression, religiosity and egocentricity in association with the psychoses. They also pointed out, on the basis of a follow-up study, that in contrast to the expected deterioration with schizophrenia, the schizophrenia-like psychoses tend to leave the personality substantially undamaged. Thus, on their follow-up of 93% of their patients, 16% had ceased having seizures, and the schizophrenia-like symptoms had resolved or improved in 68%.

Slater & Beard pointed to the predominance of temporal lobe abnormalities, and the clinical phenomenology. They then discussed the aetiological relationships that could exist between the epilepsy and the psychoses, either seizures themselves being the adequate cause, or there being a basic

disorder of function manifesting itself both as seizures and as psychosis. Their data supported the second hypothesis, namely that underlying the epilepsy was some process which at one stage was liable to lead to seizures, and at another to the psychosis. The process they suggested was an organic lesion in the temporal lobes, pointing in their series to the high frequency of a history of head injuries, the evidence of organic personality change, and the air encephalography changes. They acknowledged that the patients rated by them as hebephrenic may be aetiologically different.

The necessity to distinguish between phenomenological types emerges in this thesis since epileptic patients rated as nuclear schizophrenia clearly have a number of distinguishing clinical features when compared with those classified as other forms of schizophrenia.

The view that the emergence of the psychosis is associated with identifiable structural brain damage was supported by the studies of Kristensen and Sindrup (1978), the pathological studies of the temporal lobectomy series by Taylor (1975), and by Jensen and Larsen (1979) and Bruton (1988). However, evidence for links to a specific pathology, either hamartomas or specific gangliogliomas can not be held up, patients with MTS also develop psychoses (Jensen and Larsen 1979; Sherwin et al 1982; Bruton 1988).

The suggestion that seizures themselves are more relevant than underlying structural lesions emerges from several sources. Flor-Henry (1969) emphasised links between seizures and psychosis as had earlier been shown by Landolt, and the links between psychosis and infrequent expression of seizures in his series. He criticised the data of Slater and Beard (1963) on the grounds that there were no controls, and emphasised that in his own controlled study the incidence of identifiable organic abnormalities was the same in psychotic and non-psychotic epileptic patients. Flor-Henry concludes:

> "Epileptic psychoses are not 'organic' psychosis, in the general non-specific sense of the term but are truly 'epileptic' psychoses fundamentally related to epilepsy rather than to associated brain damage" (p389).

He reflected that underlying patterns of abnormal neuronal activity, especially in the dominant temporal lobes, were fundamentally responsible for the schizophrenic syndrome. In contrast, manic depressive psychoses associated with temporal lobe epilepsy were related to infrequently manifested generalised seizures hinting that neuronal systems responsible for generalised seizures were more critical in determining the appearance of the manic depressive states. The link here to the biological antagonism of ECT is obvious.

Symonds (1962), in a discussion of Slater's findings, noted that damage to the temporal lobes occurred in other neurological conditions, but usually did not

cause a schizophrenia-like condition. He then referred to the "epileptogenic disorder of function". He acknowledged that abnormalities of function continued interictally, and said "this background disorder may cause symptoms other than seizures" (p4). The continuing interictal abnormality of function has now been noted in many studies, including depth electrode studies, and more recently the metabolic PET data. Symonds (I962) further continued:

> "It is not loss of neurones in the temporal lobe that is responsible for the psychosis, but the disorderly activity of those that remain, and that this disorderly activity is of the kind that is also likely to cause seizures" (p5).

These ideas have much more to do with the continuing process of epilepsy, and clearly make the distinction between epilepsy viewed purely as a disorder of seizures, and epilepsy viewed as a disorder of cerebral function of which seizures are but one manifestation. A similar theme was taken up by Taylor (I975) where he discussed abnormal cerebral organization, especially referring to areas outside the immediate temporal focus.

The radiological evidence presented here using CT, MRI and PET, has, emphasised that structural lesions do not underlie that psychoses but may influence the pattern of symptoms, while disturbance of function interictally is not only extensive in psychotic patients, but it also affects areas outside the

immediate anterior temporal lobes. The studies with MRI reveal fairly well circumscribed structural changes in the anterior temporal lobe in patients with temporal lobe epilepsy, but the metabolic changes revealed with PET are more widespread affecting temporal, basal ganglia and frontal regions. These data touch on underlying anatomical connections between the medial temporal structures, maximally affected in temporal lobe epilepsy, and other areas of the limbic system. The direct links between the anterior temporal lobes and the basal forebrain and frontal cortex reveal how the influence of damage to circumscribed areas of the temporal lobe may be wide. These ideas emphasise the value of distinguishing patients who suffer from limbic epilepsy, and the distinctions between different forms of temporal lobe epilepsy. The data are reinforced by the medial temporal site of origin of pathology in patients who are psychotic who come to surgery (Bruton 1988).

One issue which has created considerable discussion has been the finding of Slater and Beard (1963) of a fairly constant relationship between the age of onset of epilepsy and the age of onset of psychosis. Stevens suggested that this relationship was an artefact based on the number of patients with anterior temporal lobe spikes on the EEG rising with age in a manner which correlated with the age related incidence of presentations with psychosis. Toone (1981) did not accept this explanation, noting that the age of onset for temporal lobe

epilepsy peaks between 25 and 50, whereas the first admission for schizophrenia lies between 20 and 40 for the majority of patients. The peak for psychomotor seizures in the series given by Gibbs and Gibbs seems to be between 15 and 30.

An important aetiological link between seizures and psychosis is suggested by the laterality findings, especially that between the left hemisphere and the schizophrenia-like psychoses. Again, this has been criticised on the grounds that patients with epilepsy without psychoses tend to have an increased frequency of left sided pathology, especially if selected populations such as hospital referral patients are examined. These criticisms cannot explain the more circumscribed association between specific forms of psychoses reported here, especially schizophrenia-like psychoses with first rank symptoms of Schneider (nuclear schizophrenia) and the left hemisphere. Further, they must counter the increased number of findings now which clearly emphasise a laterality effect with a predominance of left sided abnormalities in patients with schizophrenia who do not have epilepsy, reviewed above. Finally, the laterality of the focus in epileptic populations without psychoses are variable, depending on the series. For example, in the extensive series of Juul-Jensen (1964), where laterality could be established it was left sided in 52%. In the series of Gibbs (1952) the focus of psychomotor seizures was left in 35% right

36%, and bilateral 29%. Currie et al (1971) give a figure of 60% left and 40% right.

Explanations for the development of the schizophrenia-like psychoses in epilepsy therefore need to take into account age of onset of epilepsy, the site of the underlying pathology, the length of time between the onset of epilepsy and the onset of the psychosis, and maximum disturbance of function in the dominant hemisphere. Some authors (Taylor 1975) have postulated that the disorganised left hemisphere leads to a susceptibility to develop abnormalities of symbolic language, especially if the disturbance is present during the time of language development and when emotional bonding to peers and parents is paramount. Taylor (1977) puts it succinctly:

> "Supposing there were, in the developing brain, a lesion which provoked epilepsy but which was not gross enough to produce a major reorganization of developmental strategy in the brain. Such a lesion would, in youth, not necessarily produce serious consequences while the language system was extensively deployed through the hemisphere, though it may create some diffusion of language organization. As the normal contraction and condensation of language proceeds, however, the disruption created by the lesion may increase quite markedly and suddenly" (p36).

Or, as he also said (Taylor 1975):

> "It is scarcely surprising that schizophrenic symptoms should exist in the presence of dysfunction, throughout early development, in those territories critical for speech and integration" (p253)

There is indeed evidence that patients with temporal lobe epilepsy show language disturbances (Hermann and Wyler 1988) and that some of the memory deficits associated with epilepsy may represent anomic problems (Mayeux et al 1980).

The studies reported in this thesis and reviewed in the introduction suggest an association between schizophrenia-like disturbance and temporal lobe epilepsy raising the issue as to whether this model for schizophrenia with positive symptoms differs from some forms of schizophrenia in the absence of epilepsy by not having associated frontal lobe abnormalities. There is absence of symptoms and signs associated with frontal lobe dysfunction as seen in more chronic forms of schizophrenia with personality deterioration. Frontal lobe function in patients with epilepsy has been poorly investigated, but in schizophrenia in the absence of epilepsy there is now considerable evidence from EEG, neuropsychological, and radiological structural and functional studies that the frontal lobes are involved at least in a significant percentage of patients (For review seem Trimble 1988). Studies of frontal lobe function in the schizophrenia-like psychoses of epilepsy, using more sophisticated neuropsychology and radiological investigations with PET and SPET should be rewarding in testing such an hypothesis.

Psychoses can develop after temporal lobectomy (Trimble 1992). This provides support for the idea that the cerebral disorganization underlying the psychoses is not totally related to the anterior temporo-limbic area, but must represent more widespread limbic dysfunction. Two mechanisms that have been suggested relate to alterations of amine metabolism, and kindling.

Lamprecht (1973) and Trimble (1977) have emphasised the anti-thetical relationship between dopamine and schizophrenia, dopamine agonism tending to be psychotogenic but also having anticonvulsant properties, dopamine antagonism provoking seizures but being antipsychotic. This mechanism may play a role in chronically developing psychoses, gradual increasing dopamine activity explaining the disappearance of seizures in some patients. The only data that relate to this in the psychoses of epilepsy are those of Peters (1979) who noted low CSF HVA which might suggest up-regulation of post synaptic receptors, and the recent PET study of Sherwin and Colleagues (Dyve et al 1989). The later investigation quantitatively assessed dopa decarboxalase activity in epileptic patients with a left unilateral mesial temporal epileptic focus using radioactively labelled fluoro dopa. The amygdala and hippocampus showed significant increased in dopa decarboxylase activity, suggesting enhanced dopamine turnover.

Kindling, while being an experimental model for epilepsy may have clinical relevance beyond epilepsy, (Bolwig and Trimble 1989). Kindling is most easily elicited from medial-temporal limbic structures, for example the amygdala, but when forebrain areas are experimentally kindled, particularly catecholaminergic regions, disturbances of behaviour rather than seizures are elicited (Stevens and Livermore 1978). There is experimental animal data showing that following kindling of the amygdala, meso-limbic dopaminergic sensitivity increases, and there are increased D2 receptor densities in the nucleus accumbens (Csernansky et al 1988). The suggestion is that ongoing subictal activity in medial temporal structures may thus kindly down stream limbic nuclei altering their neuromodulator function and, with regards to dopamine, increasing activity and hence the liability to psychosis. It is difficult to ignore the growing literature on the neurochemistry of schizophrenia in which the same dopamine-rich limbic forebrain areas are thought to be related, at least in part, to the development of the psychoses (for review see Trimble 1988).

The evidence that kindling is an important mechanism for the development of the psychoses of epilepsy is however conjectural. Although there are cases of kindling recognised in humans (for review see Bolwing and Trimble 1989), they are rare. The main argument against kindling relates to the follow-up

studies of patients with epilepsy and psychosis. Slater and Glithero (I963b) commented that "the excellent epileptic result was accompanied by a favourable development in the psychosis". In another recent follow-up study, Kenwood and Betts (I988) presented data on a group of hospitalized psychotic epileptic patients followed-up for twenty years. Again, there was a relationship between improvement of seizures and a diminution of the psychoses. In contrast, Feinstein and Ron (I990) followed up 65 psychotic patients with unequivocal evidence of brain pathology, 37 of whom suffered from seizures. Patients with epilepsy were more likely to have psychotic relapses and to receive psychiatric care than those without epilepsy, and the occurrence of the psychotic relapse did not seem to be related to the extent of the seizure control. Further exploration of the kindling hypothesis, especially with regards to dopamine function is now possible with both PET and SPET using new dopamine, ligands, and would be rewarding.

Positive and Negative Symptoms

Hughlings Jackson (1875) elegantly discussed the relationship between cerebral lesions and symptoms. His introduction of the terms positive and negative symptoms has recently been reviewed in neuropsychiatry, although often without an understanding of the mechanism behind this theory (Trimble I986). Although Hughlings Jackson explicitly adopted psychophysical parallelism in his understanding of mind brain-interactions, in explaining his

concept of positive and negative symptoms, he frequently discusses "mental" changes. Before integrating some of his ideas into an understanding of the epileptic psychoses, it is germane to turn to the writing of Jaspers (I922). He developed a descriptive psychopathology and made certain fundamental distinctions, notably between understanding and explanation, or what is meaningful and what is causal. Essentially, casual connections are directly related to the somatic realm and are deduced by the methods of the natural sciences. However, phenomenology demands both explanation and understanding and draws a distinction between form and content. The interpretations of epileptic psychoses have been variously those which depend upon understanding (people who have sudden repeated loss of consciousness and thus are in danger, who are unable to get an occupation, and who are unpopular amongst their peers will become paranoid), and explanation (disturbance in the temporal lobes at a certain point in life leads to the development of phenomena which are beyond the nature of meaningful connections. The latter changes may be seen as a consequence of process rather than development, the process being linked with that which, at various times, provokes epileptic seizures).

Jaspers himself was pessimistic about neurological localisation in relationship to psychic entities, and while Hughlings Jackson ostensibly took the same

phenomenological by acknowledging the presence of a disrupting focus in one or other of the temporal lobes, particularly during crucial phases of development. This leads to the development of negative symptoms, perhaps in the form of memory deficits, or loss of insight, but also to positive symptoms, ultimately with delusions and hallucinations. The latter for their presence are dependent upon cortical and sub-cortical areas removed from the site of the abnormal focus. The concept of "reaction" here is also important. Thus, the reaction of the brain to various exogenous insults and endogenous aberrations, which might include a pathological lesion that may lead to a seizure, will lead to a skewing of the relationship of other areas of brain in relationship to that focus of change, and ultimately towards their function in relationship to environmental events. Such reaction will differ from individual to individual, again reflected by Jackson who, in his four factors in insanities (Jackson 1984) discussed not only the different depths and rates of dissolution, but also:

> "Different persons who have undergone that dissolution ... different local bodily states and different external circumstances of the persons who have undergone that dissolution" (p415).

Stevens (1988) has developed a biochemical variant of this view, hinted at earlier by Landolt's concepts of the development of forced normalization, suggesting increase reactivity of some parts of the brain to loci of dysfunction. She notes that "microseizures" not uncommonly arise within the brain during

position, he actually wrote a considerable amount about "mental" activity and its relationship to brain disorder. He did not believe in the strict concept of cerebral localisation, and his theories of brain action depended on several features, especially positive and negative phenomena, and the concept of dissolution. Destruction of tissue would result in negative symptoms, but release of subjacent activity from other healthy areas of the brain would lead to positive symptoms. He noted that in all cases of insanity the principal of dissolution, the level of evolution that remained and the positive and negative symptoms needed to be considered.

In discussing post-epileptic mania he referred to the negative and positive element. The negative element is related to loss of consciousness, while dissolution leaves the activity of other "nervous arrangements" to "spring into activity", and hence the development of the mania. Although this model applied to ictal events (Jackson 1880-81) he also applied it to cases of insanity in other settings. For example:

> "Illusions, delusions, extravagant conduct, and abnormal emotional states in an insane person signify evolution, not dissolution; they signify evolution going on in what remains intact of the mutilated highest centres - in what disease affecting so much dissolution, has spared" (Jackson 1894).

The negative mental state could be slight, while the positive one elaborate. With regards to epileptic psychosis it is possible to unite the biological and

normal brain function, and in order to prevent spread of these microseizures, inhibitory circuits must have developed in surrounding areas. These would involve inhibitory neurotransmitters such as GABA, dopamine and noradrenaline. Increased inhibition of physiological microseizures, indeed the development of microseizures at times or in situations when they are not physiologically required, could lead to an enhanced inhibitory surround ("reaction") in limbic areas, such reaction being related to the development of the psychosis.

Stimulation of limbic system structures, notably the hippocampus and amygdala, leads to experiential phenomena (Gloor et al 1982), essentially positive phenomena. Gloor (1989), based on data obtained from stimulation studies, noted that it is illogical to assume that reproduction of experiences known to be dependent on the anatomical and functional integrity of medial temporal structures should arise as a consequence of their inactivation. He suggested that experiential phenomena are positive expressions of the activity of neurones involved in or affected by epileptic discharges. He based his arguments on the concept of a distributive matrix of excitation and inhibition which related to the neuronal representation of experiences, and how activation at one point within a network can recreate a whole pattern. Thus, limited discharge in a group of neurones in medial temporal structures may

lead to the recreation of experiences dependent on widely distributed matrixes. In the setting of a seizure, when neuronal activity becomes very disturbed, loss of consciousness will occur and the positive phenomena will be obliterated. Using this model however, it is possible to see how recurrent abnormal function in these structures, which may possibly be recorded interictally as abnormal electrical activity when electrodes are in the right place and represented by hypometabolism PET studies, could also lead to a "kindling" of long lasting emotional and behavioural changes. The emphasis here is on the development of symptoms, possible syndromes and not of disease. In this context, the development of chronic interictal psychoses following bouts of paroxysmal peri-ictal psychoses, seen and recorded in several patients (eg, Slater and Beard 1963) must be relevant.

The results presented here suggesting that first rank symptoms may be specially linked to temporal-limbic dysfunction are of interest. Thus, Schneider himself referred to first rank symptoms as "grouped together under the concept of permeability of the barrier between the individual and his environment ..." Anatomically the medial temporal structures, especially the hippocampus and parahippocampal gyrus may be seen as the correlates providing such permeability.

Using such models, the development of the schizophrenia-like psychoses of epilepsy, with their association to the left side of the brain, using the developmental models of Taylor become more plausible. Possibly similar mechanisms may relate to affective disturbances and the right temporal lobe, although findings in this area are far more restricted, and theoretical mechanisms less clearly developed. Further, non-NS seems to have differing associations compared with NS, emphasising the importance of precision when defining clinical pictures, and not assuming all psychoses fall under the same umbrella.

An important issue is why do only a certain percentage of patients with temporal lobe discharges develop psychoses? A possible explanation rests with the pathological data. Scheibel (l990) has drawn attention to the similarities of both schizophrenia and temporal lobe epilepsy, especially from pathological studies. He noted that in both syndromes the hippocampus is the main site of structural change with loss of neurones in MTS and disarray of pyramidal cells in the hippocampus of brains from schizophrenics. He concludes, in comparing temporal lobe epilepsy and schizophrenia:

> "The schizophrenic syndrome is considered here, not necessarily as a closely-related disease process, but rather as an example of another, long-term incapacitating syndrome apparently related to limbic lobe dysfunction".

Thus, in schizophrenia, the most prominent changes are pyramidal cell

disarray at interface zones, namely between proscibiculum and CA1, CA1 & CA2 and at CA3 and CA4. If the study of Jeste and Lohr is replicated the major changes in schizophrenia are found in CA3 and CA4 and CA1 is relatively unaffected. The pathology of temporal lobe epilepsy is variable. Lesions such as hamartomas occur more frequently in the amygdala, while in MTS it is the CA1 region of hippocampus that is most involved (Margerison and Corsellis 1966). It may be that patients with temporal lobe epilepsy, with sparing of the CA1 and dentate gyrus, but who have cell loss and gliosis, or some other pathological change in CA3 and CA4 will be the patients with maximum vulnerability to the psychosis.

The predominant links of CA3 and CA4 are to the septum and the opposite hippocampus, while CA1 and CA2 have different afferent connections. The role of the septum in psychotic states has been discussed above. In this context, it is of interest that a distinguishing feature of patients with endfolium pathology in the series of Margerison and Corsellis (1966) was age of onset of seizures being similar to that recorded in psychotic groups by others. However, in the study of Dam (1980) there was no association between the site of pathology in patients with epilepsy and the presence of psychosis, inspite of CA4 being the area maximally affected by MTS.

Finally, the more obvious involvement of the parahippocampal gyrus in studies of schizophrenia suggests another possible difference that may underlie the pathology of the two syndromes. The parahippocampal gyrus has received little attention in the studies of the pathology of epilepsy.

In summary, attempts to understand the development of the epileptic psychoses, particularly schizophrenia-like psychoses, in epilepsy requires a willingness to go beyond direct localizationist views of neurological processes and permit some attempt to blend both psychic and somatic levels of explanation.

The suggestion that temporal lobe epilepsy is a good biological model of the development of positive symptoms in neuropsychiatry has been made, and an understanding of this could be further developed through the phenomenological methodology of Jaspers, and ideas of Hughlings Jackson. Future research on the abnormalities of function and structure of the brains of patients with epilepsy and psychoses, whether derived from neuropathological, electrophysiological or radiological studies as reported here will lead to better understanding of the fascinating connection between the brain and the mind.

SECTION 7:

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REFERENCES

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