CHAPTER 7

SCHIZOPHRENIA

Schizophrenia a serious mental disorder which affects 1% of the population. With peak onset at 18-25 years, schizophrenia causes loss of productivity and high medical and social services costs. The suffering of patients with schizophrenia and their families is usually great. Some fortunate individuals manage relatively uninterrupted lives. However, sustained recovery maintained 5 years after the initial episode is only 14% (Robinson et al, 2004).

The term 'schizophrenia' is considered unsatisfactory by many – it describes not a single disorder but a 'heterogeneous syndrome' – it can be used to describe groups of patients which have few symptoms in common (Henderson and Malhi, 2014). It is likely this name will change in the life of the reader.

Schizophrenia is diagnosed (at the moment) by the presence of hallucinations, delusions and formal thought disorder. This is like diagnosing heart disease only at the time of myocardial infarction. Recently, schizophrenia has been conceptualized in four phases. 1) Risk phase – this mainly includes genetic, intrauterine (infection) and obstetric risks, although other risks may occur later in life, such as cannabis abuse. 2) Prodromal stage – which may include social isolation, reduced performance in school or work and odd (but not psychotic) thinking. 3) Psychotic phase. 4) Chronic disability phase – this may include some psychotic symptoms, but "negative" symptoms (loss of drive and emotion, for example) are prominent.

By the time hallucinations and delusions appear, brain changes have occurred; early detection and prevention has become an area of research interest (Insel, 2010).

In 1893, Emile Kraepelin (German) drew a distinction between "manic depressive insanity" (bipolar disorder) and "dementia praecox" (meaning dementia of the young; now called schizophrenia).

In the early 20th century Eugene Bleuler (Swiss) coined the term schizophrenia (split mind). (He was **not** referring to "split personality" in which an individual is said to have two or more complete but separate personalities.) He was referring to the separation, or splitting, of various mental functions, such as the emotions and drive being disconnected from the thoughts. Bleuler believed that formal thought disorder (FTD) in which the patient slips off one track of thought onto another is the primary/defining feature of schizophrenia, rather than the more obvious positive symptoms of hallucinations and delusions.

Symptom clusters

The psychosis episodes and disability of schizophrenia manifest a range of symptoms - and different authors have sorted them into different groups.

An early categorization divided the symptoms into two groups: "positive" and "negative" (Andreasen et al, 1982).

The **positive symptoms** (phenomena which are in addition to normal experience), are the remarkable features of the acute/psychotic phase, that is, hallucinations, delusions and FTD. These may also be present during the chronic phase, but with the passage of time they usually decrease or at least have less impact on the patient's life.

The **negative symptoms** (Andreasen et al, 1982; loss of personality features and abilities) are the most troublesome symptoms of the chronic phase of schizophrenia. The DSM-5 sub-classification is as follows: 1) Affect impairment (flattening or blunting) - diminished emotional expression, with reduced expression of emotion in the face, speech and bodily movements, 2) Anhedonia - reduced ability to experience pleasure, reduced interpersonal skills, 3) Asociality – apparent lack of interest in social interaction, 4) Avolition (apathy) - reduced self-initiated purposeful activities, 5) Alogia – diminished speech output (this is another view of poverty of speech, discussed in Chapter 6). These are discussed in detail below. While the negative symptoms are regarded as the predominant feature of the chronic phase, they may be detected as early as the first psychotic episode.

Some researchers found that certain symptoms did not easily fit into the two category model, and developed a **three category/factor model** (Bilder et al, 1985). Along with the positive and negative symptom groups, a third group was designated "**disorganisation**" - this included some thought disorder, bizarre behaviour, impaired attention and some cognitive dysfunction.

A range of other ways of grouping the symptoms of schizophrenia have been suggested, but will not be described.

Medical students only require knowledge of the positive/negative symptom division; those wanting to do exceptionally well in psychiatry should be aware the third set of disorganized symptoms/cognitive dysfunction.

Symptoms (Psychotic/acute)

Hallucinations
See Chapter 5.

Delusions
See Chapter 4.

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Illustration. These items were kept by a young man with schizophrenia. He was socially isolated and secretive and brought to hospital by his parents. He initially denied all symptoms. His parents explained that he had written "Cursing Jar For Good" on the lid of this jar, and had written multiple "curses" concerning "enemies" which he placed inside. These "curses" all began, "I cast…" (as when magical folk 'cast spells'). His parents told that he behaved as if these curses were a serious matter, and he expected them to be effective.

While not proof, this activity was highly suggestive of psychosis. The idea of a "cursing jar" appeared to have come from the fashion of maintaining a "cussing jar" in work-places and pubs, into which people were obligated to place money if they "cussed" (cursed/swore) – at intervals the contents to be donated to charity or similar "good" cause. The evidence suggested the patient believed he could cast spells or curses on other people (delusion). This was not appropriate in his culture and suggested a delusion. "For Good" may refer to a permanent arrangement, or it may refer to the Good-versus-Evil dichotomy. There is a suggestion of FTD.

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Illustration. A well groomed young man (clothes in the background) was brought to hospital. He had been backpacking around Australia. He was suspicious and lacked insight. When staff unpacked his belongings, they found a bag of human faeces. When he recovered, the patient explained he had believed his faeces contained gold dust, which he had intended to extract.

The delusions described above are spectacular – the majority are far less so.

Form of thought – Formal Thought Disorder (FTD)
See Chapter 6.
As mentioned above, derailment, incoherence and neologisms are ranked with the positive symptoms, while poverty of thought is ranked with the negative symptoms.

Symptoms (Negative/chronic)

The symptoms mentioned in DSM-5 will be discussed first.

Affect
The term 'affect' has been used in different ways. It was once used synonymously with the term mood. Accordingly, the mood disorders of current times [depression/mania] are still sometimes referred to as "affective" disorders, but this is not recommended.

In examination of the mental state, the term affect refers to "the external manifestation of the internal feeling state". It is said that affect is to mood as weather is to climate, introducing the notion of immediacy and brevity.

We expect the internal feelings of healthy individuals to change somewhat in response to changes in topic, and we expect to observe some external changes: a smile perhaps, at the mention of children, a frown perhaps, when discussing a deceased parent. In our interactions with others we expect some "emotional contact", interest or personal warmth. We expect some animation, some facial, hand and body movements, some variation in tone of vice and speed of speech, or some sign of vigour or energy, during discussion of different topics.

People with schizophrenia may have "blunted", "flat" or "restricted" affect. These terms mean much the same. Such patients tend to have relatively immobile face, limbs and trunk, with little change in speed of speaking or pitch of voice, irrespective of the topic of conversation. There appears to be reduced interest and personal warmth.

It is assumed from these external manifestations that the internal feeling do not vary in the usual manner. This is a fair assumption, particularly in view of the fact that many people with flat affect also complain of lacking the ability to feel emotions. See the section on anhedonia.

A less common symptom is "inappropriate" affect. This occurs when an individual is thinking/talking on a subject, but displaying inappropriate feelings. For example, a patient talking of the death of a much loved relative may laugh uncontrollably.

Anhedonia
Anhedonia is the inability to experience pleasure. It is observed in various types of depressive disorder and schizophrenia. Clinically, a distinction should be made between the absence of pleasure and sadness (low mood). The anhedonia of depressive disorders usually responds to antidepressant treatment. The anhedonia of schizophrenia does not respond to antidepressant treatment [unless, of course, it is a feature of a concurrent depressive disorder].

Patients may complain that the things or activities which once gave them pleasure no longer do so, or that they simply no longer bother with them.

Humans have close emotional bonds with family members. Parents and grandparents, for example, usually "brighten up" at the mention of their children and grandchildren. People with anhedonia may not "brighten up" to the usual degree. However, some degree of learned, automatic response is usually retained. Some insightful people with schizophrenia may be aware that they no longer feel as warm and loving toward their family members, and complain of this loss. We see here, that affect and anhedonia are interrelated.

Avolition
Avolition refers to a lack of drive or motivation, which is common in chronic schizophrenia. It may pervade all aspects of life from studying and working to house-keeping and personal hygiene. People who have lost skills, social contacts, and meaningful activities may be helped to regain some function. However, rehabilitation success is proportional to participation, and when motivation is low, rehabilitation success is limited.

Asociality (social withdrawal and isolation)
People with schizophrenia may avoid social contact and live isolated lives. Again, it is difficult to know whether this is simply an expression and loss of affect, anhedonia and loss of drive. There is certainly some loss of "Theory of Mind" (Chapter 33), which means a loss of the ability to understand what other people know and how they are likely to respond.

Alogia
'Alogia' [without words] - another term for poverty of thought (Chapter 6).

Self-neglect
Self-neglect is not a DSM-5 sub-category – but it is a useful concept. People with schizophrenia may not clean themselves or their clothes regularly. They may not groom their hair or beard in the usual manner. They may not eat at the usual times and may not eat a healthy diet. They may not sustain satisfactory housing. People with schizophrenia feature prominently among the ranks of the homeless, known in Australia as "derelicts", and in the USA as "bums" or "hobos".

Whether self neglect is a separate entity or the result of others, such anhedonia and avolition, is unclear. Disorder of the form and content of thought can contribute to neglect.

Illustration. This man with chronic schizophrenia had his left arm broken in an altercation with police. Conservative treatment (use of a sling) was recommended and he was maintained in hospital. However, he would not rest his arm and kept removing the sling. He would not agree to surgical treatment. He understood that his arm was broken, but he had severe disorder of the form, and some disorder of the content of thought. Thus, his inability to co-operate with the treatment of his arm was underpinned by many symptoms of schizophrenia. Eventually he developed a painless "false joint". His level of function was further reduced by this abnormality. In the picture on the left, he is seen from the side and no abnormality is apparent. On the right, he is facing the camera and lifting his arm sideways. His arm is bending at the false joint, above his elbow.

The interaction of negative symptoms
There is difficulty deciding the boundaries of the various negative symptoms.

For decades, it has been speculated lack of the ability to feel emotions (reflected in flat affect) could reduce the experience of "rewards". Reduced experience of rewards could directly reduce motivation and drive. Reduced motivation and drive could be expected to lead to self-neglect and social isolation. Further, if one is not engaging company (with an unresponsive immobile face - flat affect) and lacks good hygiene one will not be sought out by others, and any primary tendency to social withdrawal and isolation will be compounded. Low income (due to lack of drive or poverty of thought) will encourage homelessness, and so on.

A recent paper by Lee et al (2015) supports the interconnectedness of anhedonia and avolition. They find that people with these symptoms have the ability to experience "consummatory pleasure" – the ability to 'like' what they are consuming. However, they lack the ability to experience "anticipatory pleasure" – the ability to 'want' to consume something. The authors speculate that part of the learning process has been damaged, and suggest a neurological basis which involves pleasure centres.

Illustration. An man living on the streets. It is not known that this man suffers a mental disorder. However, his self-neglect suggests, chronic psychopathology.

Cognitive dysfunction

Cognitive dysfunction can sometimes be detected before the first psychotic episode and persists throughout the course of the disorder. However, these are not the dramatic deficits seen in dementia, such as the inability to remember whether or not one has eaten breakfast. These are subtle. Their detection is difficult in the presence of disorder of the form of thought (which is itself evidence of cognitive dysfunction), as one may be unsure whether the patient understands questions and what is meant by his/her answers.

Cognitive dysfunction can be detected in 60-78% of people with schizophrenia (Goldberg et al, 1988). More recently, cognitive dysfunction has been proposed as the central feature of schizophrenia (Insel, 2010), which means it is present in all cases.

(In the early 20th century, Bleuler emphasised the centrality of disturbance of "associations" – by which he meant much the same as cognitive dysfunction.)

While dysfunction may occur in every aspect of cognition in schizophrenia [IQ, memory, language, executive functions, and attention (Fioravanti et al, 2005)], dysfunction of working memory (executive functions) may be the core deficit. Working memory allows us to hold particular information for a short time while we consider problems and decide on a course of action (when asked to list all the birds we can think of, one needs to remember the task and sort through chairs, telephones and things which are not birds, without saying them, but remembering to say sparrows and eagles, as they come to mind). Working memory dysfunction may underpin many symptoms of schizophrenia, most obviously impaired goal directed and bizarre behaviour.

Disorganized/chaotic behaviour

When attempting to understand the behaviour of the individual we attempt to identify the possible underpinning components (e.g., thought form and content, history, circumstances). However, at times we cannot be any more precise than describe the behaviour as disorganized/chaotic.

Illustration. A young woman with schizoaffective disorder brought this object along and gave it to the author. It is a shop mannequin head, of the type used to display hats or jewellery. The irises have been painted red (a colour which does not occur in

nature). On the top of the head is a bowl containing a chocolate pudding. The patient was preparing the chocolate pudding and it was not turning out as planned. It was then placed on the mannequin's head. This may have been an act or anger or frustration. It is not understood why the patient (some days later, when the pudding had solidified) gave this object to the author. The patient was never able to give a clear account. Such events sometimes cannot be described with more precision and are designated disorganized/chaotic behaviour.

Catatonia

The catatonic symptoms occur in several disorders in addition to schizophrenia (including bipolar and depressive disorders).

When they appear in schizophrenia, they are difficult to classify using positive/negative dichotomy.

Voluntary actions may be conceptualized as the "out-put" of will, and some consider catatonic signs arise from a disturbance of will.

DSM-5 states "The essential feature of catatonia is a marked psychomotor disturbance that may involve decreased motor activity, decreased engagement during interview or physical examination, or excessive and peculiar motor activity".

Mild catatonic signs include odd postures of parts of the body and awkward, ungraceful movements. More marked signs include mutism and immobilization of the whole patient in a fixed posture. The term stupor is ill defined, but is best reserved for instances in which there is both mutism and immobilization of the whole patient.

The immobile patient may resist his/her arms and legs being moved by other people. On the other hand, the immobile patient may passively allow their limbs to be moved, and may then hold his/her limbs where they have been placed (sometimes for hours). This is termed "waxy flexibility".

Other puzzling symptoms include 'negativism' in which the actions are the opposite of what might be expected – a patient may extend his/her hand to the doctor (as when shaking hands), but when the doctor extends his/hers in response, the patient withdraws the initially offered hand. There may be grimacing, echolalia (mimicking what is said by another) and echopraxia (mimicking the movements of another).

Such signs are less frequently encountered in current times, at least at the primary presentation. However, odd postures and echopraxia and can often be detected on close examination. Why the florid form of catatonia is no longer encountered is difficult to explain, it may be because treatment is now readily available.

Depression and anxiety

People with schizophrenia frequently report feelings of depression and anxiety. This does not mean they have the full criteria for a depressive or anxiety disorder, and

often, dysphoria (generalized feeling of anxiety, restlessness and depression) may be a more appropriate term.

People can, of course, develop full depressive and anxiety disorders in addition to schizophrenia. Becoming aware that one has developed a psychotic illness is naturally distressing. However, some evidence indicates that dysphoria is an integral, rather than a secondary, feature of schizophrenia.

Neurochemistry

The molecular basis of schizophrenia is yet to be determined. The **"dopamine hypothesis"** posits excessive dopamine release (Howes and Murray, 2013). This is based on the facts that the antipsychotic drugs block dopamine receptors, and that amphetamine, which increases the release of dopamine, can trigger psychosis.

Dopamine neurons from the ventral tegmental region release dopamine at the ventral stiatal region (nucleus accumbens) and regions connected to the limbic system (hippocampus, amygdala, thalamus and parts of the prefrontal cortex). The pleasure centres are activated by dopamine. Reductions in dopamine have been correlated with negative symptoms.

There is evidence suggesting some symptoms are due to altered excitatory-inhibitory balance in the prefrontal lobes (Insel, 2010).

[Excess detail: A role of **serotonin** is suggested, based on the facts that the atypical antipsychotics have a high affinity for 5-HT 2A receptors, and that LSD, which is a serotonin agonist, induces hallucination and may trigger psychosis. A role for **glutamate** is suggested as phencyclidine and other antagonists of the NMDA subtype glutamate receptors can trigger psychosis. Further, excessive release of glutamate, an excitatory neurotransmitter, is neurotoxic (which could help to explain disease progression). MRI spectroscopy has demonstrated decreased N-acetylaspartate (NAA) in the temporal lobes of people with schizophrenia (Abbott and Bustillo, 2006) and these authors suggest this may be the result of excessive glutamate activity.]

Histology

Histological studies have demonstrated that cortical (pyramidal) cells of the hippocampal and dorsolateral prefrontal regions and the cerebellum tend to be smaller than normal and more densely packed. There is evidence of a reduction of synapses and dendrites in the hippocampal and prefrontal cortices. Thus, loss of neuropil appears to explain why the neurones are more densely packed (Harrison, 1999).

There is disorganization of the cellular patterns (dysplasia) in certain regions of the cortex, indicating that some neurones have not reached their expected position (Kovelman & Scheibel, 1984).

There is no evidence of gliosis – this has been interpreted as meaning immunological factors are not of etiological importance – however, this interpretation is probably

incorrect – an imbalance of inflammatory cytokines has been demonstrated and is a likely etiological factor (Altamura et al, 2013) – see later.

Recently, there may have been an important discovery. Chondroitin sulphate proteoglycans (CSPG) has been shown to be massively increased in the extracellular matrix of the nuclei of the amygdala and layer II of the entorhinal cortex of people with schizophrenia (Pantazopoulos et al, 2010, 2013). These results point to a substantial, specific abnormality in CSPG expression by astrocytes. In a more recent study the same authors (Pantazopoulos et al, 2015) demonstrated abnormalities of particular CSPG components in the amygdala of people with schizophrenia, and to a lesser extent, bipolar disorder.

Neuroimaging

In normal development, changes in cortex (grey matter) and myelination (white matter) continue into the mid-20s. Later developments including the removal of redundant synapses (synaptic pruning) which improves the efficiency of connections between regions.

The first structural imaging finding in schizophrenia was enlargement of the lateral ventricles (Johnstone et al, 1976). A meta-analysis and reported a 2.7% increase in ventricle size compared to healthy controls (Steen et al, 2006). This is a group/statistical finding and is not diagnostically useful in individual cases.

Progressive grey matter volume loss is associated with the development of negative symptoms (McKechanie et al, 2015) – most clearly in the left temporal lobe, left cerebellum, left posterior cingulate, and left inferior parietal sulcus.

White matter pathology has been demonstrated in recent onset schizophrenia (Rigucci et al, 2015) – most clearly in the corpus callosum, left inferior and superior fronto-occcipital fasciculus, forceps, thalamic radiations and cingulum bundle.

A study of great interest demonstrated increased blood oxygen level-dependent [BOLD] signal in **Heschl's gyrus (auditory area of the dominant temporal lobe)** of people experiencing **hallucinations** (Dierks et al, 1999).

With respect to **hallucinations**, disruption of white matter tracts connecting the left frontal lobe to temporal regions has been demonstrated (Curcic-Blake et al, 2013).

In Chapter 5 '**Hallucinations'** the work of Whitford et al (2014) is reported – where interested readers will find more details. Using tractography in schizophrenia, researchers identified two regions of abnormal construction in the 'cingulum bundle' , one associated with positive symptoms and another associated with negative symptoms.

The severity of **thought disorder** has been correlated with **the grey matter volume** of left superior temporal gyrus, left temporal pole, the right middle orbital gyrus and the right cuneus/lingual gyrus (Horn et al, 2010).

In Chapter 6 **'Form of Thought'** the work Kuhn et al (2012) is reported – where the interested reader will find more details. These researchers used special scanning techniques to examine the cerebellum and demonstrated a correlation of 'form of thought disorder' and grey matter deficits in the left Crus I and II (also known as superior and inferior semilunar lobules) of that structure.

[The superior temporal gyrus appears to be involved in both formal thought disorder and hallucinations.]

Neurodevelopmental model of schizophrenia

Various factors support the view that schizophrenia is a neurodevelopmental disorder, and is on a spectrum with intellectual disability, autism, ADHD, and bipolar disorder.

These factors include that schizophrenia displays progressive brain tissue loss, and shares genetic features with some of those disorders.

Cognitive deficit is common to all these disorders - greatest in intellectual disability and least in bipolar disorder (Owen, et al, 2011).

The key variables in the neurodevelopmental disorders are the number and nature of neuronal circuits disrupted (which determine the syndrome) and the severity of disruption (which determines the severity of the syndrome).

With respect to schizophrenia, the failure of some cells to reach their expected position suggests a neuronal migration problem during the middle stage of intrauterine life (Bloom, 1993) or the perinatal period, and has been termed an "early neurodevelopmental" change.

The changes which continue beyond the point of diagnosis have been termed "late neurodevelopment" changes. These include reduced cell size and reduced neuropil (Glantz et al, 2006).

Schizophrenia as a disconnection syndrome

Studies have identified many brain abnormalities in schizophrenia, but replication is sometimes not achieved. One possible explanation is that schizophrenia is heterogenous disorder, with each patient manifesting a unique constellation of lesions/symptoms. One approach now being pursued is the study of patients selected according to symptoms (such as hallucinations, for example) rather than the broad diagnosis of schizophrenia.

The disconnection syndrome model of schizophrenia may bring together the clinical and neurobiological findings (Weinberger, 1987). The notion is that schizophrenia is not located at any one brain region, but occurs as a result of faulty communication between various brain regions, disturbing a wide range of functions.

White tract lesions listed under 'Neuroimaging' support this concept.

Genetics of schizophrenia

The lifetime risk for schizophrenia in the general population is around 1%. The risk of for first degree of an individual with schizophrenia is around 12%. The risk for the dizygotic twin (non-identical) of an individual with schizophrenia is around 16%. (That the risk is greater for dizygotic twins is greater than that for siblings, suggests the importance of the intrauterine experience.) The risk of schizophrenia for monozygotic (identical) twins is at least 3 times higher than for dizygotic twins. The heritability (the proportion of the variance in a population that can be traced to inherited factors) is around 85% (Cardno et al, 1999), which is similar to type I diabetes, and greater than coronary heart disease and breast cancer.

Simple genetic explanations for schizophrenia have been found in only a few isolated families. The vast majority of studies have identified multiple genes, and many findings have not been replicated. Slow progress has been disappointing.

In July 2014, Nature published a paper by the 'Schizophrenia Working Group of the Psychiatric Genomics Consortium' – which is most encouraging. This is a Genome-Wide Association Study (GWAS) which examined 36,989 people with schizophrenia. 108 loci of significance were identified. These loci supported existing theories and treatments, added support to emerging areas of interest, and suggested 'entirely new insights into aetiology".

An association involving the gene for dopamine receptor 2, supports the dopamine hypothesis of schizophrenia, and the current treatment by dopamine blockade. Other identified genes included many involved in glutamate neurotransmission, and voltage-gated calcium subunits (supporting another prominent etiological theory). Also, an association was identified with loci containing genes involved with acquired immunity (major histocompatibility complex (MHC), and other regions). An Editorial focusing on this breakthrough remarks on previous interest in a role for acquired immunity in schizophrenia and adds, "Surely this idea should start to be taken seriously".

Related matter - Epigenetics appears to have great potential for explaining many psychiatric disorders, including schizophrenia (Mahgoub and Menteggia, 2013)

Endophenotypes

To assist in finding the genes of schizophrenia the concept of "endophenotypes" was introduced (Gottesman & Gould, 2003). Endophenotypes are "biological markers". The plan was to deconstruct schizophrenia and use simpler clues in the task of identifying genes.

But, a decade later, we still don't have any proven endophenotypes. Four of the most promising are the P50 suppression test, smooth pursuit eye movements, soft neurological signs, and working memory.

The P50 suppression test (Adler et al, 1982) measures the EEG positive event-related response to two auditory stimuli which are separated by 500 msec. In the normal individual the amplitude of response to the second stimulus is less than the first. This suppression is less clear in many people with schizophrenia and some of their first-degree relatives. This is consistent with the theory that people with schizophrenia have defect in sensory gating.

"Smooth pursuit eye movements" (Holzman et al, 1973) are examined by having a patient watch an object move at constant velocity. Jerky movements occur in 40-80% of people with schizophrenia, 25-45% of their first-degree relatives and 10% of the general population.

Soft neurological signs (SNS; Bombin et al, 2005) are nonlocalizing neurological abnormalities which are revealed during clinical examination. The sensitivity of SNS examination depends on the particular assessment protocol and the definition of what constitutes a positive sign. Generally speaking SNS are reported in 65% of people with schizophrenia and 5% of the general population, with first degree relatives at an intermediate position.

Working memory is impaired in people with schizophrenia and to a lesser extent in their relatives. Working memory is primarily located at the dorsolateral prefrontal cortex (DLPFC). Post-mortem examination of people with schizophrenia reveal DLPFC abnormalities, and imaging studies of people with schizophrenia performing working memory tests reveal reduced activity.

Inflammation/immune etiological factors

The theory that immune reactions play a role in the etiology of schizophrenia was advanced in the mid-20th Century (Heath & Krupp, 1967). The inflammatory/immune theory then received little attention for some decades, but a surge of interest has arrived.

It will be remembered that an important genetic study has given support to this field (Schizophrenia Working Group, 2014).

Cytokines and evidence of an immune reaction in the blood, CSF and brain has been demonstrated in up to 40% of people with schizophrenia (Fillman et al, 2012). This is not in the form of the classic or florid inflammation/infection - nevertheless, immune markers have been clearly demonstrated.

Borovacanin et al (2012) looked at the blood of drug naïve people with first onset psychosis and found decreased levels of IL-17, and increased levels of IL-4 and transforming growth factor (TGF) beta.

Miller et al (2011) conducted a meta-analysis of CSF studies in schizophrenia and found significant elevation of IL-1 beta.

Arion et al (2007) studied Brocas' Area 9, and Fillman et al (2012) studied BA 46 in post mortem brains, and found various immune reaction changes, including changes in IL-6, IL-8, IL-1beta and SERPINA.

A leading theory - these changes are the long-term signature of in utero infection. Early efforts to link epidemics and later waves of schizophrenia were successful - but could not be replicated. The methodology was replaced by birth cohort studies. First trimester exposure to influenza was found to be associated with a 700% increase in schizophrenia (Brown et al, 2004).

Preclinical studies include rodents dams exposed to influenza virus and other agents which induce **maternal immune activation** (MIA). It is believed mothers' IL-6 impacts on the fetal brain, leading to cytokine changes in fetal frontal and cingulate cortices and hippocampus (Garay et al, 2012).

Other observations suggest an immune-genetic basis for schizophrenia:
- Autoimmune disease in individuals and their first degree relatives are associated with an increased risk for schizophrenia (Eaton et al, 2010). More specifically, people with schizophrenia has an increased risk of Graves' disease, psoriasis, celiac disease and type 2 diabetes and a reverse association with rheumatoid arthritis (Chen et al, 2012; Ferentinos & Dikeos, 2012);
- Limbic encephalitis has been renamed autoimmune encephalitis. In this disorder patients often present with psychiatric symptoms (hallucinations and delusions) but progress to bizarre movements, seizure and death (Dalmau et al, 2008).
- Autoimmune encephalitis is due to autoantibodies:1) Anti-N-methyl-D-aspartate (NMDA)-receptor antibodies; 2) Voltage gated potassium channel (VGKC) antibodies, 3) Anti-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor antibodies, and 4) Anti-gamma-aminobutyric acid type B (GABAB) receptor antibodies, among others.
- A small proportion of people (6.5-8%) with schizophrenia and no evidence of the physical decline associated with autoimmune encephalitis have autoimmune antibodies (Zandi et al, 2011).

In summary, evidence indicates that intra utero infection may lead to long-term changes resulting in schizophrenia. And, a small proportion of those with schizophrenia are anti-NMDA receptor antibody positive (Pollak et al, 2014).

If the centrality of infection is accepted in a proportion of those with schizophrenia, investigation of anti-inflammatory agents for use in the management of psychosis requires investigation (Chaudhry et al, 2012).

Prognosis

Prognosis in schizophrenia is complicated. Different outcome measures can be used including the likelihood of 1) relapse, 2) gaining employment, 3) a satisfactory social life, and 4) living independently.

In general terms, about one quarter of individuals have a good prognosis and are able to lead a relatively unimpaired life; rare individuals suffer a single acute episode. About half of all people with schizophrenia have a poor outcome with multiple acute admissions and severe negative symptoms which impair their ability to function socially, earn an income and even live independently. Repeated acute episodes, which may feature some aggression, sleepless nights and paranoid delusions, are difficult for relatives to tolerate and frequently lead to the patient living in other than the family home. Patients with severe negative symptoms require the constant attention from mental health professionals and live in "supported accommodation".

Prognostic indicators give some guidance, but no certainty. Good prognosis indicators include:
1. Female gender. This may be because females tend to have a later onset and therefore the personality is more fully developed and coping strategies are better established at the time of onset. Important Australian work indicates a protective role for estrogen (Kulkarni, 2009).
2. Older age of onset. See 1 above.
3. Premorbid higher intelligence and robust, resourceful personality.
4. A significant mood component as part of the clinical picture, or a relative with a mood disorder. This suggests the disorder is more like a mood disorder, and mood disorders, in general, have a better outcome.
5. Nil or minimal cognitive impairment and negative symptoms.
6. Sudden onset and rapid response to treatment.
7. Treatment early in the course of the disorder. The longer the disorder goes untreated, the poorer the prognosis (Loebel et al, 1992). Evidence indicates that acute psychosis is 'toxic', causing progressive brain damage.
8. Compliance with treatment.
9. Rejection of illegal substances

The prognosis of schizophrenia may be better now than it was 50 years ago. This may be because the disease itself has changed, or because the current biopsychosocial approach to treatment is superior to past treatment.

Management

Acute attacks of schizophrenia (certainly the first) often require acute hospital admission. In this stable environment the patient can be closely observed, investigations can be conducted to exclude intracranial pathology and other psychiatric disorders (mania, substance misuse, personality disorder), and the correct diagnosis can be confirmed.

Acute treatment reduces the risks of self harm, and may be necessary for the protection of others. Acute treatment relieves the suffering of the patient.

The ward milieu should be calm and humane. High standard nursing care is imperative for the best outcome.

The patient and family must be provided with comprehensive information about the disorder, management aims and methods, and community follow-up options – but this, in itself, is not an argument for admission.

Pharmacological intervention is mandatory, using (at least initially) an atypical antipsychotic medication (dopamine and serotonin receptor blockers) such as risperidone, olanzapine, quetiapine or aripirazole. Medication is considered in more detail in Chapter 15.

One to one talking therapy is essential. The patient needs to feel secure and to be provided with a rational explanation so as to understand and challenge symptoms. Cognitive behaviour therapy (CBT) may be commenced.

Discharge from the acute hospital may be to a rehabilitation facility or to home. Rehabilitation may take the form of social skills training, stress coping strategies, life enriching activities, and assistance toward gainful employment. There is some evidence that cognitive rehabilitation training prevents delays/prevents relapse (Tao et al, 2015).

Work with the family aims to create situations in which the patient is encouraged to be active, with a minimum of stress and interpersonal conflict.

On discharge from hospital the patient should have regular medical review. Regular contact with a community based mental health worker who can review and respond appropriately to eventualities, is highly recommended. Regular medication should continue for at least 6 months after the first acute episode. Medication is helpful in preventing relapse.

Prevention

There is strong interest in the prevention of the psychotic phase of schizophrenia. Prevention efforts at the moment focus on people who appear to be at risk of schizophrenia either because of genetic factors (being closely related to a person with schizophrenia, or because of suggestive features, such as personality change). However, there are difficulties in identifying which individuals will progress to psychosis, and the field is in its infancy.

Brief psychiatric rating scale (BPRS)

The purpose of rating scales is not to make a diagnosis, but to quantify signs and symptoms (and provide a basis of assessing severity and progress).

The BPRS (Overall & Gorman, 1962) was one of the first rating scales developed for use in people with severe psychiatric disorders. It has remained in use for 5 decades,

and is applied particularly in schizophrenia and severe mood disorder. (The 1962 version had only 16 scales, but subsequent versions add two more: Excitement and Disorientation.)

A version, modified from the original paper, appears after the references.

Case history 1

Phil Brown was 18 years of age. He was exceptionally clever at physics and mathematics and was to commence at University in a few weeks. His life was otherwise unremarkable. His mother was a science teacher; his father was a pharmacist. He enjoyed football and skateboarding. He had some male and female friends and took no illegal drugs.

Over six weeks Phil had become isolative and hostile. In the days before the following interchange, it became clear that he had a delusion about bikies threatening him, and was experiencing auditory hallucinations which he believed was the voice of Stephen Hawking. It is widely known that Stephen Hawking is an eminent physicist who has motor neuron disease and speaks with the assistance of a machine which gives his voice a metallic, robotic timbre.

Phil Brown was interviewed in a psychiatric ward by a young doctor. After introducing herself as "Grace" and stating that the interview was to gather information so that he could be helped with his difficulties, she asked,
"So, could you, please, just tell me what's been troubling you over the last couple of days?"
Phil was slow to answer. "Nothing at all…They can stay out of trouble…If they're in time."
"Sorry", Grace said. "When you say 'They', who do you mean? Who is it that can stay out of trouble?"
"Bikies." Phil was silent for ten seconds, then finished with, "Everyone really. Because of Stephen King."
"Do you mean Stephen Hawking?" Grace asked.
"Yes, Stephen King," he nodded. He paused, then continued, "He'll put the bikies in another time force if they make trouble."
"Phil, I asked, what's been troubling you over the last couple of days. Can we go back to that? What's been troubling you over the last couple of days?" Grace repeated.
"I'm going to University next month. If the bikies come, Stephen King….he can change the secret of time."

Normal thought, reflected in speech, is a string of ideas which are connected in a logical way such that the listener or reader can make sense of the message. This man demonstrated derailment, meaning his ideas slip off one thought track onto another. His derailment (or slippage) was so severe that his thinking approached incoherence. In the second phrase of his response to the question about what had been troubling him recently, Phil introduced the topic "They" and stated that this unknown group of people (presumably) would be able to stay out of trouble. He has slipped off the track of what had been troubling him, perhaps onto what may be troubling others. The

listener does not know the identity of "They", this was another indicator of derailment, but some healthy people also make such oversights.

In his next phrase, Phil spoke about being "in time", this also suggests derailment. It is known that he had been hearing the voice of Stephen Hawking, who has written many books about "time" and Phil may have derailed onto this topic. There is the impression that pieces of connecting information have been lost, which makes the message difficult to follow.

When the interviewer sought to clarify the identity of "They", she was initially told, "bikies". This was no surprise, it was known that Phil had a delusion which involved bikies. In the same response, the name of Stephen King was introduced. This man is a famous writer of science fiction, thriller and horror books. He may have been incorporated into Phil's abnormal thought content (delusion); on the other hand, as King shares a first name with Hawking, and they are both well known writers, there may simply be an abnormal thought connection (derailment) from Hawking to King. The question had been about, who was meant by "They", in Phil's response, the word "because" indicated the beginning of a new, derailed, direction.

The patient was asked whether or not he meant Hawking. He confirmed that he did, but immediately repeated the name of King, suggesting that he had immediately slipped off the Hawking track back onto the King track. He then spoke of a "time force", a phrase which does not have meaning in normal conversation. It is impossible to know the origin of this utterance without asking the patient for details. It may have had roots in either delusional thinking or abnormality of the form of thought. It may have been that Phil had a delusional system and he meant that if bikies showed up and caused trouble, Stephen Hawking would put them into another time period or parallel universe. However, the word "force" does not express that idea clearly and appears to represent another derailment. Alternatively, "time force" could have been an arrangement of words which had an idiosyncratic, private meaning to the patient.

Phil was again asked what had been troubling him in the recent past. In the last sentence of the excerpt he immediately derailed from that question and said what he would be doing in the immediate future (going to University). He went on to say, of Stephen King, "...he can change the secret of time." Again, it is difficult to be sure what he meant. While there was probably a strong delusional basis, there may also have been an abnormality of the form of thought. The aim of responding to a question is to communicate information. In this instance the listener did not know what was meant by "the secret of time", but the patient did not clarify the issue.

Phil was successfully treated with standard medication, discharged and able to commence the university year. Before the end of the semester he relapsed. He had ceased taking medication. His father said that even before he ceased taking medication, Phil had not been doing well. He had not had delusions, but he did not seem able to think clearly and his performance on assignments was below what had been expected of him, given his pre-university scholastic achievements. On this basis, on his second admission, Phil was commenced on clozapine, a highly effective medication which may have dangerous side-effects. Phil recovered remarkably and completed his university degree with excellent marks. At follow up visits his

psychiatrist was unable to detect any signs or symptoms of mental disorder. He developed no significant side-effects.

Case history 2

Roy Webster was 58 years of age and lived in a boarding house. He had never married and had no children. He had been an apprentice butcher, but he developed delusions and hallucinations and did not recover sufficiently to work again. Both his parents were alive and lived in their own unit. He had two brothers, Brian, 57 and Phillip, 55, and no sisters.

The boys had been raised in the country. Starting as children, they had been hunters, going after kangaroo, rabbits, pretty much anything that moved. When the steam trains stopped running, their father, a stream-train driver, lost his job and brought his family to the city. At the weekends they would go back to the country to go shooting. Roy had been named after Roy Rogers, an early motion picture cowboy.

He had little interest in school. With his country upbringing he was physical and tough and was good at school football. He smoked and wanted to get out to work. He was rebellious and reckless and attractive to females of the same age. He had a string of conquests in his teen years. He left school to take up his apprenticeship at 16 years of age.

Two years later he stopped going hunting at the weekends. At first the others thought he wanted to stay in the city to go carousing. But that was not the case; he was not leaving the house. He became suspicious and broke the shooters' rule – he kept his gun loaded.

He began to "talk a lot of rubbish". The family couldn't follow what he said but it became clear that he believed Roy Rogers was out to kill him. Roy believed the film star thought the patient had stolen his (the movie star's) "identity" and wanted revenge. The patient heard a voice outside his head calling him "a homosexual", "a poofter", "a queen" and "a queer". He believed this was the voice of the movie star.

The family let Roy go his own way until he stopped going to work. His boss was pleased to be able to sack him for failing to turn up, as Roy was no longer a useful worker. The family then took him to the doctor and he was put in a psychiatric hospital. He was given medication which helped with his delusions and hallucinations. But he had lost his energy and sense of fun, and he couldn't carry on a conversation any more.

Over the first ten years he had half a dozen acute attacks, when his delusions and hallucinations got worse. During these times he was sometimes angry and would raise his hand to anyone. He would be put into hospital until he settled down. Over the last twenty years, however, there had been no such attacks. Roy's florid symptoms had diminished or at least, no longer distressed him.

One brother came to take him for a drive every Saturday. Phillip came along the narrow, damp passage and knocked at Roy's door. He waited a few seconds and

knocked a second time. Knocking was a formality, Roy rarely answered the door to knocking.

"Come on, Roy, let me in, please. It's Phillip."

He gave a third, frustrated knock. There was movement on the other side of the door. Then the click of unlocking. The released door went back one centimetre from the jam. Roy never pulled the door open for his brothers. Phillip pushed it and went in.

Roy was already lying down again. His movement back was faster than his movement from his bed. The air was cigarette smoke soup. Roy was unshaven, his clothes were dirty, his fingers were brown with nicotine and he stank of body odour. You could smell him from the door.

"G'day, mate. How are you doin'?" asked Phillip.

Roy did not respond immediately. After half a minute he said, "Ahh…" It was not clear what this utterance was meant to indicate. It could have been a mumbled, shortened, "All right". It could have been the thinking time at the start of a sentence, "Ahh…Not bad, thanks". If this was it, the second part never came. Experience had taught Phillip to wait a while, but not to wait too long.

"You need to open a window, mate. Listen, have you had a shower today?"

After another silence, Roy said, "Naa…" which sounded like, and other evidence suggested, "No".

"Well listen mate, I want to take you for a drive. But you need to have a shower first."

Roy made no response to the suggestion that he take a shower. He looked past his brother.

"I need cigarettes," he said.

"OK, sure, we can get some when we go out. Where's your shower stuff?" Phillip went to the where a towel was clumped over the towel rack. It was dry and stiff. There was no sign of soap. "You need a clean towel. I'll go and see the bloke in charge. And you need some soap. I'll go and get you some. I'd take you with me, but you smell terrible."

Roy slowly put his legs over the side of the bed and let gravity drag him into the sitting position.

Roy had severe negative symptoms. He had reduced drive – this was one of the reasons he had not returned to work, it may also have underpinned his failure to clean his body and engage in activity other than lying on his bed. He had a loss of ability to experience pleasure – this underpinned his failure to engage in even passive pursuits such as listening to music or collecting stamps. He had loss of interest in others – he didn't open the door and greet his brother with any enthusiasm. He had social withdrawal – he lay on his bed day after day, he had to be approached, he made no effort to engage others.

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BRIEF PSYCHIATRIC RATING SCALE

(Overall J, Goodman D. Psychological Reports 1962; 10:799-812)

NAME   _____

RATER   _____

DATE   _____

The following words are taken from the original paper:

"The primary purpose in developing the BPRS has been the development of a highly efficient, rapid evaluation procedure for use in assessing treatment change in psychiatric patients while at the same time yielding a rather comprehensive description of major symptom characteristics."

"Raters using the scale should become thoroughly familiar with the scale definitions (presented in the original paper) after which the rating scale statements should be sufficient to provide recall of the nature and delineation of each symptom area."

"An 18-min interview is proposed: 3 min, establishing rapport; 10 min, non-directive interaction; 5 min, direct questioning".

"Raters familiar with the instrument can make the required judgements and complete the ratings in 2 to 3 min, following the interview."

"In making ratings of the degree of symptomatology – As compared with the population of patients who do have the symptom in question, what is the degree of severity of the symptom in this particular patient?"

"For evaluation patient change during treatment, the use of a 'total pathology' score which is the simple sum of the 16 scale is recommended."

BRIEF PSYCHIATRIC RATING SCALE
(Overall J, Goodman D. Psychological Reports 1962; 10:799-812)

As compared with the population of patients who do have the symptom in question, what is the degree of severity of the symptom in this particular patient?"
Draw a circle around the appropriate term. Calculate the total.

1.   SOMATIC CONCERN
Degree of concern over present bodily health. Rate the degree to which physical health is perceived as a problem by the patient, whether complaints have realistic basis or not.

0 = Not Present	1 = Very Mild	2 = Mild	3 = Moderate
4 = Moderately Severe	5 = Severe	6 = Extremely Severe	

2.   ANXIETY
Worry, fear or over-concern for present or future. Rate solely on the basis of verbal report of patient's own subjective experiences. Do not infer anxiety from physical signs or from neurotic defence mechanisms.

0 = Not Present	1 = Very Mild	2 = Mild	3 = Moderate
4 = Moderately Severe	5 = Severe	6 = Extremely Severe	

3.   *EMOTIONAL WITHDRAWAL
Deficiency in relating to the interviewer and the interview situation. Rate only degree to which the patient gives the impression of failing to be in emotional contract with other people in the interview situation.

0 = Not Present	1 = Very Mild	2 = Mild	3 = Moderate
4 = Moderately Severe	5 = Severe	6 = Extremely Severe	

4.   CONCEPTUAL DISORGANISATION
Degree to which the thought processes are confused, disconnected or disorganised. Rate on the bases of integration of the verbal products of the patient; do not rate on the basis of the patient's subjective impression of his own level of functioning.

0 = Not Present	1 = Very Mild	2 = Mild	3 = Moderate
4 = Moderately Severe	5 = Severe	6 = Extremely Severe	

5.   GUILT FEELINGS

Over-concern or remorse for past behaviour. Rate on the basis of the patient's subjective experiences of guilt as evidenced by verbal report with appropriate affect; do not infer guilt feelings from depression, anxiety or neurotic defences.

0 = Not Present	1 = Very Mild	2 = Mild	3 = Moderate
4 = Moderately Severe	5 = Severe	6 = Extremely Severe	

6.   *TENSION

Physical and motor manifestations of tension, "nervousness" and heightened activation level. Tension should be rated solely on the basis of physical Signes and motor behaviour and not on the basis of subjective experiences of tension reported by the patient.

0 = Not Present	1 = Very Mild	2 = Mild	3 = Moderate
4 = Moderately Severe	5 = Severe	6 = Extremely Severe	

7.   MANNERISMSN AND POSTURING

Unusual and unnatural motor behaviour, the type of motor behaviour which causes certain mental patients to stand out in a crowd of normal people. Rate only abnormality of movements; do not rate simple heightened motor activity here.

0 = Not Present	1 = Very Mild	2 = Mild	3 = Moderate
4 = Moderately Severe	5 = Severe	6 = Extremely Severe	

8.   GRANDIOSITY

Exaggerated self-opinion conviction of unusual ability or powers. Rate only on the basis of patient's statements about himself or self-in-relation-to-others, not on the basis of his demeanour in the interview situation.

0 = Not Present	1 = Very Mild	2 = Mild	3 = Moderate
4 = Moderately Severe	5 = Severe	6 = Extremely Severe	

9.   DEPRESSIVE MOOD

Despondency in mood, sadness, rate only degree of despondence; do not rate on the basis of inferences concerning depression based upon general retardation and somatic complaints.

0 = Not Present	1 = Very Mild	2 = Mild	3 = Moderate
4 = Moderately Severe	5 = Severe	6 = Extremely Severe	

10.   HOSTILITY

Animosity, contempt, belligerence, disdain for other people outside the interview situation. Rate solely on the basis of the verbal report of feelings and actions of the patient toward others; do not infer hostility from neurotic defences, anxiety nor somatic complaints. (Rate attitude toward interviewer under "unco-operativeness").

0 = Not Present	1 = Very Mild	2 = Mild	3 = Moderate
4 = Moderately Severe	5 = Severe	6 = Extremely Severe	

11.   SUSPICIOUSNESS

Belief, delusional or otherwise that others have now, or have had in the past, malicious or discriminatory intent toward the patient. On the basis of verbal report, rate only those suspicions which are currently held whether they concern past or present circumstances.

0 = Not Present	1 = Very Mild	2 = Mild	3 = Moderate
4 = Moderately Severe	5 = Severe	6 = Extremely Severe	

12.   HALLUCINATORY BEHAVIOUR

Perceptions without normal external stimulus correspondence. Rate only those experiences which are reported to have occurred within the last week and which are described as distinctly difference from the thought and imagery processes of normal people.

0 = Not Present	1 = Very Mild	2 = Mild	3 = Moderate
4 = Moderately Severe	5 = Severe	6 = Extremely Severe	

13.   *MOTOR RETARDATION

Reduction in energy level evidenced in slowed movements and speech, reduced body tone, decreased number of movements. Rate on the basis of observed behaviour of the patient only; do not rate on basis of patient's subjective impression of own energy level.

0 = Not Present	1 = Very Mild	2 = Mild	3 = Moderate
4 = Moderately Severe	5 = Severe	6 = Extremely Severe	

14.   *UNCO-OPERATIVENESS

Evidences of resistance, unfriendliness, resentment and lack of readiness to co-operate with the interviewer. Rate only on the basis of the patient's attitude and responses to the interviewer and the interview situation; do not rate on basis of reported resentment or unco-operativeness outside the interview situation.

0 = Not Present	1 = Very Mild	2 = Mild	3 = Moderate
4 = Moderately Severe	5 = Severe	6 = Extremely Severe	

15.   UNUSUAL THOUGHT CONTENT

Unusual, odd, strange or bizarre thought content. Rate here the degree of unusualness, not the degree or disorganisation of thought processes.

0 = Not Present	1 = Very Mild	2 = Mild	3 = Moderate
4 = Moderately Severe	5 = Severe	6 = Extremely Severe	

16.   BLUNTED AFFECT

Reduced emotional tone, apparent lack of normal feeling or involvement.

0 = Not Present	1 = Very Mild	2 = Mild	3 = Moderate
4 = Moderately Severe	5 = Severe	6 = Extremely Severe	

17.   EXCITEMENT
Heightened emotional tone, agitation, increased reactivity.

0 = Not Present	1 = Very Mild	2 = Mild	3 = Moderate
4 = Moderately Severe	5 = Severe	6 = Extremely Severe	

18.   DISORIENTATION
Confusion or lack of proper association for person, place or time.

0 = Not Present	1 = Very Mild	2 = Mild	3 = Moderate
4 = Moderately Severe	5 = Severe	6 = Extremely Severe	

SUB TOTALS	0	1	2	3	4	5	6
GRAND TOTAL							

*BASED ON OBSERVATION