1. Various attempts have been made to formally classify psychiatric disorders, the two major systems being:

    1.1. The **ICD-10 Classification of Mental and Behavioural Disorders** (World Health Organisation, Geneva) is part of the 10th edition of the International Classification of Disease. This appendix follows the common abbreviation of **ICD-10**. It is the international system used by the majority of clinical psychiatrists in Great Britain.

    1.2. The **Diagnostic and Statistical Manual of Mental Disorders (fourth edition)** (American Psychiatric Association Washington DC). References to it in this appendix follow the common abbreviation of **DSM-IV**. It is a system devised mainly by and for workers in the USA, however UK psychiatrists were consulted in its formulation.

2. The two systems above have been in existence for many years but only in their current editions have they been closely comparable.

3. This appendix discusses the clinical features and aetiology of schizophrenia, schizoaffective, delusional and acute psychotic disorders. It is generally based on the ICD-10 system with any major comparisons and distinctions with DSM-IV being discussed where relevant. The ICD-10 codes (numbers usually prefixed with F) are also provided.

SCHIZOPHRENIA

DEFINITION AND CLINICAL MANIFESTATIONS

4. Schizophrenia is characterised by a fundamental distortion of thinking, perceiving and communicating which is accompanied by an abnormal affect (observed mood state), the most common abnormality being lack of reactivity (“blunting”).

5. The disordered mental state and the individual’s reactions to it produce the subsequent highly heterogenous clinical picture with many phases (acute, resolving, residual, remitted) and a widely varying course between individuals. Most patients improve with medication but some go on to “struggle with lingering deficits in areas such as attention, concentration, short-term memory, motivation, planning, decision making, sense of pleasure, empathy and sustained focused behaviour. Such patients often display chronic disabilities in self-care, social relationships and work capacity. They are often unemployed, socially isolated, dependent on their family and public welfare”.

6. The symptoms are extremely complex and diverse. Efforts have been made to simplify the concept of the illness by subdividing it into natural categories of “positive” and “negative” symptoms, with some workers recognising a further subdivision of the positive symptoms into “psychotic” and “disorganised” groups. Positive symptoms are clinically very noticeable, being the main focus of attention in the acute stages of the illness; they are often more responsive to treatment than the negative symptoms.

Positive symptoms

7. **Psychotic symptoms** include the following:

7.1. Delusions

A delusion is defined as “a belief that is firmly held but on inadequate grounds, is not affected by rational argument or evidence to the contrary and is not a conventional belief that the person might be expected to hold given his cultural background and level of education”.

Delusions are not specific to schizophrenia and may be found in many other psychotic illnesses. However there are some delusions which are most commonly found in schizophrenia including:

7.1.1. **primary delusion** (also called an apophanous or autochthonous delusion). The cardinal feature is that it must not be secondary to any other experience or idea and it arrives in the mind fully formed. For example the patient “suddenly knows” that the two halves of his brain have been transposed. This type of delusion is almost pathognomonic of schizophrenia however it does occur in the psychoses related to epilepsy.

7.1.2. **delusional perception** in which a completely new meaning is given to a normally perceived occurrence, which to other people is incomprehensible. For example a patient knew he was on another planet because the man opposite was sitting with his legs crossed.

7.1.3. **delusional mood**. Not all primary delusional experiences start with an idea and they often take the form that the patient says he knows “something is going on”. It is an unpleasant sensation which causes great suspicion in the patient. Delusional perceptions (above) may occur in this abnormal mood state.

7.1.4. **secondary delusions** arise from previous morbid experience, most often hallucinations. For example the person who hears voices may believe he is being followed. These delusions may become elaborated and form a complex system of interrelated ideas, understandable to a greater or lesser extent by the preceding ideas. This state is often referred to as “systematized” delusions and is more commonly seen later in the disease.

7.1.5. **delusions of control** are the ideas that thoughts, impulses and actions are under the control of some other person or force. This is not to be confused with the actions which may follow auditory hallucinations, they being more immediate. For example in delusion of control the patient on feeling his arm move believes someone else made it move.

7.2. Hallucinations

Hallucinations are false perceptions in the absence of an adequate stimulus or object. In schizophrenia they are almost always auditory (prominent visual ones being more commonly indictive of an acute organic state) and may take several forms:

7.2.1. Hearing voices giving a running commentary on the person's actions.

7.2.2. two or more voices discussing the patient or arguing about him, referring to him in the third person.

7.2.3. "imperative hallucinations" in which the voices command the patient; he may or may not feel obliged to carry out the instructions.

7.2.4. hearing his own thoughts being spoken out loud or hearing a voice anticipating his thoughts.

7.3 Abnormalities in thinking

7.3.1. "thought blocking" - this is a sudden arrest of the train of thought (not merely "losing the thread" due to tiredness or loss of concentration).

7.3.2. "thought alienation" - the experience that thoughts are under the control of others.

7.3.3. "thought withdrawal" - the feeling that thoughts are removed by an outside agency.

7.3.4. "thought insertion" - the thoughts are put into the mind by others.

7.3.5. "formal thought disorder" in which the thoughts (manifest by speech) are incomprehensive due to inappropriate condensation of ideas, lack of connections between ideas, an inability to maintain the boundaries of an idea, thoughts becoming derailed and resuming on a completely different track. The speech can appear totally disorganised.

7.3.6. Other less common abnormalities include "word salad", total gibberish, and the formation of new words or "neologisms". The latter often sound as though they may be normal words but they have been concocted by the patient.

7.4 Incongruous affect

This is the presence of an inappropriate emotional response, such laughing at bad news or giggling for no apparent reason.

7.5 **Catatonic behaviour**

These symptoms have become more rare and include catatonic stupor and excitement, negativism (doing the very opposite of a request without any motivation) and motor abnormalities including waxy flexibility. This is the ability of the examiner to move the patient into odd positions without any resistance. The patient feels to the examiner that they are malleable, like wax. There may also be posturing in which the patient holds himself in abnormal postures for long periods without apparent discomfort.

7.6 The "disorganised positive symptoms" are a cluster of thought disorder, incongruous affect and disorganised behaviour.

Negative symptoms

8. These include psychomotor slowing, affective blunting (lack of emotional reactivity to situations), underactivity, passivity and lack of initiative, poverty of speech and poor non-verbal communication as shown by lack of facial expression, abnormal eye contact and lack of voice modulation.

9. It is possible that the positive and negative symptoms reflect differing neural system involvement and numerous studies have shown that negative symptoms are strongly associated with structural brain abnormalities. Negative symptoms must be distinguished from the side effects of neuroleptic medication, the acute and transient psychotic disorders and mental retardation.

10. Schizophrenia has a peak incidence of onset between the age of 15 and 24 years in males and approximately 4-5 years later in females. The condition varies greatly in its presentation varying from an apparently acute, florid onset to a more insidious one. In many cases the course of the illness is characterised by episodes of florid psychotic symptoms against a background of negative symptoms. In these cases the exacerbations are most common in the first four to ten years of the illness, the patient characteristically then being left with what is often termed a "chronic defect state" which roughly equates to the negative symptoms. Systematised delusions are often present in this quiescent period if rigorously enquired after, although the patient frequently is able to "keep them to himself". Acting on these hidden delusions may be one of the reasons for suicide in those patients who appeared to be making a reasonable adjustment.

SUBGROUPS OF SCHIZOPHRENIA

11. Traditionally schizophrenia has been divided into four subgroups, paranoid, catatonic, hebephrenic and simple. However apart from some evidence for a possible slightly different genetic basis to paranoid schizophrenia, they are of dubious significance and patients may rarely fit completely into a group, presenting with symptoms from different groups throughout the course of their illness.

11.1. **Paranoid schizophrenia** F20.0

Characterised by relatively stable delusions of persecution, being on a special mission, being of exalted birth or “delusions of reference” (this being when the patient believes television programmes, newspaper items etc are referring specifically to him). Auditory hallucinations are common, with threatening voices, whistling or laughing. The patient may be mildly thought disordered but manages to give a reasonably clear account of his delusions and hallucinations. Affect is not usually blunted but may be incongruous with sudden anger, fearfulness and suspicion. The course may be episodic or chronic, in the latter the ideas persisting over many years. Negative symptoms do not predominate and the onset tends to be later than hebephrenic or catatonic types.

11.2. **Hebephrenic** F20.1

This is characterised by a prominence of affective symptoms with a shallow and inappropriate mood, giggling, self-satisfied smiling, grimaces, mannerisms and pranks. The mood however seems empty and purposeless. Thought is disorganised and there is often incoherence. There is usually a rapid development of negative symptoms; volition and drive are lost so that the behaviour becomes empty and without purpose. They may discuss philosophy and religion however it is in a very superficial and manneristic form. This type of schizophrenia starts roughly between 15 and 25 years of age and should only be diagnosed for the first time in adolescents or young adults (hebe = youth).

11.3. **Catatonic** F20.2

The essential and dominant features of this subtype are the psychomotor disturbances as described in para 8.5 above. Postures may be maintained for long periods interspersed with extremes of excitement or stupor. They may also show speech disturbance or perseveration (the use of a word beyond the point at which is relevant), giving the same response to all questions.

11.4. **Simple** F20.6

This is a very uncommon disorder characterised by an insidious decline in performance, with oddities of behaviour. Delusions and hallucinations are not evident and the “negative features” (above) gradually develop without the overt positive psychotic symptoms. The person becomes increasingly socially impoverished and self-absorbed and aimless vagrancy may ensue. The symptoms must be present for at least a year before the diagnosis is made.

11.5. In addition to the traditional groups above, both classification systems recognise a state in the course of an illness as “residual schizophrenia” (F20.5). This is a stage which has been clearly preceded by frank psychotic symptoms, the subsequent stage being characterised by long term (although not necessarily irreversible) negative symptoms.

Comparison between ICD-10 and DSM-IV

12. Both systems point out that the diagnosis of schizophrenia should not be made in the presence of dementia, delirium, brain damage, alcohol and drug abuse, recent work showing that the most common psychoses in young adults were related to drugs in particular cannabis (F12.5) and alcohol (F10.5).

    12.1. The criteria in ICD-10 specify that the condition should be present for at least **one month**, with care taken to avoid false positive diagnoses in those with subnormal intelligence or in certain cultures.

    12.2. The DSM-IV requires the condition to have been present for at least **six months** and that there has been significant occupational or social dysfunction.

Equivalent labelling in ICD-10 and DSM-IV

13.

ICD-10	DSM-IV
Paranoid	Paranoid
Hebephrenic	Disorganised
Catatonic	Catatonic
Simple	No equivalent
Undifferentiated	Undifferentiated
Residual	Residual

As stated above, the residual state proceeds from any of the above categories and should not be diagnosed in the absence of a previous history.

CLINICAL MANIFESTATIONS OF SCHIZOPHRENIA-LIKE DISORDERS

14. There are other psychotic disorders which have some features in common with schizophrenia. However they differ significantly from the strict definition of schizophrenia. They can be classified into four main groups.

    1. Delusional and paranoid disorders (F22)

    2. Acute and transient psychotic disorders (F23)

    3. Disorders accompanied by prominent affective symptoms (F25)

    4. Disorders which do not fulfil the full criteria for schizophrenia.

15. They are classified slightly differently in the two major classification systems, the rough equivalents being;

	ICD-10	**DSMIV**
1.	Delusional disorder Induced delusional disorder	Delusional disorder Induced delusional disorder

2.	Acute and transient psychotic	Brief psychotic disorder disorders (2 weeks - 3 months) with marked stressor (few days - 1 month)
	Acute polymorphic psychotic disorder without symptoms of schizophrenia	Brief psychotic disorder without marked stressor (few days - 1 month)
	Acute polymorphic psychotic with symptoms of schizophrenia	Brief psychotic disorder with post partum onset (within 4 weeks of birth)
	Acute schizophrenia-like psychotic disorder	Schizophreniform disorder (1 month - 6 months)
3.	Schizoaffective disorder manic type depressed type	Schizoaffective disorder bipolar depressed
4.	Schizotypal disorder	This is classified under personality disorders.

DELUSIONAL DISORDER F22

16. These are psychotic disorders in which the main feature is delusions with few other florid symptoms. There may be hallucinations however these are not prominent and there is none of the deterioration in personality and general function associated with schizophrenia. The delusions are most commonly systematised (see above) and often have persecutory features, for example the patient may believe his neighbours have some device for observing him.

17. There are several forms of delusional or paranoid disorder which may be identified by the content of the delusion. Only the more common are listed here.

    17.1. **pathological (morbid) jealousy** in which the spouse is convinced of his or her partner's infidelity, sometimes to the point of murder.

    17.2. **erotomania**: the delusion that someone is in love with the individual. The object of the patient's attention is often of higher status and many of their innocent actions are interpreted as "proof" of their affections.

    17.3. **paranoia querulans**: these patients indulge in never ending litigation in which they become passionately involved, sometimes threatening the magistrates etc.

    17.4. **body dysmorphic disorder**: in which the patient has the delusion that there is something abnormal in the appearance of part of his body.

    17.5. **grandiose type**: delusions of inflated worth, power, knowledge or of being related to royalty etc.

17.6. **monosymptomatic hypochondriacal psychosis**: this refers to a delusional belief of the presence of an illness in the absence of any mood disorder or other psychotic symptoms. The "evidence" of disease is sometimes carried around by the patient such as pieces of grit in a matchbox which they feel are evidence of infestation. Reassurances have no effect whatsoever, some improvement occurring however with neuroleptics.

Induced delusional disorder F24

18. This is also known as "folie a deux" and is characterised by acquired delusions which have developed in a person who is living in close proximity to someone with a primary delusional disorder. Those concerned often live an isolated life, the person suffering from the primary delusional disorder being the dominant individual. Separation of the individuals often leads to the resolution of symptoms in the recipient of the disorder although not inevitably.

SCHIZOPHRENIFORM PSYCHOSIS F23.2

19. The original meaning of this term (which was coined in 1961 by Langfeldt) indicated a type of disorder which had some of the features of schizophrenia but was acute in onset, often with clouding of consciousness and more significantly, had a good prognosis. DSM-IV however uses the term to indicate a condition which is indistinguishable from schizophrenia but lasts less than six months.

THE ACUTE AND TRANSIENT PSYCHOTIC DISORDERS

20. The main feature of this group of disorders is their sudden onset, short duration and relatively good prognosis. Before a diagnosis is made it **must** be clear that the individual is not abusing alcohol or drugs such as amphetamines, cannabis or hallucinogens as these substances can produce brief psychotic reactions very similar to these disorders and are separately classified and discussed in the appendices on alcohol and drug abuse.

20.1. **acute polymorphic psychotic disorder without symptoms of schizophrenia** F23.0

This is a very variable condition with hallucinations, delusions, emotional turmoil, intense transient feelings such as ecstasy or anxiety but the criteria for the major psychotic illnesses are not fulfilled. The disorder is likely to have an abrupt onset with rapid resolution of symptoms, the condition lasting no longer than 3 months. A large proportion of cases occur without any precipitating stress.

20.2. **acute polymorphic psychotic disorder with symptoms of schizophrenia** F23.1

This condition is as described above but the more usual symptoms of schizophrenia are present such as thought broadcasting, delusions of control, passivity, and auditory hallucinations giving a running commentary on the patient and catatonic behaviour.

20.3. They may or may not be associated with a marked precipitating stressor and are defined as such, **"with associated stress"** or **"without associated acute stress"**.

20.4. There may be pro-dormal symptoms before the florid onset or it may be observed as abrupt (ie within 48 hours) or over a longer period of up to two weeks, the symptoms remitting completely usually within 3 months. If this period is much prolonged then the diagnosis should be reconsidered. Disorders included in this group are the formerly named **"bouffee delirante" and cycloid psychoses.**

21. **Acute schizophrenia-like psychotic disorder** (F23.2)

Symptoms of schizophrenia have been present but for less than 1 month. There is none of the emotional turmoil as seen in the polymorphic disorders above. Disorders included in this group are brief schizophreniform psychosis and "schizophrenic reaction".

22. **Acute predominantly delusional psychotic disorders**

Include paranoid reaction and psychogenic paranoid psychosis.

Differences in DSM-IV

23. DSM-IV subdivides these brief reactive psychoses into brief psychotic disorder with marked stressor, without marked stressor, or with post-partum onset. The condition should last for more than one day but with return to full function in less than a month.

23.1. They are all characterised by the presence of one or more of the following symptoms: delusions, hallucinations, incoherence of speech or grossly disorganised or catatonic behaviour.

SCHIZOAFFECTIVE DISORDER F 25

24. This disorder is characterised by the equal presence of both affective symptoms (ie depressive or manic) and schizophrenic symptoms. The depressive symptoms must be marked and comprise symptoms such as psychomotor retardation, early morning waking, loss of weight, guilt and feelings of hopelessness. At the same time typical schizophrenic symptoms must be present such as thought broadcasting, auditory hallucinations discussing the patient in the third person and delusions of control. The two sets of symptoms must either occur simultaneously or within a few days of each other for the diagnosis to be made. When manic symptoms are present they may be of the elated and grandiose type or be represented by irritability and aggression. There is overactivity in both of these types together with impaired concentration and loss of inhibition. The typical schizophrenic symptoms must again be present. The manic type is often presents abruptly and although the initial picture is grossly disturbed, full recovery usually takes place within a few weeks.

25. It must be differentiated from schizophrenia with a superimposed “depression”, this often being characterised by a lack of energy, difficulty concentrating and sleeping. These patients may also have serious suicidal thoughts possibly as a result of hearing voices urging them to kill themselves. However they do not have the full picture of biological symptoms as described above.

SCHIZOTYPAL DISORDER F21

26. This condition was formerly considered to be a personality disorder and remains thus classified in the DSM-IV, however the frequency of the condition in families with schizophrenia sufferers has led to it being included within that spectrum of disorders. It is characterised by odd or eccentric behaviour, abnormalities of thinking such as vague, circumstantial, metaphorical and overelaborate thoughts expressed in abnormal content of speech. The affect is abnormal in that the person is aloof and cold and there is poor rapport with others. The individual may express odd or magical beliefs which influence their behaviour and may occasionally experience quasi-psychotic episodes with intense illusions and delusion-like ideas. The disorder may fluctuate in intensity and occasionally it evolves into frank schizophrenia.

AETIOLOGY OF SCHIZOPHRENIA

27. The World Health Organization examined the incidence of schizophrenia in different cultures by studying ten centres in different nations including Denmark, India, Colombia, United Kingdom, Nigeria, Japan, Czechoslovakia and the USA. Their findings showed that the incidence is the same whatever culture is studied, despite the population composition, climatic differences, social differences and degree of industrialisation or the lack of it.

28. The conclusion of the study was that schizophrenic illnesses are ubiquitous, appear with similar incidence in different cultures and have clinical features that are more remarkable by their similarity across cultures than by their difference. It concluded that schizophrenia “is a characteristic of human populations, not of the circumstances in which they exist”.

Genetics

29. Family studies have shown that there is a life time risk of developing schizophrenia of 5% among the first degree relatives of schizophrenics as opposed to 0.2-0.6% amongst controls. Estimates of heritability are in excess of 70%.

30. Many twin and adoption studies (which differentiate the genetic contribution from early family influences) have shown that there is greater concordance between monozygous (identical) twins than dizygous (non-identical) ones. Representative figures for monozygous being 50%-70% and 17% for dizygous twins.

31. A more precise estimate of the relative importance of genetic factors can be obtained by comparing monozygous twins separated at birth and reared apart: studies show that the rates of schizophrenia are very similar in both groups which suggests a major genetic contribution. Furthermore the adoption of a child away from a schizophrenic family does not reduce the adoptee’s risk of developing schizophrenia.

32. Studies of children born to schizophrenic mothers which were then adopted away show that about 11% of these children developed schizophrenia compared to none of the controls. Adoption studies however cannot rule out causes related to the family situation in the adopting parents however they indicate that if any such variables exist they act only on genetically predisposed children. Adoption studies have also shown that in cases in which siblings develop schizophrenia, it strikes at the same age rather than at the same time, this suggesting that intrinsic genetic factors rather than extrinsic factors determine the onset.

Mode of inheritance

33. Schizophrenia has a complex non-Mendelian mode of inheritance. The precise nature and site of the genetic abnormality is yet to be precisely identified. Some forms of schizophrenia appear to be due to several genes of minor effect but some appear to be related to a gene on the short arm of chromosome 6. Further complicating the picture is the possibility of a gene/peri-natal interaction (see below).

Cell and molecular genetics

34. Recent research has revealed various abnormalities which may occur in the earliest stages of cell division when genetic material is being reproduced, the main ones being genetic mutation, unstable DNA sequences and genomic imprinting.

35. **Genetic mutation**

New germ line mutations occurring in parental gametes appear to be a cause of some single gene disorders: this is well recognised in such conditions as tuberous sclerosis. Up to half of cases of this condition, known to be dominantly inherited occur in people with unaffected parents. Genetic mutations may also occur in somatic cells that are actively dividing in the earliest stages of development. It has been postulated that in some cases of schizophrenia a gene is inherited which predisposes the individual to the illness, this being followed by a somatic mutation occurring early in the development at a time when there is active division of neuronal stem cells. It is further postulated that these mutations may occur randomly or possibly as a result of such factors as maternal influenza or other abnormalities during embryonic development.

36. **Unstable DNA sequences**

Other pathological mutations which may occur have been shown to be the result of unstable DNA sequences. Variations arise in the repeats of fragments of the gene resulting in disruption in function: this has been well documented in Huntingdon's chorea and fragile-x syndrome. It appears that these malfunctions affect variables such as the age of onset and the severity of the condition. It is postulated this phenomenon may explain certain variations in schizophrenia.

37. **Genomic imprinting**

Genomic imprinting is the third major genetic abnormality which may affect the presentation of schizophrenia. This is the suppression of a gene at the earliest stages of embryonic development (blastocyst stage) and expression of the abnormality depends on whether the gene was inherited from the father or mother. This phenomenon may possibly explain the differing rates and clinical course between males and females and may account for earlier and more severe presentation of a disease in the offspring of sufferers.

Neurodevelopmental abnormalities

38. In the last decade firm evidence has been adduced to support the presence of structural abnormalities in the brain in schizophrenia. Abnormalities have been found at all levels.

39. Neuropathological studies have shown and an absence of gliosis in the brain (gliosis being scar tissue in the brain due to inflammation, degeneration or neuronal loss in the **developed** brain: this reaction does not occur if the inflammation occurs in perinatal life ie pre-natally and up to 6 months of age).

40. There is also failure of migration of alpha cells, the migration of these cells normally being completed by the neonatal period. These findings strongly suggest the abnormality is developmental rather than degenerative and most workers in this field consider the lesions to be non-progressive, structural and fixed, the lesions being present from a very early stage of development.

41. Other neuropathological studies have revealed a proportion of schizophrenia sufferers have smaller temporal lobe structures than controls. Some studies have suggested this is due to smaller pyramidal cells. Other findings include enlarged basal ganglia.

42. Neuro-imaging studies have shown enlargement of the cerebral ventricles in a proportion of schizophrenics. This finding is present at the onset of symptoms, is not the result of treatment, is associated with poor pre-morbid adjustment and in some cases is associated with obstetric complications (see below). Neuro-imaging studies have also shown the frontal lobe in some schizophrenics is hypofunctional with reduced blood flow and reduced glucose utilisation patterns. Some studies have also shown abnormalities in the normal asymmetry in the cerebral hemispheres and cortical-striatal-thalamic pathway abnormalities, although other studies have found no difference.

43. The clinical features associated with these findings are cognitive impairment, negative symptoms, poorer response to neuroleptics and poor outcome ie chronicity of symptoms. Males are more likely to exhibit these brain abnormalities both morphologically and neuro-pathologically and on CT or MRI scanning.

44. There is an excess of minor physical abnormalities (MPAs) in schizophrenia sufferers, for example malformed ears, palate or dermatoglyphs (finger print patterns). Development of these features in the foetus closely parallels the development of the central nervous system, MPAs being common in individuals with neurodevelopmental disorders. One of the most consistently reported findings of abnormal ectodermal development in schizophrenics is that of abnormal fingerprint patterns. Although these are genetically determined it has been shown that intra-uterine infections (especially between weeks 14 and 21 of the pregnancy) may cause changes in the patterns. A recent study of monozygotic twins, only one of whom is schizophrenic, has shown an increase of these abnormalities in the schizophrenic twin.

Neurochemical abnormalities

45. More than 100 chemical neurotransmitters, gaseous messengers, growth factors and 300 receptor molecules have been identified in the human brain up to the present.

46. The view that schizophrenia is related to abnormalities in brain chemistry developed from the observation that LSD, amphetamine and mescaline were found to produce schizophrenia-like symptoms in healthy subjects and that the drugs reserpine and chlorpromazine reduced symptoms.

47. Reserpine acts by depleting stores of the monoamine neurotransmitters (serotonin, dopamine and noradrenaline). The classical neuroleptics (typified by chlorpromazine) block dopamine D2 receptors, the strength of the bond to the receptor being directly correlated, milligram for milligram, to the drug's ability to reduce symptoms. This was thought to suggest the basic neurochemical abnormality in schizophrenia was a functional overactivity of certain dopamine systems in the brain, and post mortem studies indeed have shown elevated numbers of D2 receptors in certain areas of the brain in schizophrenics. However whether this is due to previous drug therapy or a result of the illness remains unclear. PET studies of patients abstinent from neuroleptics or who have never had medication have shown no difference in D2 receptor numbers.

48. This area is currently being researched with studies suggesting differential activity being related to different subtypes of receptors in different areas of the brain. Recent studies have shown 12 different subtypes of receptor with at least 5 different variants of one of the 12 identified subtypes between individuals. All of these five variants have different affinities for the drug clozapine, one of the newer drugs acting on schizophrenic symptoms. Other neurochemical transmitters have also been implicated including glutamate, gamma aminobutyric acid, serotonin and cholecystokinin.

Neuropsychology

49. Neurocognitive and neuro-imaging studies have revealed incontrovertible evidence of abnormalities in brain physiology and diminished intellectual efficiency in schizophrenia. Studies have also shown that these neurocognitive impairments are not due to the effects of the illness, for example lack of motivation.

50. Schizophrenia sufferers often show a decline in IQ, deficits in frontal lobe tests and some aspects of secondary memory. They may also show abnormalities in attention and verbal learning. These abnormalities do not appear to change with medication, apart from some studies showing clozapine enhances certain basal ganglia related functions.

Neuroendocrinology

51. The peak incidence of schizophrenia occurs in early life and 75-80% of patients will have their first episode of illness before the age of 45 years. Although controversial, many workers consider that symptoms presenting in the older age group probably represent a different disease which is characterised by the paranoid syndromes with a lack of personality deterioration. It is well recognised that the majority of patients in the late onset group are female and it is well established that clear gender differences exist in the age at which schizophrenia becomes manifest. The peak age of onset in men is between the ages of 15 and 24 years, whilst females present on average 4-5 years later. The incidence in men then gradually falls whilst there is a second peak among women between the age of 45 and 54 years. However whether this is the same syndrome that occurs in younger males is open to debate. The theory has been postulated that oestrogen exerts a protective effect in females which is lost after the menopause, support for this theory has come from animal studies which demonstrate that oestrogen has a dopamine antagonizing effect. It is postulated that this may serve to raise the vulnerability threshold for the schizophrenia in females.

Environmental factors

52. Several lines of research have suggested that some prenatal environmental factors may play a role in the aetiology of at least some forms of schizophrenia. The observed variations in the presentation of the condition and the recent decline in its incidence may be due to varying or decreasing frequency of these pre-natal factors. Research around the world has shown that people who go on to develop schizophrenia are born disproportionately more often in the late winter and early spring months of the year. This is taken to suggest that some seasonally varying agent damages either the foetus or the infant and interacts with genetic traits, these agents being postulated as infections, nutritional factors including zinc deficiency, temperature variations at the time of conception or environmental toxins. The most favoured at present is a pre-natal viral infection, possibly influenza.

52.1. **maternal influenza**

Features found in schizophrenia such as the seasonal variation, low birth weight, increased minor physical abnormalities and abnormal finger print patterns could all be explained by cytotoxic effects of maternal viral infections during pregnancy. The studies however are inconclusive and the current opinion is that an association between in utero exposure to influenza and the later development of schizophrenia may exist but the effect is likely to be normal.

52.2. **obstetric complications**

The most consistently reported environmental factor in schizophrenia is the presence of “obstetric complications” this term indicating deviations from the normal course of events during pregnancy, birth and early neonatal life. This obviously encompasses a wide variety of possibilities which are still the subject of investigation. Opinion is divided between whether they are a) independent factors which cause a brain abnormality, or b) the obstetric complications are a result of early infection of the nervous system or genetically determined neurodevelopmental abnormalities and are in fact the cause of the obstetric complications.

Life Events and Schizophrenia

53. Studies into life events in schizophrenia have been beset with inaccuracies, the major pitfall being that no distinction is made between events which could be considered to have been precipitated by the illness from those that are completely independent. Early work in the 1960s showed that 46% of a group of 50 schizophrenics had a possibly independent life event in the 3 weeks preceding the onset of symptoms. Prior to this period the number of life events was similar to non-patients. Furthermore 35 of the 50 already had established schizophrenia. Additional difficulties were that the definition of “onset” of illness was imprecise and in 23 the “onset” was in fact a move from mild to more severe symptoms. Further work in the 1970s introduced an additional concept, that of “brought forward time” which indicated that the onset of the disorder was brought forward 10 weeks earlier than it would have been had not the individual experienced the stressful event.

54. Other studies have been attempted, however many of the conclusions are even more unreliable as they do not identify “independent” life events and repeat many of the above shortcomings, for example no distinction is made between a relapse in established schizophrenia and a completely new case.

55. The cross national study by the World Health Organisation (1987) looked at schizophrenia sufferers in 10 different centres around the world and using the same criteria for independent life events confirm the earlier work discussed above. They found that the role of stressful life events in schizophrenia appears to be of a limited nature with stressors acting at most to simply trigger episodes of illness in a disorder which is pre-determined by genetic and/or peri-natal factors.

56. Other socio-cultural influences have been identified as being of relevance to relapse including the effects of the family emotional atmosphere, this being referred to as “expressed emotion” or “EE”. It is measured by various criteria including the number of critical or hostile comments which families may make, such comments, amongst other factors, contributing to relapse. Such family comments however do not cause schizophrenia.

AETIOLOGY OF SCHIZOPHRENIA-LIKE DISORDERS

Schizoaffective psychosis

57. The relationship between schizoaffective psychosis, schizophrenia and the affective psychoses has been the subject of extensive research. The term was coined by Kasanin in 1933 when he described a florid, rapid onset condition with marked affective symptoms, the whole episode recovering within a few months.

58. There are discrepancies in the literature (probably as a result of differences in diagnostic criteria) and there is no consensus on where schizoaffective disorder stands in relation to schizophrenia and the affective psychoses. The main differences in the various theories are:

    58.1. it is a subtype of schizophrenia.

    58.2. it is a subtype of affective disorder.

    58.3. It is genetically independent of either of these disorders and is a homogeneous entity.

    58.4. it is a genetically independent heterogeneous disorder, being further subdivided according to symptoms.

    58.5. it is a mid point on a genetic continuum between schizophrenia and the affective psychoses, some therefore showing more schizophrenic symptoms and some showing more affective symptoms.

59. Although difficulties with precise diagnosis have clouded the interpretation of studies regarding the precise risks of relatives developing the disorder, it is generally agreed that there is a strong inheritable genetic component. What is not clear is whether relatives are at higher risk of developing schizoaffective disorder, schizophrenia or an affective psychosis. Some workers have postulated that bipolar disorder and schizophrenia are caused by the same genetic abnormality, however when these conditions are diagnosed using strict criteria they are distinct disorders with differing inheritance patterns. Similar loose diagnoses may therefore be confusing the picture in some studies of schizoaffective disorder.

Acute polymorphic disease

60. The aetiology of the acute polymorphic psychoses is unknown, however it is clear that some may be precipitated by stressful events and remit after the stress has passed. Psychotic reactions to alcohol and drugs may occur which are indistinguishable from these disorders and if they are prolonged may be very difficult to distinguish from schizophrenia. However they usually remit when the substance is no longer abused. Psychotic conditions due to substance abuse are coded separately.

Delusional disorders

61. The precise aetiology of the delusional disorders is unknown, however factors associated with the aetiology include:

61.1. Genetic factors: sensitive, wary personality traits are thought to have a tendency to run in families.

61.2. Predisposing personality traits sometimes associated with an obvious physical abnormality or deformity.

61.3. Immigrant or ethnic minority status.

61.4. Social isolation including being single, divorced or widowed.

61.5. Deafness, characteristically long-standing severe bilateral deafness, usually of an acquired nature.

61.6. Morbid jealously is often associated with alcohol abuse.

Schizotypal disorder

62. Schizotypal disorder is considered to be part of the genetic spectrum of schizophrenia and therefore the aetiology is as described above.

CONCLUSION

63. Earlier views of the aetiology of schizophrenia focused on ideas that the illness is caused by psychological factors or stressful life events, and on the notion that it is due to a pathological process in early adulthood just before it becomes clinically manifest. In contrast there is now compelling evidence based on extensive research that schizophrenia is a neuro-developmental disorder resulting in anatomical, biochemical, neurophysiological and cognitive abnormalities. The main body of current opinion considers that precisely defined schizophrenia is caused by defects in early brain development. These may be genetically inherited, may be the result of genetic mutation, genomic imprinting, peri-natal factors such as maternal influenza, or a combination of these factors.

64. Considerable research has been carried out to determine the role of external factors in schizophrenia and this has revealed no hard evidence that any external factor, other than the peri-natal disruptors of neurodevelopment by factors such as maternal influenza, has any part to play in the causation of schizophrenia.

65. The role of life events appears to be minimal in that, at most, they can only bring forward the inevitable onset of an episode in a susceptible person by a matter of some ten weeks, such an event having occurred within three weeks of the onset of the episode of illness. It is thought that life events may be triggering factors in relapse of established schizophrenia especially when associated with lack of maintenance medication, lack of social support and high expressed emotion in the family.

66. Schizoaffective disorder appears to be a genetically determined condition, however it is not known whether it is related to schizophrenia, the major affective psychoses or is a disorder in its own right.

67. The acute polymorphic psychotic disorders are by definition transient, lasting on average no longer than three months. The aetiology of these disorders is unknown, however it is clear that some may be precipitated by stressful events occurring within the two weeks prior to the onset of symptoms.

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