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# **Screening and treatment of adolescents with schizophrenia**

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To: The Minister of Health, Welfare and Sport

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Subject : Presentation of advisory report  
Your reference : GVM/GGZ/972470  
Our reference : U 3771/97/PB/ps/614-D  
Enclosure(s) : 1  
Date : June 24, 1999

On 29 August 1997 you have requested scientific information with regard to a number of mental health care subjects, including the desirability of (trial) population screening for schizophrenia and the possibilities for early treatment of patients with this disease.

The state of science concerning schizophrenia and the possibility of population screening for this severe psychiatric disorder has been discussed with experts from academic psychiatry departments, the psychiatric urgency service, and the association of parents and patients with schizophrenia. Enclosed you will find the advisory report based on this information, entitled 'Screening and treatment of adolescents with schizophrenia'.

In view of the advisory report, I present the following recommendations:

- It would be highly inadvisable to conduct (trial) population screening, in view of the inability to predict the occurrence of schizophrenia and related disorders with reasonable accuracy, the burden any such prediction would place both on the people who eventually develop the disease and those who do not, and the limited likelihood of being able to have any therapeutic effect on the disease.
- In general, the guidelines recently published by the Netherlands Psychiatric Association on treating patients with schizophrenia and schizophreniform disorders should be followed.
- Research is required into the duration of the period between the onset of the first psychosis and the commencement of treatment in patients with schizophrenia and related disorders in the Netherlands; depending on the results of that research, measures (or further research) could be considered for influencing this duration.

(Signed) Prof. Dr JJ Sixma

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the Minister of Health, Welfare and Sport

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No. 1999/08E, The Hague, 24 June 1999

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Preferred citation:

Health Council of the Netherlands. Screening and treatment of adolescents with schizophrenia. The Hague: Health Council of the Netherlands, 1999; publication no. 1999/08E.

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ISBN: 90-5549-329-5

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## Executive summary

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Schizophrenia is a severe psychiatric disease characterized by changes in thinking, perception and behaviour that conflict with reality as experienced by other people. A period of social isolation, neglect of hygiene or blunted emotions sometimes precedes these delusions or hallucinations. Most patients suffer the first symptoms during adolescence. Schizophrenia or a related disorder occurs in approximately 0.5% of the population; combined with the early onset and often chronic course of the disease, this leads to considerable economic and human costs.

Guidelines for treatment recently became available in the Netherlands. The antipsychotic drug treatment indicated in the guidelines generally results in an improvement, but the disease appears to be chronic in the majority of patients.

The cause of schizophrenia is unknown. Genetic as well as environmental factors appear to play an important role in the development of the disease. However, the actual genes involved in schizophrenia are not known. There is also a lack of clarity about environmental factors, except insofar as complications in pregnancy are known to slightly increase the risk. It is impossible to predict the course of schizophrenia; a statistical relationship exists between the severity and certain symptoms but this provides an inadequate basis for making predictions about individual patients.

Research into the possibility of predicting the occurrence of schizophrenia has shown that future patients generally display abnormalities in neuropsychological tests more often than control persons. These abnormalities are not specific for the disease and even occur relatively frequently in people who do not subsequently develop schizophrenia or related disorders. Investigation of other abnormalities, for example by means of

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brain-imaging techniques, also failed to produce results that could be used to predict the occurrence of schizophrenia.

Research frequently showed a long period between the onset of the first psychosis and the start of treatment. In this advisory report 'first psychosis' means the first psychotic symptoms suffered by the patient, and not therefore the first diagnosis of 'psychosis' made by a medical practitioner. Some researchers assume that the duration of the period between the first psychosis and treatment affects the final result; however this assumption is contested. On average, the final result is worse in case of a longer period before the start of treatment. However, it is not known whether this is a causal link. It may be based on a common social factor, for example, because patients with a poor prognosis are more likely to isolate themselves from the environment. A prospective study has started in Scandinavia that may provide a decisive answer to this.

Apart from the possible effect of early treatment on the final course of the disease, early treatment is also of direct importance for patients and their relatives in order to reduce the duration and severity of the psychosis and to limit possible damage to social relationships. However, there is a lack of data about the length of time between the initial psychosis and treatment in the Netherlands.

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## **Conclusions and recommendations**

- No characteristics are known that could form the basis for predicting with reasonable accuracy which adolescents are likely to subsequently develop schizophrenia or a related disease, such as schizophreniform or schizoaffective disorders. Research into the possibility of making such predictions has produced insufficient results. Moreover, investigation also leads to many false positives, i.e. people who will not subsequently develop the disease. Likewise, if a high risk is suspected on the grounds of heredity and behaviour, it is not possible to predict whether or when the disease will occur.
- The publication by the Netherlands Psychiatric Association of guidelines on the use of antipsychotic drugs in the treatment of schizophrenic psychoses has addressed the need for guidelines on treating schizophrenic patients.
- There is a lack of data on the average duration of the period between the onset of the first psychosis and the commencement of treatment in patients with schizophrenia and related disorders in the Netherlands, and on the nature of a possible link between the duration and course of the disease.



The report leads to the following recommendations:

- It would be highly inadvisable to conduct (trial) population screening, in view of the inability to predict the occurrence of schizophrenia and related disorders with reasonable accuracy, the burden any such prediction would place both on the people who eventually develop the disease and those who do not, and the limited likelihood of being able to have any therapeutic effect on the disease.
- In general, the guidelines recently published by the Netherlands Psychiatric Association on treating patients with schizophrenia and schizophreniform disorders should be followed.
- Research is required into the duration of the period between the onset of the first psychosis and the commencement of treatment in patients with schizophrenia and related disorders in the Netherlands; depending on the results of that research, measures (or further research) could be considered for influencing this duration.

# Introduction

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## 1.1 Ministerial Commission

On 29 August 1997 the Minister of Health, Welfare and Sport (VWS) wrote the following about mental healthcare issues in a letter to the President of the Health Council of the Netherlands (see Annex A):

Recent research results indicate that in a number of cases the early treatment of people with schizophrenia has a beneficial effect on the course of the disease. Based on these results, some observers are advocating (trial) population screening for schizophrenia. I would like to receive a report from you about the current level of knowledge in this area, both with regard to the categories of patients who qualify for such a programme, and with regard to the possibilities for early diagnosis/screening and intervention. I would ask you also to include the ethical and legal aspects of this issue, such as the question of whether the Population Screening Act is applicable in the case of screening for schizophrenia. Questions regarding the voluntary participation, the protection of privacy and the protection of the social position of people diagnosed (at an early stage) as having 'schizophrenia' should also be considered.

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## 1.2 Procedure

This report has been produced by the secretariat of the Health Council in response to the Ministerial Commission mentioned in section 1.1. The scientific research that has been conducted in relation to early detection of schizophrenia has been discussed with external

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experts from psychiatric departments of university hospitals, the psychiatric crisis service and the association of parents and patients with schizophrenia (see Annex B).

## **Diagnostic criteria and biological characteristics**

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**2.1****Criteria**

Schizophrenia is a complex disease and the borderline distinguishing it from related disorders is blurred. There has consequently been much discussion regarding diagnostic criteria. At present, diagnosis is usually based on criteria summarized in the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV), published by the American Psychiatric Association (Apa94). According to these criteria, in order to be given the diagnosis of schizophrenia a patient must experience bizarre delusions or hallucinations which involve either a running commentary on the patient's behaviour or thoughts, or else two or more voices talking to each other. The diagnosis is also made in the case of less extreme delusions or hallucinations, providing both symptoms occur or if they are combined with incoherent speech, catatonia (where movement is either noticeably absent or else excessive), a severe lack of drive or blunting of affect. These symptoms must last for at least one month, during which they must be present for a significant proportion of the time. Furthermore, the patient's social functioning must have been severely affected by these symptoms for at least six months. Other possible causes of the behavioural abnormalities must be ruled out. These include intoxications (especially due to drug abuse), temporal lobe epilepsy and metabolic disturbances.

These criteria have been formulated in order to allow for an unequivocal diagnosis and are based on a consensus between members of the profession. Clarity of diagnosis is of great importance to research into schizophrenia — both for clinical trials and for more fundamental research. There is, however, some discussion about the criteria. For

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example, the ICD-10 criteria for schizophrenia, drawn up by a committee of the WHO, do not include the stipulation that social functioning should have been disturbed for a minimum of 6 months (Who92). According to these criteria, the diagnosis of schizophrenia will be made in more patients. Moreover, where expectations regarding therapeutic effects are based on research, they will need to be adapted to the particular diagnostic criteria that have been applied in that research. The use of different criteria can lead to confusion among patients and their relatives. The difference between the DSM-IV and ICD-10 criteria has no bearing on the detection of future patients with schizophrenia or related disorders, or of patients with a first psychosis.

In the literature, a distinction is made between positive symptoms (delusions, hallucinations, confusion and catatonia) and negative symptoms (blunting of affect, interest and initiative and social withdrawal, which can be summarized as 'psychomotor impoverishment'). The degree to which these different sorts of symptoms occur has a bearing not only on the diagnosis but also on the prognosis. The presence of predominantly negative symptoms is, on the whole, associated with a less favourable prognosis (see section 4.2). Instead of making a twofold distinction between positive and negative symptoms, some researchers (Bos93, Buc94) have proposed that three dimensions (or compartments) be distinguished. This involves dividing the positive symptoms into psychotic manifestations (hallucinations and delusions) and cognitive disorganization. Furthermore, subtypes are identified, namely: paranoid, disorganized (hebephrenic) and catatonic. In the paranoid form, the delusions and hallucinations are the dominant features, whereas in the disorganized subtype it is incoherence and affective disorders that predominate and in the catatonic subtype it is the movement disorders. The emphasis may shift in the course of the disease and this subtyping has little bearing on treatment and the individual prognosis (Bos95, Car94). Moreover, investigation of the allocation of subtypes reveals fairly major variations between different psychiatrists (Sar93).

The literature on the early detection of patients and research into schizophrenia frequently refer to 'schizophrenia and related disorders'. The latter category includes schizophreniform and schizoaffective disorders, and sometimes also delusional disorder and brief psychotic disorder. Criteria have also been formulated for these diseases in DSM-IV (Apa94). In the case of schizophreniform disorder, the same criteria apply as for schizophrenia, except that the duration of the impaired social functioning is set at a minimum of one month, but less than six months. Schizoaffective disorder overlaps with bipolar disorder: in addition to the delusions or hallucinations that are present in schizophrenia, it is frequently — 'but not always' — associated with depression or mania. The most important criterion for delusional disorder is the presence of delusions lasting for at least one month, but these are less bizarre than in schizophrenia and do not occur in combinations. In brief psychotic disorder, the delusion, hallucination or behavioural disorder lasts for at least a day, but less than a month (Apa94). The importance of early

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detection and treatment of patients with schizophrenia applies equally to schizophreniform and schizoaffective disorders. How these conditions develop in an individual patient can, in practice, only be determined retrospectively.

A further diagnosis exists in addition to the above-mentioned conditions, namely schizotypal personality disorder (or schizotypy), whereby features of schizophrenia occur in a mild form (Mee90, Vol96). These include ideas of reference (unfounded ideas about relationships with others), unusual perceptions and beliefs, suspicion and social anxiety. Individuals exhibiting a combination of these characteristics are described by some researchers as schizotypal, a designation that refers not to a disease but to a personality structure (Apa94). Schizotypy is more often encountered in relatives of patients with schizophrenia than in controls (Ken95).

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## **2.2 Biological characteristics**

A great deal of research has been done into biological characteristics that could prove useful in the diagnosis and possibly also in the prognosis of schizophrenia. It is known from neuropathological research that the brains of patients tend to exhibit a slight dilation of the ventricular system (Pak87). This has been confirmed by means of magnetic resonance imaging (And90, Law98, War96). In an MRI study, morphological characteristics that were qualitatively judged to be abnormal were found to be present in 31% of the first-episode psychotic patients, 42% of the chronic patients and 5% of the control group (Lie92b). Furthermore, a comparison of averaged MRI scans in patients and controls revealed a slightly smaller thalamus in schizophrenic patients (And94), who had been diagnosed according to the criteria set out in DSM-III-R (Apa87). These differences probably already exist even before the first psychotic episode (Law99). The differences are too small, however, to have any practical diagnostic value. For example, in a study of patients with recent-onset schizophrenia (according to DSM-III-R), the ventricular volume was 18 ml with a standard deviation (SD) of 7, compared with 15 ml (SD 5) in the control group (Zip98). Moreover, similar changes have also been observed in healthy first-degree relatives of schizophrenic patients (Sta98) and in patients with other psychiatric diseases (Sha98).

Differences have likewise been determined between patients and controls using positron emission tomography (PET). With this technique researchers have identified both increased and decreased cerebral blood flow, which is probably related to positive and negative symptoms, respectively (Cat94, Sie93, Wol92). During hallucinations there is an increase, and thereafter a decrease, in the blood flow, which has been detected both using PET (Mcgu93, Sil95) and Doppler ultrasonography (Owe98). These changes are, however, too small and too variable to be of diagnostic use. For example, the blood flow velocity (in cm/sec) in the middle cerebral artery of schizophrenic patients (DSM-IV)

during a psychosis was 84 (SD 27), compared with 59 (SD 13) in controls and 64 (SD 10) in patients after the psychosis (Owe98).

Changes in electrical activity in the brain can be monitored using electroencephalography and magnetoencephalography. In schizophrenic patients a slight decrease in frontal activity has been reported, but the specificity is low (Wil89).

A further characteristic lies in the abnormalities which some schizophrenic patients exhibit when eye tracking in response to visual signals (Bos84, Hol73). Here too, however, the specificity is low. These abnormalities also occur in patients' relatives and in individuals with a schizotypal personality structure (Iac92, Sie94). Inferior eye tracking usually correlates with the presence of negative symptoms (Roi97) and not all patients exhibit these abnormalities (Bos84, Iac92). According to some estimates, it occurs in three-quarters of the patients and half of the healthy first-degree relatives (Iac92, Vol96). However, the percentages given by researchers are not directly comparable, since the method used is not always the same.

Extensive research has been carried out with respect to possible biochemical abnormalities in patients with schizophrenia or related disorders. Dopamine and the associated metabolites have been investigated in order to determine the antipsychotic effect of substances which act on dopamine receptors (Kah95). The concentration of the metabolite homovanillic acid, which can be measured in blood and cerebrospinal fluid, is known to increase following administration of classic antipsychotics (Dav91). Neurotransmitters other than dopamine have also been examined in detail, as have a large number of enzymes. For diagnostic purposes, however, these and other biochemical parameters are without significance (Car94). Early detection of schizophrenia based on such characteristics is therefore impossible in the present situation.

## Prevalence

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Prevalence data are required in order to make a quantitative assessment of the possible results of early detection of schizophrenia. According to a study of psychiatric disease conducted in a representative random sample of around 7,000 people in the Netherlands in 1996 (Bijl97a, Bijl97b), as part of the Netherlands mental health survey and incidence study (NEMESIS), 0.4% of those surveyed had at some time suffered from schizophrenia or another non-affective psychotic disorder. These disorders had occurred either during the month or the year immediately preceding the study in 0.1% and 0.2%, respectively, of those surveyed. These percentages are lower than the researchers had expected on the basis of research in other countries (Bijl97b). A study conducted in inner London identified a prevalence of 0.5% (DSM-III-R criteria for schizophrenia, Har96b), while a 16 - 27 year cohort investigated in North Finland revealed prevalences of 0.4% and 0.7% (based on DSM-IV and DSM-III-R criteria, respectively; Iso97, Jon98). In a major international study conducted under the auspices of the WHO, an incidence of 2.3 per 1,000 persons per year was determined (Var97). A comparison of data from the literature regarding the prevalence of schizophrenia there reveals an apparent reduction in the numbers of patients (Der90). Research in Scotland has demonstrated a decline from 40 to 50% in the period from 1969-1984 (Eag85, Eag88). A comparable decrease was established during this period in Denmark, England, Wales and New Zealand (Der90, Joy87, Mun86). The decline does not appear to be caused by a diagnostic shift in favour of bipolar disorders (the occurrence of which remains fairly stable in this period, Sym81). These quantitative data appear to tie in with earlier suggestions regarding a reduced incidence (Har74, Mah81). According to some researchers, the average severity of

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the disease has also decreased (Ble78, Sau89). This may possibly be influenced by a change in the environmental factors (Alm98). Another possibility is that the decline in patient numbers may, in part, be due to the adoption of stricter criteria in diagnosing schizophrenia (Car94, Ken93).

Research into the number of chronic psychiatric patients in the Netherlands reveals that 3 in every 1,000 of the population are receiving long-term treatment (Kro98). Of these, around 30% suffer from schizophrenia or a related disorder, a finding that agrees with the results of the above-mentioned NEMESIS study (Bijl97b, Kro98). The number of first psychoses has been investigated in, 1942-1978, birth cohorts (Mar98). Among the 8.5 million persons investigated in the period from 1970 to 1992, around 40,000 first-episode psychotic patients were recorded, 40% of whom were suffering from schizophrenia and related disorders (Mar98). Extrapolation of these results to the population today results in approximately 1,500 patients with first-episode psychosis in connection with schizophrenia or related disorders.

## Treatment and prognosis

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### 4.1 Treatment

Various methods have been recommended in the past for treating patients with schizophrenia, such as frontal lobotomy, psychoanalysis and electroconvulsive therapy. Nowadays there is an international consensus regarding the prescribing of antipsychotics as the first-choice therapy (Apa97, Dix95, Leh95, Leh98). It is also recommended that the patient, and in some cases the relatives, be offered information and supportive counselling (Leh95, Moj98).

Until recently, there was no general protocol in the Netherlands for the treatment of patients with schizophrenia or related disorders. In a random survey of general psychiatric hospitals, the Health Care Inspectorate (IGZ) only discovered treatment protocols for schizophrenia in 4 out of 43 establishments (Igz98). In December 1998, however, the Netherlands Psychiatric Association (NVP) published guidelines on the use of antipsychotic drugs in the treatment of schizophrenic psychoses (Nvp98).

Antipsychotic drugs are classified as being either classic antipsychotics (phenothiazines, e.g. chlorpromazine; butyrophenones, e.g. haloperidol; diphenylbutylamines; thioxanthines; and a few other compounds) or atypical antipsychotics (clozapine, risperidone, sulpiride, etc), depending on which type of receptor is blocked by the substance in question. Both the above-mentioned guidelines on the use of antipsychotic drugs and the Dutch Pharmacotherapy Compendium (*Farmacotherapeutisch Kompas*) recommend that medical management of schizophrenia should begin with a classic antipsychotic (Far98, Nvp98). If the response is good, a maintenance dose can be given for at least

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one year (Nvp98). Researchers in the US also consider a period of at least one year to be advisable (Apa97, Dix95). Although administration of a maintenance dose generally has a positive effect, the disadvantage of the side effects may in individual cases negate the benefit (Har98). During the stable phase, a relatively low dose is ideal (6-12 mg haloperidol daily or an equivalent dose of another antipsychotic, Nvp98).

If there is no response, or if too many side effects occur, an atypical antipsychotic is prescribed. If necessary, different atypical antipsychotics may be tried, possibly supplemented with antidepressants in the presence of depressive symptoms.

The side effects of classic antipsychotics consist of tardive dyskinesia (involuntary movements of the tongue, mouth and face) and related movement disorders such as parkinsonism (tremor, stiffness), dyskinesia, sedation, impaired sexual function, nausea and hypotension. Tardive dyskinesia occurs within one year in 5% of patients, rising linearly to 40% in eight years, (Apa92, Har98) and in many patients persists after the antipsychotics are discontinued. A rare, but extremely severe side effect of both classic and atypical antipsychotics is neuroleptic malignant syndrome, characterized by stiffness, muscle necrosis and hyperthermia.

The Cochrane database contains abstracts of publications about research into the efficacy of various treatments. There is a consensus regarding the beneficial effect of classic neuroleptics such as chlorpromazine and haloperidol. According to a meta-analysis of 42 studies on the efficacy of chlorpromazine, psychotic relapse occurs significantly less often than when a placebo is used (Tho97). On average, it is necessary to treat three patients in order to induce this effect in one patient. Approximately the same effects can be achieved with haloperidol and other classic antipsychotics, but there are differences in the side effects. One such side effect is sedation, and thus the choice of a particular drug is partly dependent on the degree of agitation and (possibly) aggression that is displayed by the patient (Lou96). Too little research has been conducted to allow a prediction of the efficacy over a period in excess of two years.

In around 30% of patients, treatment with classic antipsychotics has little or no effect (Kan93b). In these patients treatment with the newer, so-called 'atypical' antipsychotics (e.g. clozapine, risperidone and olanzapine) can sometimes produce better results (Kan93a, Mor98, Ros97). According to a meta-analysis of studies in which the efficacy of clozapine was compared with classic neuroleptics, relapses are less frequent following the use of clozapine than with chlorpromazine, while clinical improvement is greater (Wah97). However, the results achieved with clozapine are not significantly better than with haloperidol (Wah97). Use of clozapine is only rarely associated with movement disorders, but a severe deficiency of white blood cells can occur in a small proportion of patients. This agranulocytosis has been reported in 0.8% of the approximately 11,000 individuals who used this drug for one year (Lie92a). White blood-cell counts should therefore be tested regularly in patients using clozapine. As far as the relapse rate is con-

cerned, a slight reduction has been identified in connection with the use of clozapine, while the likelihood of a clinical improvement has been found to increase (from 34% to 54%, Wah97). Although no investigation of placebo effects is mentioned, earlier analysis suggests a figure of up to 40% (Tho97). The effect of the medication is therefore unclear as far as clinical improvement is concerned.

From a meta-analysis of studies into the efficacy of risperidone it has been concluded that there are only slight differences between this and haloperidol and that long-term research is required (Ken97). Research into the action of olanzapine suggests that this drug produces a greater clinical improvement and fewer side-effects than haloperidol (Tol97, Tra98). Because many of the patients studied have not responded well to previous medication (Tol97), outcome is less easy to predict in patients experiencing their first psychosis.

Maintenance therapy has a major role to play in reducing the recurrence rate of psychotic episodes. It appears from research that the continuation of medication has a marked prophylactic effect (Dav75). For example, in 347 patients who were given either an antipsychotic or placebo over a two-year period, the incidence of psychotic relapse was 48% and 80%, respectively (Hog74). In a group of 120 patients with first-episode schizophrenia, it was investigated whether the effect of continuing antipsychotic therapy was any different from that of administering a placebo. After 18 months, 46% of the treated patients had suffered a relapse, compared with 62% of the placebo group (Cro86, Joh86). Little research has been conducted into the longer-term effects of maintenance treatments.

Relatively few studies have been published on the use of electroconvulsive therapy in schizophrenia (Tha97). This form of treatment produces little improvement compared with a placebo or simulated therapy and the outcome is less favourable than treatment with antipsychotics. Other research has produced evidence that the use of cognitive therapy in some so-called 'therapy-resistant' patients leads to a reduction in the number of delusions or hallucinations (Kui97). After twenty sessions, each lasting one hour, a 50% reduction in positive symptoms was identified in 11 out of 33 patients, compared with 3 out of 28 in the control group (Tar98).

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## 4.2 Prognosis

The course of schizophrenia can vary greatly (Car94, Dav97). Reviews of large numbers of patients indicate that the onset is often insidious, but can also be acute (Ang88, Har88). First psychoses tend to occur between the ages of 17 and 30 years in men and between 20 and 40 years in women (Car94). In many patients the disease follows a chronic course. Deterioration mainly occurs during the first five years (Bir98, Eat95). These five years are therefore known as the 'critical period' (Bir98).

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The outcome of schizophrenia (i.e. the patient's condition over time) has been comprehensively investigated. When evaluating research of this kind, it is important to note that a shift has occurred in the diagnostic criteria, that the treatment varies according to time and place, and that there may possibly have been a change in the pattern of the disease. Despite these complicating factors, there is a consensus among researchers regarding the outcome of treatment with antipsychotics, namely that complete recovery occurs in around 25% of the patients and a partial recovery in around 50% (Cio80, Ram92). This is borne out by a 15-year follow-up of patients from an incident cohort in the Netherlands: complete recovery occurred in 25%, partial recovery in 41%, while 23% remained psychotic and 11% died (most of them by suicide, Wie95). The outcome of a German study of around 500 patients who were reviewed an average of 22 years after the first diagnosis was: 22% complete recovery, 43% partial recovery and 35% with psychotic symptoms (Hub97).

The outcome of the therapy in the longer term is associated with a diversity of factors. One such factor is the occurrence of life events: retrospective analyses demonstrate that crises are frequently preceded by periods of stress (Bro68, Nor93). Prospective research appears to confirm this assumption, although it should be noted that no sharp distinction can be drawn between cause and effect (Hir96). In the latter study, 20% of the patients who continued to use medication and experienced an average number of life events suffered a relapse within one year. Where 2-4 times the average number of such events occurred, this figure rose to between 25 and 32%. Without medication, relapse occurred within one year in 70% of the patients who experienced an average number of life events and in 80-95% of patients who experienced 2-4 times as many events (Hir96).

Compliance has an important bearing on the efficacy of treatment with antipsychotics. However, a considerable number of patients discontinue treatment after a certain period, thereby increasing the risk of psychotic relapse (Goa90, Kan83). Compliance is worse with oral medicines than with depot injections (Joh90), and better for in-patients than out-patients (Put90b). The major reason why patients stop taking medication is probably the occurrence of side-effects (Bri98, Put90a). Proper patient education can bring some improvement in compliance, as illustrated by a study of patients in which between four and six information sessions were held, lasting between 20 and 60 minutes. In this case, researchers also noted a tendency towards an improvement in global functioning (Kem96). Evaluation of efficacy is complicated, however, by the high drop-out rate (31%).

The use of cannabis is associated with a less favourable course, with patients displaying a greater tendency to psychotic relapse (Lin98b). It is unclear whether use is a causative factor, since cannabis users also appear to develop schizophrenia more often (see section 4.2).

Intensive counselling of patients appears to have a positive impact on the course of the psychosis and in the months that follow, but relapse nevertheless occurs over time. In a case-control study of 76 patients with schizophrenia and related disorders, two out of three patients suffered a psychotic relapse within four years (Lin98a). Counselling and support of the patient's family can also play a positive role during treatment, as revealed by a review of 12 studies in which five or more meetings with the family were held (Mar97). The risk of a relapse is reduced, resulting also in fewer hospital admissions. Medication compliance improves with family counselling. However, statistical analysis shows that the improved results are not only attributable to the improved compliance. The effect is not great: on average, between six and seven families need to receive counselling in order to avoid one psychotic relapse for one year. Research shows that if the patient receives intensive psychosocial counselling (18 meetings following discharge from hospital), comprehensive counselling and support of the family does not produce any extra improvement (Lin96, Lin98a).

Further research into factors that influence the outcome of therapy in the long term (Mur98) has shown that there is also a link with family history, past medical history, sex, the occurrence of tardive dyskinesia and the presence of negative symptoms. Where schizophrenia has previously occurred in the family, the outcome is less favourable. The prognosis is better for women and where particular events in the patient's life may have triggered or exacerbated the psychosis (Mur98). In an analysis of the factors that played a role in outcome after thirteen years in 99 patients with schizophrenia and related disorders, the most important parameters appeared to be the course of the disease over the first two years and the sex of the patient (Har96a). If the medication leads to tardive dyskinesia, the outcome is considerably poorer — probably because some patients discontinue the treatment after experiencing this severe adverse reaction (Kem96). It appears from a review of research into possible links between symptoms and therapeutic results that outcome is, on average, better in the case of a severe pathology with positive symptoms (Kah95). The positive symptoms may possibly be related to the increased dopamine activity, on which the antipsychotics exert a blocking effect, while the negative symptoms may relate to structural changes such as an increase in the volume of the cerebral ventricles (She92).

Research has also demonstrated a link between outcome and the expression of emotion within the patient's family (Bro72). A critical attitude and over-concern have a negative effect, and families in which such factors play a role are referred to in the English-language literature as EE (expressed emotion) families. The risk of psychotic relapse is somewhat greater for patients in EE families (Lin96, Lin98b).

A link has also been discovered between outcome over time and the length of the period between the first symptoms and the commencement of therapy: where this period is prolonged, the outcome tends to be poorer (Cro86, Wya91). Possible explanations ad-

vanced for this finding are that rapid treatment limits the damage inflicted on the brain in some other way, or that symptoms associated with late treatment are also associated with a poorer prognosis. It does, in fact, appear from research that outcome is generally less favourable in the presence of negative symptoms (Dav97, Kah95, Mur98, Tam98). A more detailed discussion of the relationship between the duration of the period without treatment and outcome can be found in Chapter 6.

Evidently, countless diverse factors have a bearing on outcome. Since each factor in isolation appears to have only a limited effect, predictions based on particular factors have little value in individual cases.

## **Genes and environmental factors**

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### **5.1 Genetic predisposition**

It is generally assumed that schizophrenia is caused by a combination of inherited and environmental factors (And99, Car94, Mcgu95). It appears from family studies that there is an increased risk of schizophrenia in first- and second-degree relatives. A review of research in first-degree relatives of patients reports a 4-6% risk of schizophrenia, compared with 0.2 - 0.7% in the control groups (Ken88a, diagnosis according to DSM-III). Depending on which diagnostic criteria are used, higher percentages are also reported (Mcgu95).

As far as the difference between genetic and other factors is concerned, research has been conducted into schizophrenia in twins and adopted children. The studies of twins have employed various diagnostic criteria over the years, while the methods of investigation have also varied. Consequently, the results are not directly comparable. There does, however, appear to be a marked difference between the risks of schizophrenia in monozygotic twins (i.e. those derived from a single ovum) and dizygotic twins (derived from two separate ova). In a series of studies conducted between 1934 and 1984, the risk of schizophrenia in both twins was discovered to range from 31 - 78% in monozygotes compared with 6 - 28% in dizygotes of the same sex (Ken88a). Differences in the diagnostic criteria used in these studies have less influence on the relative risks than on the risks themselves. The relative risk in monozygotes and that in dizygotes therefore also varies less, namely from 2.2 to 4.8. In two studies which applied the criteria according to DSM-III and DSM-III-R, respectively, the risk in monozygotes was found to be 48%,

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and that in dizygotes 10% and 5%, respectively (Far87, Ons91). The weighted averages from a series of European studies in twins are 46% for monozygotes and 14% for dizygotes (Mcgu95). If the influence of environment on monozygotic and dizygotic twins is the same, it follows from these twin studies that the genes are an important factor. Because one of the twins is not sick in approximately 50% of the monozygotic twins in whom schizophrenia occurs, it follows that non-hereditary factors must also have a great bearing on the development of schizophrenia. These conclusions are confirmed by results from research involving the children of monozygotic twins where one twin has schizophrenia. It appears from this research that the risk of schizophrenia lies between 10 and 15% for both the affected twin and the 'unaffected' twin (Got89).

In order to arrive at a closer definition of the influence of hereditary factors, research has been conducted in children with one schizophrenic parent who have been brought up in adoptive families. In a Finnish study involving 155 adopted children of schizophrenic mothers, 5.2% of these children were found to suffer from schizophrenia, compared with 0.5% in the control group (adopted children of biological parents without schizophrenia, Tie94). The researchers report that schizophrenia was only discovered in adoptive families in which disturbed relationships occurred. The significance of the latter finding is unclear, however, since the boundaries that were set for these characteristics were rather broad: 47 of the 105 families with adopted children of schizophrenic mothers and 44 of the 118 control families fell within those boundaries (Tie94).

According to earlier studies, the percentage of adopted children who develop schizophrenia varies (Ken88a). This is due both to the diagnostic criteria that are applied and the small numbers involved. However, the risk for adopted children of biological parents with schizophrenia will probably always be greater than for the controls. An extensive Danish study was based on adopted children who had developed schizophrenia. In the first-degree relatives of these children the risk of schizophrenia is 5% compared with around 0.5% in the control group (Ket94). These research results therefore confirm that heredity plays a major role, without offering any further qualitative insight into the problem.

Other indications of the importance of genetic factors are the relationships between genetic markers in patients within a single family (She88) and the discovery of chromosomal abnormalities such as translocations and deletions in a small proportion of the patients (Bas89, Bas92, Lin95). It can be assumed that more than one chromosome — and therefore more than one gene — is involved in the development of schizophrenia (Ken88b, Pul94). From studies of the extent to which various genetic markers are detected in related patients it is possible to derive a localization for such genes (Von98). However, the results that have been reported in this connection are inconclusive (Blo98, Lev98, Moi98). Moreover, no one has yet succeeded in identifying a 'schizophrenia gene'.

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The heredity data outlined above may have a bearing on the detection of patients at an early stage in the disease. In the majority of patients ('between 60 and 80%'), however, there is no evidence of schizophrenia in the immediate family (Mcgu95, Var97).

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## 5.2 Environmental factors

Research has not only been conducted into genetic factors that might play a role in the development of schizophrenia, but also into environmental influences. In large numbers of patients investigations have been conducted to determine whether a connection exists between the disease and complications during pregnancy or delivery. Malnutrition in the prenatal period increases the risk of schizophrenia. Research into the possible effect of the Dutch 'hunger winter' of 1944-1945 demonstrates that where the first trimester of the pregnancy falls in this period, the risk of schizophrenia is approximately double that applying to the control group (Sus92). In the United Kingdom and Scandinavia a slightly increased risk has also been identified following the occurrence of influenza during pregnancy (Ada93, Med94). In the Netherlands, on the other hand, no connection has been identified between the occurrence of schizophrenia and the influenza epidemic of 1957 (Sel98, Sus94). A further virus that is being studied as a possible causative factor is the Borna virus (Iwa98, Sal97).

Other complications during pregnancy and delivery have been associated with an increased risk of schizophrenia and related disorders. In one study it emerged that problems had occurred during delivery in 24 of the 65 schizophrenic patients that were investigated, and in 11 of the 65 controls. No relationship was identified with earlier miscarriages or the birth-weight (Oca92). An investigation of the Rhesus blood group revealed that incompatibilities between mother and child increase the risk of schizophrenia to 2.1%, compared with 0.8% in the control group (Hol96). Comparison of the past medical history of patients and controls in Scotland showed a higher incidence of pre-eclampsia (10 and 2 cases, respectively, out of 115 patients) and admission to a neonatal unit (18 and 6 cases out of 115 patients) (Ken96). In Finland, perinatal brain damage was registered in 6 out of 76 schizophrenic patients (from a cohort of 11,000 persons), with these six patients accounting for five per cent of those who survived this perinatal brain damage (Jon98). In an investigation of the birth cohorts from 1973-1979 in Sweden, a connection was established between the occurrence of schizophrenia in men and the following factors, low birth-weight, being born as a fourth child or later and the occurrence of bleeding during the pregnancy (Hul99). Maternal diabetes may possibly be a risk factor as well (Hul99). Complications during pregnancy are not only associated with a greater subsequent risk of schizophrenia, but onset of the disease also occurs at a younger age (Ged95, Ver97). Research also indicates that the season in which a child is born may

also have a slight effect in the Northern Hemisphere, with the risk of schizophrenia appearing to be between five and ten per cent greater in individuals who are born in winter (Ada93, Dal88, Hul99).

A further possible causative environmental factor is residence in an urban area (Lew92, Mar98, Mor99). In a study involving around 50,000 Swedish men, an incidence of 51 per 100,000 person years was discovered in urban areas (principally Stockholm; confidence interval 49-65) and 31 in rural areas (interval 25-39). The difference is not related to migration from rural to urban areas, but to living conditions in the urban environment (Lew92). In Denmark and the Netherlands too, it has been discovered that in urban areas the risk of developing schizophrenia or a related disorder is approximately twice the risk in the countryside (Mar98, Mor99). There is no explanation for this phenomenon.

A further non-genetic factor that has repeatedly been demonstrated is the use of drugs (And87, Bre74). Hallucinogenic substances can induce psychoses. In some patients with schizophrenia the condition has become manifest following the use of such substances. The relationship between cannabis use and schizophrenia was also investigated in the above-mentioned study in Sweden. The relative risk compared with non-users appears to be 6.0 (And87). One cannot conclude from this that the use of drugs causes schizophrenia, since use may be associated with a predisposition to schizophrenia.

The effect of the environmental factors mentioned above is considerably less marked than that of a hereditary defect. As reported in the studies with twins, however, the overall effect of environmental factors (detrimental and/or protective) must be considerable. Researchers suggest that effects on the development of the central nervous system can play a role during early adolescence (Har97, Wad93, Woo98).

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## **Relationship between the duration of the period without treatment and outcome**

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Research into factors that influence the course of the disease has produced evidence that early treatment of schizophrenic patients leads to a better final result (Bir93, Wya91). This conclusion has been drawn retrospectively from the results of various studies into therapeutic effects (Cro86, Lo77, Rab86), although the connection was not identified in all of the studies (Kol85, Lin98a, See98). Prospective research in 70 patients in the US appears to confirm the hypothesis (Loe92). This study identified an average duration of 155 weeks, with a reported standard deviation (SD) of 171 weeks, between the onset of the symptoms and treatment. The psychotic period lasted for an average of 52 weeks (reported SD 83 weeks) before treatment was administered. For three years after treatment with various drugs, the researchers monitored patients for the initial recurrence of symptoms and the severity of the psychotic relapse. The longer the so-called untreated period lasted, the earlier the relapse was and the more severe the course of the disease. According to the researchers, there is a long period of pre-psychotic symptoms (99 weeks on average). The severity of the relapse appears to correlate strongly with the duration of this pre-psychotic period. However, the researchers do not mention the average duration of the period between treatment and relapse and they make no distinction between positive and negative symptoms (Loe92). Furthermore, it is not always possible to unequivocally determine the onset of the symptoms, and hence the duration of the untreated period (Haa99).

A further study investigated the course of disease in 227 patients (Edw98). After 12 months, 7% of the patients were still psychotic, whereas the remainder had either fully or partially recovered. The researchers assume that there is a connection with the untreated

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period, which lasted 418 days (reported SD 696) in the patients who were still psychotic compared with 195 days in the others (SD 608 days, Edw98). However, because schizophrenic patients accounted for 93% of the first group (14/15) and 56% (119/212) of the second, the significance of the connection is unclear. Research has also been conducted in 88 long-term in-patients with an average age of 63 years (SD 13 years), whereby the untreated period 'from the time before the introduction of antipsychotics' lasted an average of 17 years (reported SD 3 years). Mutism was encountered in 24% of the patients and appeared to be correlated with the duration of the untreated period (Wad95). After prolonged treatment, mutism was still present in 8% of the patients. The researchers conclude from these findings that the duration of the untreated period has no significant effect on outcome provided it is 6 weeks or less (Wad98).

In a Dutch study of the course of psychoses following intensive treatment in 76 patients, no connection was discovered between the duration of the untreated period and outcome (Lin98a). After four years, two of the three patients suffered a relapse. The duration of the untreated period was 25 weeks (reported SD 46), considerably shorter than the 52 weeks recorded in the above-mentioned US study (Lin98a, Loe92).

Research has also been conducted into the benefits of early detection and treatment at the Early Psychosis Prevention and Intervention Centre (EPPIC) in Australia (Mcgo96a). Around 250 new patients are referred to that centre every year from a population of around 200,000. Comparison of the results obtained at the EPPIC with historical controls indicates that the EPPIC commences treatment at an earlier stage. As has been reported by the researchers themselves, however, this is due to the omission of outliers (Mcgo96a). The outcome after 12 months exhibits only minimal differences between present and past patients. The comparison is complicated by the fact that the dosage of neuroleptics was lower and the period of hospitalization was shorter than was the case with the historical controls. A further complication is the large number of drop-outs: of the 51 patients from the EPPIC period, 37 remained after 12 months, while 34 of the 51 historical controls remained (Mcgo96a). An additional problem encountered in interpreting the EPPIC results is the large variation in outcomes: the duration of the untreated psychosis averaged 191 days in the EPPIC group and 237 in the control group, whereas the standard deviations reported by the researchers were 484 and 703 days, respectively, and the medians were 52 and 30 days, respectively (Mcgo96a). Furthermore, it is important in schizophrenia research involving the use of historical controls that a reduction should be reported over time in the incidence and average severity of this disease (see Chapter 3). Based on this study, it is therefore not possible to draw any conclusions regarding an association between the duration of the untreated period and other parameters.

There can be various reasons for a possible relationship between the duration of the untreated period and the course of the disease (Cro86, Haa99). It is conceivable that sus-

ceptibility to psychotic relapse is reduced by treatment with antipsychotics (e.g. in so far as brain damage is limited). It is also possible that the symptoms associated with a poorer prognosis may also tend, on average, to result in a longer period of treatment (e.g. because negative symptoms predominate). As far as the possibility that psychoses may cause brain damage is concerned, it has been pointed out that this is inconsistent with the finding that antipsychotic therapy does not significantly affect long-term outcome (Car98). There is, indeed, a relationship between negative symptoms and a less favourable prognosis, as reported in section 4.2. It has also been demonstrated that a long untreated period correlates with the presence of negative symptoms (Haa92, Lar98). This appears to be due to avoidance behaviour and impaired social functioning (Lar98). It is, as yet, unclear whether a reduction in the duration of the untreated period results in a better final result.

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## **Pre-psychotic detection of schizophrenia and related disorders**

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Those researching and treating schizophrenia emphasize two reasons why schizophrenia should, if possible, be detected pre-psychotically. Firstly, early treatment lies in the interests of those concerned and secondly, there is a statistical connection between the duration of an untreated psychosis and the subsequent course of the disease (see Chapter 6).

The importance of early treatment for all concerned is evident: the patient stands to benefit from the alleviation or resolution of the psychosis and it is important that the family and other relatives should be given information about the disease and how to manage it. In many cases, the disease manifests itself at an age at which the individual concerned is either still engaged in education or embarking on a career. Postponement of adequate treatment may therefore have lasting consequences. Because schizophrenia and related disorders sometimes have an insidious onset, it may be some time before the disease is identified. This may lead to the patient's social relationships suffering more damage than is necessary. In some cases, the occurrence of undesirable behaviour influenced by the undiagnosed disease can bring the patient into contact with the law or even imprisonment. It is likely that pre-psychotic detection will increase the possibility of early treatment.

Whether the occurrence of schizophrenia can be predicted by means of psychological testing has been investigated in around 5,000 English subjects born in 1946 (Jon94). After the age of 40, schizophrenia was identified in 32 (0.63%) of them (according to the criteria outlined in DSM-III-R). These patients appear, on average, to have been assessed by their teachers at 15 years of age as being less socially competent. The predictive value of this assessment is minimal, however, due to the large overlap between patients

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and controls and the paucity of patients exhibiting a particular characteristic. For example, in teachers' assessments of the behaviour of around 3,500 students aged 15 years, 11 of the 20 subsequently schizophrenic patients were placed in the highest third of the 'nervous behaviour' category (Jon94). The sensitivity of the 'nervous behaviour' characteristic is thus 55% (11 out of 20 patients) and its specificity is 67% (two out of three students do not exhibit that characteristic). If one were to use that characteristic to predict schizophrenia, the result would be a group of 1,166 students, of whom 11 will actually develop schizophrenia. A further characteristic used in this study -- namely, 'unusual behaviours' -- proved to have a specificity of 99.5%, whereas the sensitivity had fallen to five per cent: 14 of the 3,500 students conform to this characteristic, including one of the 20 subsequent patients (Jon94).

The predictive value of teachers' assessments of their pupils has also been comprehensively investigated in Denmark (Oli96). A prediction of emotional or psychotic problems made by teachers in the course of the 1962 Copenhagen project appears to have a sensitivity of 30% and a specificity of 97% for females, compared with levels of 43% and 88% for males (Oli96). In the context of research into a low-prevalence disease, this level of specificity results in a large number of false positives, i.e. individuals who test positively but will not develop the disease (Osj98). By taking the 0.4% prevalence identified for the Netherlands in the NEMESIS project (Bijl97b) as the baseline, it would be possible to detect half of the patients at the level of sensitivity and specificity identified in the Copenhagen project, with around 40 false positives for each patient.

The question of whether it is possible to predict the future occurrence of schizophrenia based on a personality test that is geared towards psychiatric morbidity has been explored in around 50,000 Swedish army recruits (Mal98). The subjects were tested at 18 years of age and then, 15 years later, the occurrence of schizophrenia (if any) was compared with the test results. In this study, diagnosis was based on the ICD-8 guidelines. Habits, social functioning and behaviour during adolescence were charted in this group by means of a checklist comprising 36 questions. From the study, there would appear to be an association between subsequent occurrence of schizophrenia and ('in order of importance') the following features: having no steady girlfriend, a feeling of being more vulnerable than others, a preference for small groups in social situations, and having no more than one close friend. The four features cited above are encountered in nine per cent of the patients, but also in one per cent of the other subjects (sensitivity 9%, specificity 99%). The researchers conclude that relational problems are the most important pre-morbid feature and that early screening and preventive programmes are probably impractical (Mal98). Screening that is based on the presence of all four features would only identify one in ten future patients, while the application of three of the four features leads to a sharp rise in the number of false positives.

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A similar study has been conducted among students in the US (Cha94). Having screened 7,800 individuals, researchers selected around 500 students with possibly pre-psychotic features. Ten to fifteen years later, they investigated whether psychoses had, in fact, occurred. In the subgroup of 182 individuals who scored highly on the scales for perceptual disturbances and magical thinking, three schizophrenic patients were identified — who, incidentally, displayed reasonably good social functioning (diagnosis according to DSM-III-R). In a control group of 153 students, one patient was identified (Cha94). Assuming that 0.4% of those originally screened developed schizophrenia, the sensitivity for the abnormal score on the scales for perceptual disturbances and magical thinking is 10% and the specificity is 98% (31 patients, of whom 3 tested positive; 179 of the remaining 7,769 had a false-positive test). It appears from the study that high scores on the scales for non-conformity and apathy have even less predictive value.

Retrospective studies have also been performed in which researchers have looked for childhood characteristics with a predictive value (Don94, Jon94). Reduced social adjustment and a preference for playing alone are more commonly encountered in future patients than in their peers. Here too, however, the difference is too small to have any predictive value. It was found that those patients for whom information was available about early childhood (Jon94) had, on average, begun to walk later (1.5 months) and experienced more problems in learning to speak. The parenting skills of their mothers were judged by a social worker to be below average (Jon94). Social adjustment was assessed by teachers, who awarded the future schizophrenic patients an average score of 4.3 at 7 years of age (SD 2.4) compared with 3.1 (SD 2.0) for the control group. At 11 years of age too, these scores display a substantial overlap (4.9 SD 2.2, compared with 3.1 SD of 2.1 in the controls, Don94).

A further means of detection is through the screening of individuals with prodromal symptoms such as social isolation, significant deterioration in social functioning and abnormal ideas which could precede the onset of a psychosis. A study of such symptoms has been conducted in 16-year old children, with around half of the 657 children examined conforming to the prodromal phase as defined in the DSM-III-R criteria. If only prolonged symptoms are counted, this was the case in 10-15% of the children (Mcgo95). If one assumes that the prevalence of schizophrenia is less than 1%, the presence of prodromal symptoms has only minimal predictive value. Furthermore, efforts to establish the reliability with which these symptoms can be determined have led researchers to conclude that reproducibility is poor (Jac94, Jac96). In order to detect prodromal symptoms as described in DSM-III-R, 25 patients with schizophrenia or schizophreniform symptoms were subjected to a semi-structured interview. In 25 to 30% of the patients, the researchers were unable to reach a consensus. Discrepancies were identified whenever the patient was seen by two researchers simultaneously and also where there was an interval of 1 or 2 days between these interviews. This poor reproducibility with regard to

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the identification of prodromal symptoms by different observers had also been encountered in earlier studies (And91, End82). It is partly on account of these research results that the concept of prodromal symptoms has been omitted from the DSM-IV and the ICD-10.

The possibility of predicting the occurrence of schizophrenia has also been investigated by means of neuropsychological tests such as the *continuous performance test*, which measures the extent to which subjects can maintain their attention to a long series of signals (Cor94). In this test, the score of patients with schizophrenia is, on average, lower than that of controls. Its specificity and sensitivity in predicting future behavioural disorders in adolescents was estimated to be 90% and 30 - 35%, respectively. Below-average scores are also found in patients with other psychiatric disorders and in first-degree relatives of schizophrenic patients. The researchers have come to the conclusion that the specificity of this test is too low to permit pre-psychotic detection and the use of this detection method would result in unnecessary and prolonged treatment of false positives (Cor94). Another possible predictor of schizophrenia is family history. A child of a parent who has, or has had, schizophrenia is at greater risk for developing this disease him-/herself, as demonstrated by various studies (see Oli96 for a summary). As noted in section 4.1, the risk in first-degree relatives is around ten times greater than the average. At first sight, the number of false positives appears to be ten times lower if the pre-psychotic detection is directed at first-degree relatives. Research shows, however, that pre-psychotic features and (for example) low scores in the above-mentioned *continuous performance tests* occur more frequently than average in first-degree relatives of schizophrenic patients (Cor94, Dwo91).

The above-mentioned studies indicate that attempts at pre-psychotic detection of schizophrenia and related disorders will lead to a large number of false positives, or else that only a small proportion of the future patients will be identified.

At the Australian EPPIC treatment centre mentioned in Chapter 6, research has been conducted into the occurrence of psychoses in persons aged 16-30 years who had been selected for the following features: 'mild or transient psychoses' or 'manifest functional decline and a first-degree relative with a psychotic disorder' (Yun98). One in three referrals to the treatment centre appears to concern a patient who conforms to these criteria. The researchers have reported as an interim result the fact that 8 of the 20 individuals thus selected proceeded to develop a psychosis within six months. The research shows that the scores recorded for these 8 patients in psychopathological tests performed upon referral were already high. The researchers state that further research is needed in order to be able to make predictions about the occurrence of psychoses (Yun98).

A strategy such as that adopted in the EPPIC obviates the need to follow up a large number of false positives. In this way it may be possible to reduce the period between

the first psychotic symptoms and treatment. However, the length of this period in the Netherlands has not been quantified.

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## Early detection of first psychoses

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As stated in Chapter 7, early treatment of psychoses is of great importance both for patients and members of their family. This means that early detection is valuable even though research into the results of early treatment (Chapter 6) does not indicate that the outcome is any better (Mcgl96b).

The application of different criteria in diagnosing schizophrenia can lead to differing conclusions with regard to the point in time at which early detection of this disease is possible. The most significant difference in this regard relates to the stipulation that a patient's life must have been seriously affected by the symptoms for at least six months, as stated in DSM-IV, but not in ICD-10 (see section 2.1). In this report, early detection is understood to mean the detection of the first psychotic phase, even though it is not generally possible at this juncture to determine whether the patient will develop schizophrenia. Besides the schizophrenia-related disorders mentioned in section 2.1, psychoses also occur in connection with other conditions, such as bipolar disorders. Treatment of psychoses can be delayed by patients not seeking help, or even avoiding it. It is also not always clear whether a patient is psychotic. In particular, assessment may be hindered by suspicion (a relatively common symptom of schizophrenia) and possible adolescent problems (Mcgo96b). If positive symptoms predominate, the (first) psychosis will usually be easier to identify.

Research has been conducted into the first onset of psychosis in England (Fal92). Over a period of four years a population of 35,000 persons in two small towns was monitored by a team of trained physicians, nurses and social workers (17 persons). During that time, they discovered one patient with schizophrenia and one patient with a psycho-

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sis, who may possibly have developed schizophrenia had he/she either not been treated or been treated at a later date. This indicates an incidence of 0.8 per 100,000 persons per year — around one-tenth of the level that one would expect based on hospital admissions for first-episode schizophrenia during the same period in England (Fal92). The researchers offer no explanation for this major difference, but they do suggest that patients may possibly shun investigation in the initial phase.

Because general practitioners and other primary-care providers will frequently be the first to be consulted at the onset of psychotic symptoms, they can play an important role in the early detection of psychoses (Mcgo96b). However, the number of patients per primary-care provider is low. From the data reported in Chapter 3, it can be concluded that the number of first-episode psychoses in the Netherlands will be around 3,600 per year, of which 1,500 will be associated with schizophrenia or a related disorder (Mar98). In an average general practice, a first psychosis will, on average, present once every two years, and a new patient with schizophrenia or a related disorder once every five years. It is not known how quickly patients with a first psychosis are referred for psychiatric care.

There are in the Netherlands around fifty Regional Institutions for Out-patient Mental Health Care (RIAGGs), to which patients can be referred if (for example) they exhibit seriously disturbed behaviour. Every year around 250,000 new clients are registered with the RIAGGs (Ggz96). There are, in addition, over 200 psychiatric outpatient departments ('polyclinics') attached to psychiatric, general and university hospitals, to which 95,000 patients aged 18 years and over are referred every year, and 700 independent psychiatrists with around 25,000 new patient registrations each year (Ggz96). The number of psychiatric admissions to hospitals (general psychiatric, general and university hospitals) is around 25,000 per year, one in six of which are compulsory admissions (Ggz96).

The estimated 1,500 patients who are registered each year with first-episode psychosis in association with schizophrenia or a related disorder (Chapter 3) therefore only account for a small proportion of the new referrals. According to the guidelines issued by the Netherlands Psychiatric Association (NVP), treatment should be managed in such a way as to allow for a rapid response where symptoms of schizophrenia are identified (Nvp98). However, the average length of time between referral and treatment is not known. What is clear, however, is that the RIAGGs play an important role in this regard.

Research into the duration of the above-mentioned period has been conducted in Scandinavia, Australia and the US (Hel90, Lar98, Mcgo96a, She97). In these countries it appears that an average of two years elapse before treatment is commenced, although it should be noted that the standard deviations are large. In the Netherlands, a period of six months was encountered in a group of patients who were treated in a university hos-

pital (Lin98a). In a cohort of 82 patients studied in 1978 and 1979 in the two northern provinces, around half were admitted to hospital directly after the onset of the psychosis, while in forty per cent of the cases there was an average delay of three months before initial contact was made with mental health care providers (Wie98). It is unclear how representative these data are of the situation in the Netherlands today.

In view of the importance of early treatment both for patients and for their relatives (see Chapter 7), it is desirable that research should be conducted in the Netherlands into the duration of the period in question. What is at issue is the time between the first psychotic symptoms (and not the pre-psychotic or prodromal period) and the commencement of treatment with antipsychotics. The duration of this period can be influenced both by the patient's behaviour and by the manner in which care is provided. Depending on the outcome of this research, one might explore whether it is desirable (or indeed possible) to change the way in which first psychoses are managed. Besides possible changes in the handling of referrals, one might also consider the possible effects of public information.

## **Ethical, legal and social aspects**

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### **9.1 Ethical aspects**

Ethical aspects of early detection of schizophrenia relate primarily to detection in the pre-psychotic phase. Early diagnosis and treatment of an existing psychosis do not raise any particular ethical questions and their importance for the patient is both evident and conclusive.

Early treatment is usually also important for the family and close friends of the patient. Pre-psychotic detection, on the other hand, raises various ethical problems. Schizophrenia is an important health problem with both high economic and human costs. Furthermore, guidelines exist for the treatment of patients with this disease and facilities for diagnosis and treatment are available in the Netherlands. Thus the first three criteria for a screening programme, as laid down by Wilson and Jüngner, are satisfied (Wil68). The fourth criterion — ‘there should be a recognizable latent or early symptomatic stage’ — does, however, raise a problem. In the present situation, those patients who are recognized at a latent (pre-psychotic) stage will include a considerable number of false positives (as explained in Chapter 7). Even if these individuals can be carefully counseled and do not shun contact with the researchers, a certain degree of stigmatization is unavoidable (Yun97). There is a high risk that family and close friends, in particular, will begin to view the patient in a different light. It is therefore conceivable that those patients will begin to regard themselves as a problem, which can have particularly negative repercussions for further development during the adolescent period. This can adversely

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influence contact with a partner, the choice of career and the formation of a social network. It is unclear what might be done to overcome these negative effects.

Aside from the false positives, early detection is also not without its drawbacks for true positives (those who do, in fact, ultimately develop a psychosis). The advantage of timely commencement of therapy is obvious, even if there is no causal relationship between the duration of the untreated period and the outcome (see Chapter 6). It is possible, however, that several years may elapse between the time of detection and the first onset of a psychosis (schizophrenia typically manifests itself at between 20 and 35 years of age). In the case of those for whom this period is protracted, the disadvantages — in terms of uncertainty and the time spent on supportive counselling — may outweigh the ultimate benefit. The concern that pre-psychotic detection arouses in family and friends — although ultimately justified — also becomes more of a burden the longer the period lasts.

If pre-psychotic detection could mean the difference between the patient recovering or not, then the above problems would not appear to be decisive. Even if it were to be demonstrated that detection under these circumstances brings a substantial improvement in the quality of life, one could look for a method that incorporates the best possible forms of counselling. As explained in Chapters 4 and 6, however, this does not apply in the case of pre-psychotic detection of schizophrenia and related disorders. The experts consulted during the preparation of this report therefore felt constrained to advise against (trial) population screening.

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## **9.2 Legal aspects**

Screening of individuals with a disease is subject to a number of legal precepts. As is the case with other forms of medical research, participation is only possible on a voluntary basis and privacy needs to be carefully protected. Because the investigation in question is offered in an unsolicited manner and for the benefit of the subjects, this can be regarded as population screening as defined in the Population Screening Act (WBO). Under the WBO, screening requires a permit if it involves the use of ionizing radiation or if it relates either to a malignant disease or a serious disease for which prevention or treatment is impossible. These qualifying conditions do not apply in the case of schizophrenia. Although in many cases complete recovery is not achieved, effective therapies are available (see Chapter 4). The above-mentioned Act is being reviewed in the course of 1999, partly with regard to its scope. In view of the above-mentioned problems in relation to population screening for schizophrenia, it should be possible for this review to consider whether serious psychiatric disorders also fall within the scope of the WBO.



Any legal complications with regard to the involuntary admission and treatment of patients fall outside the ambit of this report. (An advisory report on involuntary admission and treatment is, in fact, being prepared by the Health Council.)

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### **9.3 Social aspects**

From a social point of view, early detection of schizophrenia is important due to the possibility of reducing the harm which the disease does to social relationships and educational and career opportunities. Early treatment can, at least, reduce the duration and severity of a psychosis. Detection is all the more important because schizophrenia is a disease which occurs at a relatively young age. However, the degree of social benefit that is to be derived from detection in the pre-psychotic phase (in terms of working years, for example) is unclear. Furthermore, the detrimental effect which negative expectations for the future could have on a large number of false positives may negate this advantage. It is difficult to assess the direct costs of a pre-psychotic screening programme in the absence of a clear picture of the methodology that is to be applied. However, it can be assumed that conducting psychological tests on large numbers of people and intensive counselling by health-care professionals will require considerable expenditure. Because the specificity and the sensitivity of screening programmes are low (Chapter 7), the disadvantages for society probably outweigh the advantages. As was stated in Chapter 8, too little is known about the duration of the period between the first psychotic episode and treatment to allow for screening of patients with first-episode psychosis. Evaluation of the social impact will only be possible once more data has been gathered.

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A      The request for advice

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B      Experts

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## Annexes

## The request for advice

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The Minister of Health, Welfare and Sport wrote the following in a letter to the President of the Health Council of the Netherlands on 29 August 1997 (letter ref: GVM/GGZ/972470):

I agree with your analysis with regard to the issues on which the Health Council is able to offer advice. The outcomes of the analysis are such that the Health Council will need to examine the following issues:

- the care of acute psychiatric patients in the community
- the application of the Special Admissions to Psychiatric Hospitals Act (the ‘Bopz’ Act);
- the health effects of sexual abuse;
- the diagnosis and treatment of ADHD;
- post-traumatic stress disorder.

Of the issues mentioned, it is the first two that, in my opinion, cannot be regarded separately from each other and should have the highest priority. I would therefore request that they be given primary consideration. Please note, incidentally, that the Council for Health and Social Service (RVZ) has also been commissioned to advise on these two issues in connection with an advisory report on ‘The Role of Coercion and Force in Health Care’. I would ask you to take this fact into consideration. First of all, however, I have one further question with regard to the early detection of schizophrenia, which I shall explain as follows.

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## **Screening and treatment of adolescents with schizophrenia**

Recent research results indicate in a number of cases that early treatment of people with schizophrenia has a beneficial effect on the course of the disease. Based on these results, some observers are advocating (trial) population screening for schizophrenia. I would like to receive a report from you about the current level of knowledge in this area, both with regard to the categories of patients who qualify for such a programme and with regard to the possibilities for early diagnosis/screening and prevention. I would ask you also to include the ethical and legal aspects of this issue, such as the question of whether the Population Screening Act is applicable in the case of screening for schizophrenia, as well as questions regarding voluntariness, the protection of privacy and the protection of the social position of people diagnosed at an early stage as having 'schizophrenia'.

## **Care of acute psychiatric patients in the community and the application of the Special Psychiatric Admissions Act**

The fact that timely treatment of people suffering their first psychotic episode can reduce the risk of permanent defects arising raises the following question. The Special Admissions to Psychiatric Hospitals Act ('Bopz') only allows such rapid treatment on a voluntary basis. However, people who are experiencing the first symptoms of schizophrenia do not, as a rule, possess sufficient insight into their illness such that they are willing to allow themselves to be admitted to hospital and treated on a voluntary basis. In practice, therefore, these individuals usually remain untreated until such time as their situation has deteriorated to such an extent that they satisfy the criteria stipulated in the 'Bopz' Act with regard to involuntary admission and compulsory treatment.

If rapid treatment is, in fact, advisable from a medical point of view, should the 'Bopz' Act be applied to this group of patients? To put this question in more concrete terms: In view of the potentially permanent health impairment that might result from treatment that is late (or too late), should it not be possible to administer treatment earlier than is currently allowed by this Act and against the wishes of this category of patients?

With regard to the first point which you raised concerning the care of acute psychiatric patients in the community, it is also important to consider what out-patient care and supportive counselling is (or should be) available for individuals who urgently require treatment otherwise than by involuntary admission via the 'Bopz' Act. In this connection, consideration needs to be given to relations with the public mental healthcare services and the problems of severely neglected individuals with psychiatric (and/or addiction) problems. Also relevant in this context are the opportunities (or perhaps the lack of opportunities) for 'compulsory treatment in the community'.

As already stated, I believe that the above-mentioned topics take priority over the other issues mentioned in your letter. I would, however, at some later date like once again to discuss depression and traumatic stress disorder with you as possible topics for further advice by the Health Council. The same applies to the question of the health effects of sexual abuse. This is, incidentally, a subject which I firmly believe needs to be emphasized in its own right. It is for this reason that I have already set in motion various activities aimed at improving the provision of care and the development of initiatives designed to prevent sexual violence. The Netherlands Foundation for Health Care Research (ZON) will also be promoting and initiating a number of related research and development activities. These initiatives will, at a later stage, provide me with a firm foundation on which to base a Ministerial Commission to the Health Council.

Yours sincerely,

The Minister of Health, Welfare and Sport,

(signed) Dr E Borst-Eilers



## Experts consulted

- 
- C Bernardt, team leader at the Crisis Service for Central/Old-West/North Amsterdam
  - Dr RJ van den Bosch, Professor of Psychiatry at the University of Groningen
  - Dr BPR Gersons, Professor of Psychiatry at the Academic Medical Centre (AMC), Amsterdam
  - Mrs R van der Heijden, contact person and founder of Ypsilon, the association of relatives of people with schizophrenia or psychosis
  - Dr RS Kahn, Professor of Psychiatry at the University of Utrecht
  - Dr DH Linszen, Head of Clinic at the Adolescent Psychiatry Clinic of the University Medical Centre (AMC), Amsterdam
  - Dr HGM Rooijmans, Professor of Psychiatry at the University of Leiden Medical Centre

This report was written by Dr PA Bolhuis, Secretary of the Health Council.