Panic Disorder, a specific clinical entity?

an exploration into psychological and biochemical aspects.

Paniekstoornis, een specificke ziekte eenheid?
een verkenning naar psychologische- en biochemische aspecten.

Proefschrift

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"Many lamentable effects this fear causeth in men, as to be red, pale, tremble, sweat; it makes sudden cold and heat to come over all the body, papitations of the heart, syncope & c."

From: The anatomy of melancholy by Robert Burton 1651

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COURSE AFTER SIX AND NINE MONTHS

DISCUSSION ON THE GROUP OF PATIENTS NOT ON MEDICATION AT INCLUSION

INTRODUCTION

The prevalence of panic disorder with or without avoidance behavior during life is 2%. The percentage of people who suffer from panic attacks without satisfying the criteria for panic disorder is much higher and has a prevalence of 10% during life. There is a great deal of similarity between panic disorder and another frequently occurring psychiatric disorder namely major depression. Not only do patients with panic disorder have a nineteen times higher risk of developing a depression during life then may be expected by chance alone, but the relationship between the two afflictions also appears from a certain degree of similarity in association with response to provocation tests such as the lactate infusion test, the CO2 inhalation test and from a considerable level of similar response to treatment with psycho-pharmaceutical drugs such as various tricyclic antidepressants and inhibitors of serotonin uptake.

There are a number of hypotheses for explaining the co-morbidity between panic disorder and depression. Some of these explanation models are:

1. There is a symptomatic overlap between two etiologically different afflictions.
2. One can speak of a continuum between panic disorder and depression. This continuum may be of etiological-, chronological- and/or psychopathological nature.
   In other words: Panic disorder not only has its own etiology, but may also be an etiological factor in the development of depression.
3. Panic disorder and depression are in essence one and the same psychiatric disorder but one can speak of multiple presentation forms. Clusters with a profile composed of more symptoms of panic disorder or more symptoms of depression may arise from a large number of possible symptoms.

Multi-dimensional investigations into panic disorder are described in this thesis.

The principal question was whether there was a single central biologically determined disorder in patients suffering from panic disorder and/or depression. Differences in psychological defense organization and coping strategies would then possibly determine whether a patient either develops panic disorder or depression.

In our investigations, in addition to psychological aspects such as defense organization and indicated coping strategies, several biochemical parameters including serotonergic, amino acids and the ß-carboline norharman and the inter-correlationship between biochemistry and psychology were also investigated in groups of patients and a reference group.

Following the first part of this investigation, treatment of the 3 groups of patients (with depression, panic disorder and depression with panic disorder) with antidepressants and cognitive therapy according to protocol was undertaken.

The effects of this treatment on the complaints of the patients, on the psychological characteristics such as defense organization & coping strategies and on a number of biochemical parameters were all assessed after treatment for six months. Three months after the termination of the treatment and discontinuation of the antidepressant, a follow-up investigation was undertaken in a limited number of patients in order to assess the eventual remaining therapy-associated changes in the personality characteristics and biochemical parameters

Chapter 1

CHAPTER 1. PANIC DISORDER, AN UPDATE

Introduction

The modern division of anxiety syndromes or anxiety disorders has a history of more than a hundred years. The current classification and insights arose from investigations and assumptions from clinical presentations and syndromes such as neurasthenia, heart neurosis, anxiety neurosis, Da Costa's syndrome, effort-syndrome, irritable heart, nervous exhaustion, neurocirculatory asthenia, vaso-motor neurosis, psycho-vegetative syndrome and so forth [Kelder 1989].

Most of the above mentioned diagnostic entities indicate that a particular aspect of what we until today refer to as anxiety disorders stood central as heart neurosis or "soldier's heart" for the investigators and clinicians of that period.

In 1871, Da Costa described the irritable heart. He observed that during the American civil war, not only sudden pain in the heart region accompanied by severe heart palpitations, but also impaired vision and dizziness occurred in otherwise healthy young men. Interestingly enough, fear was not mentioned. Da Costa attributed one and the other to hyperaesthesia in the nerve centres of the heart.

This syndrome was later renamed as "effort syndrome", considering the limited tolerance for physical effort.

Later, the term neurocirculatory asthenia and even later the concept of heart neurosis appeared.

Soon after the description by Da Costa, Beard introduced the term neurasthenia, also known as "American nervousness" in which he postulated that a deficiency in nervous energy was the cause of many of these symptoms. Many solid anxiety illnesses and phobias are come across in his description. Beard attributed the syndrome to the stressed and exhaustive American way of living.

In the DSM-IV, anxiety disorders are divided into phobias and anxiety states which include panic disorder and generalized anxiety disorder, obsessive-compulsive disorder and post-traumatic and acute stress disorder.

Panic disorders are subdivided into those with and those without avoidance behaviour and a quantitative norm concerning the frequency of panic attacks and duration of complaints has been added to the definition of panic disorders [DSM-IV 1994].

Agoraphobia is now classified under panic disorder with avoidance behaviour. Agoraphobia without panic attacks is considered separately.

The assumption that panic attacks are connected with agoraphobia is almost a hundred years old. In 1895, Freud commented that " in the case of agoraphobia, we frequently find the reminder of an anxiety attack and what the patient fears most in reality is the occurrence of such an attack under particular situations which he considers to be unavoidable" [Freud 1961].

The **symptomatology** of panic disorders consists of psychic and somatic symptoms (see table 1).

The somatic symptomatology includes dizziness, tachycardia, increased sweating, dyspnea, flushes,polyuria, nausea, lump in the throat (choking) and paraesthesia.

The psychic symptomatology includes feelings of unrest, fear of dying, fear of going crazy or doing something impulsive, tendency to faint, distorted perception and feelings of depersonalization and derealization.

Table 1. Symptomatology of panic disorders

1. Acute anxiety/panic, occurring spontaneously or in particular situations in which the patient without the trusted companion feels lost in busy crowds, open spaces, public transport etc.
2. Fear, often converting to fear of dying, fear of going crazy or losing control of oneself.
3. Vegetative complaints such as dyspnea, choking, dizziness, feeling faint, palpitations, tachycardia, chest pain or discomfort, trembling, shivering, sweating, cold and/or hot flushes, nausea, paraesthesia.
4. Depersonalization and derealization, sometimes also distorted perception of environment and own body.

Source: The Practitioner 9, 2 February 1992, p. 2. L. Pepplinkhuizen.

There is a definite sequence in which the symptomatology of the phenomena in panic attack develops. The early symptoms are dyspnea, flushes, pain in the chest and palpitations. Dizziness, increased sweating, feelings of derealization and tendency to faint all occur later. The psychic anxiety feelings mostly occur late. This may indicate that psychic anxiety depends on a response to the somatic phenomena [Katerndal 1988]. The experience from the cognitive therapy is that panic attacks are mostly accompanied by hyperventilation, evoking physical sensations which are misinterpreted by the patient as "catastrophic" and which induce psychogenic anxiety.

Hyperventilation probably causes distress in those who have a predilection to fear and misinterpret their bodily responses to lowered CO2 [Chambless 1990].

Epidemiology

From investigations in different parts of the world, it appeared that the prevalence of anxiety disorders was rather uniform. A prevalence of 2.9% to 8.4% was observed in population studies [Marks 1986].

Recent investigations into the epidemiology of panic disorders showed a 6- months prevalence of 0.6% to 1.5% (USA, Zurich, Munich, Kangwha Islands, Korea) [Humble 1987]. It was noteworthy that more women than men suffered from panic disorders. The difference between men and women varied from 50% to 200% in various studies.

Table 2. Prevalence of panic disorder at different sites

Community survey		Prevalence period Prevalence (%)		
Prevalence period		**Total**	**men**	**women**
New Haven[a]	6 months	0.6	0.3	0.9
Baltimore[a]	6 months	1.0	0.8	1.2
St. Louis[a]	6 months	0.9	0.7	1.0
Zurich[b]	1 year	1.5	0.7	2.2
Munich[c]	6 months	1.1		
Kangwha Islands[d]	lifetime	1.4		
Stockholm county[e]	1 year	0.8	0.5	1.2

Source: M. Humble. Acta Psychiat Scand 1987; 76: 22.

The prevalence of anxiety disorder during the lifetime varied from 10% in men to almost 20% in women, 3.8 % being contributed by panic disorder [Rorseman et al 1987].

In a large study in 18000 adults in America, Robins observed that during their lifetime, 24% of the investigated adults had the feeling of nervousness, 9% had isolated panic attacks, 3.6% had relapsing panic attacks which did not completely satisfy the criteria for panic disorder with regards to insufficient symptoms, duration or frequency of attacks and 1.5% satisfied the DSM-III-R criteria for panic disorder during their lifetime [Robins 1990].

The same prevalence in panic disorder was observed in Edmonton, Puerto Rico, New Zealand, Munich, Florence and Seoul [Weissman 1992].

Panic attacks mostly occurred for the first time in the second decennium of life. The average age at which panic disorder began was 26 years [Crowe 1983]. Occurrence after the age of 40 years is rare, but panic attacks in children are relatively frequent and may be diagnosed as separation anxiety disorder and school phobia.

Genetic aspects of panic disorder

During more than a hundred years, investigators observed that anxiety disorder was frequently "in the family".

Long before our modern specific diagnostic categories for anxiety disorders were established, it was known that neurasthenia, soldier's heart and other anxiety disorders occurred more frequently in family members of patients with anxiety disorder than in family members of healthy individuals. In older studies, the incidence of anxiety disorders in the first degree relatives of patients with anxiety disorder was observed to be about 15% [Carry 1981].

In a more recent study in family members of patients with panic disorder or generalized anxiety disorder, the incidence of panic disorder in the first degree relatives was observed to be 24.7%. In a control population, this figure was 2.3%.

A similar difference was not observed for generalized anxiety disorder. The chances of occurrence of panic disorder in female family members was twice that in male family members of patients with panic disorder [Crowe 1983].

Although family studies indicate a genetic basis for psychiatric disorders, environmental influences should also be investigated because they may be the cause of familial occurrence of such disorders. Studies in twins offer a way to investigate whether genetic factors are really important for familial occurrence. The principle behind such studies in twins is that the percentage of afflicted patients of each genetically determined disorder would be higher in monozygotic than in dizygotic twins. Concordance for each pair of twins can be determined. If the concordance in the monozygotic twins is higher than that in the dizygotic twins, it is likely that genetic influences predominate over environmental influences. For panic disorder, this concordance was observed to be five times as frequent in monozygotic compared to dizygotic twins, but no difference was observed for generalized anxiety disorder [Slater 1979; Parkinson 1983].

Kendler et al. [1993] found in a population based twin study that the familial aggregation of panic disorder was due largely to genetic factors.
They estimated that the heritability of liability ranged from 30 to 40%.
From a familial perspective, panic disorder with phobic avoidance appeared to represent a more severe form of the syndrome than panic disorder without avoidance.
Prevalence of panic disorder in the first degree relatives of patients with panic disorder varied between 7% and 20% [Weissman 1990].

Life events and panic disorder

Although for the patient, the first panic attack occurs as a most unpleasant "spontaneous" surprise, it seems that frequently, some important event has occurred in thelife of that patient in the month preceding the first panic attack. It is not uncommon that the first panic attack occurs during a serious illness, after an accident, after loss of an important individual (separation trauma), but it can also occur in the period post-partus or after use of alcohol, marijuana, cocaine or amphetamines [Blaser et al 1987; Fagaval et al 1989].

A disrupting factor in the sense of a life event was demonstrated in 40% of the cases (see table 3) and 52% of the patients suffered from prodromal depression or from generalized fear before the first panic attack [Lelliott et al 1989].

Table 3. Precipitating factors in the first panic attack

Quarrels in family or marriage	11%
Illness in the family	8%
(Pending) divorce	6%
Pregnancy and birth	4%
Death of a friend or a family member	4%
Physical illness	2%
Financial problems	2%
Other events	6%
Total with direct causes	43%

Source: Lelliott et al. AGP 1989; 46; 1000-4.

Attempts to type **personality disorders** in patients suffering from panic disorder progress with great difficulty. Dependant, avoiding as well as hysterical characteristics have been described, in addition to borderline personality disorders and patients with underlying eating disorder [Class et al 1989; Mavissakalian et al 1988; Reich et al 1987].

The association between personality disorder and panic disorder in general can be regarded as weak.

Similar personality profiles were obtained in a heterogeneous population of psychiatric outpatients or patients with social phobia, obsessive-compulsive disorder and major depression.

At the same time, it should be remembered that personality disorder may be secondary to panic disorder.

A number of patients mentioned that prior to panic attacks and complaints of phobia they led an independent life with a certain amount of confidence. This was in sharp contrast to their frightful clinging to their partners in the period when panic disorder first struck.

However, personality pathology does predict a poorer response to treatment in patients with panic disorder [Reich 1991].

There is a link between separation anxiety and separation trauma in early life and symptoms of panic in adulthood. This is possible due to a endogenous neurophysiological vulnerability expressed as a heightened sensitivity to separation. There is a tendency for separation anxiety to aggregate in families [Klein 1980,Silove & Manicavasagar 1993].

Co-morbidity: panic disorder and depression

The distinction between panic disorder and depression has caused much scientific controversy and clinical confusion. Some investigators speculated that panic disorder

may be a form of depression. This speculation was supported by the observation that patients with panic disorder and agoraphobia demoralized quickly. Life with recurring panic attacks or extensive phobic avoidance eventually leads to despair and hopelessness. Others regarded panic disorder and depression as different entities. Marks suggested that treatment of panic disorder with antidepressants was only effective if the patient was also depressive [Marks 1983].

Meanwhile, there is substantial evidence that this theory is incorrect [Klein et al 1989]. Indeed, the co-diagnosis of depression in patients suffering from panic disorder is frequently made and those suffering from depression have frequent panic attacks, particularly if the patient also suffers from social phobia [Angst et al 1985; Stein 1990].

In a narrower sense, the prevalence of depression in patients with panic disorder is 30%-70%, whereas 20%-30% of the patients with major depression develop panic disorder during their life [Pelicier 1992].

It has been suggested that anxiety disorders and depressions have common diathesis and shared vulnerability (see also chapter 3). This hypothesis implies that anxiety disorders and depressions are expressions of the same affliction [Coryell et al 1992].

Genetic studies, however, tend to indicate that depression and anxiety disorders coexist rather than being casually related. Less often, it represents an associated independent entity [Cassano 1989]. Goldstein et al [1994] examined in a family study of 1047 adult first degree relatives of 193 probands in four diagnostic groups:panic disorder, panic disorder with major depression, early onset major depression and screened normal controls. They concluded that panic disorder is a specific familial entity that is not associated with a broad range of other anxiety or other psychiatric disorders, with the possible exception of social phobia. Depression seen in the course of panic disorder most commonly represents symptomatic elaboration or complication of panic disorder.

Apart from the risk of developing depression, there is a high risk of parasuicide and successful suicide in patients suffering from panic disorder [Coryell et al 1991]. There is a 40% chance that during his life, a patient suffering from panic disorder will make a (para)suicidal act.

The development of alcohol and/or medication dependence is another important risk in patients suffering from panic disorder. About 30% of such patients run the risk of developing secondary abuses of alcohol [Reich et al 1987; Helser et al 1988]. There is also a 30% chance of benzodiazepine "addiction" [Cox 1989].

Outcome studies

The most important methods for treating panic disorder are psychotherapy, namely cognitive/behaviour therapy, treatment with tricyclic antidepressants, monoamine oxidase inhibitors (MAOI) or benzodiazepines. Often, a combination of treatments is used.

In a study published in 1981, a follow-up for 5-10 years in 54 outpatients who were treated for anxiety neurosis was reported. Thirty-two of these patients suffered from

primary panic disorder. Most of the patients (28 of the 32) reported that already as a child they were nervous or had phobias. In later life, 24 of the 32 patients developed depression which was serious enough to warrant professional treatment [Cloninger et al 1981].

Sixty patients with panic disorder and agoraphobia were interviewed 2 to 4 years after completing a 4 months treatment with medication and behaviour therapy. During the follow-up interview, 18 patients had stopped the medication, 36 patients used a low-dose, 3 patients used the originally prescribed dose and 3 patients used an increased dose of medication. During the initial phase of the investigations, the number of panic attacks was 4-5 per week, but during the follow-up the number of panic attacks was 1-2 per week. As far as the behaviour variables were concerned, an improvement was noted in all patients. Patients who had been depressive tended to relapse inspite of continued medication [Nagy et al 1989].

Personality disorders are quite common and are of predictive value. Medication for treating panic disorder was less effective in a group of patients with personality disorders than in a group without personality disorders [Mavissakalian et al 1988; Reich 1988].

The oldest studies on the treatment of panic disorder with **medication** are with imipramine and MAOI [Klein 1964; Klein et al 1978].

The average dose of imipramine that was required to completely block panic attacks was 150-200 mg/day [Zitrin et al 1983].

From the group of MAOI, fenelzine was investigated. In one study, fenelzine was observed to be superior to imipramine [Sheehan et al 1980]. The disadvantage of fenelzine was that the patients had to be put on a diet without tyramine to avoid hypertension crisis. Some patients on this medication also suffered from serious orthostatic hypotension and sleeplessness. At present, clomipramine is usually selected when treating panic disorders with tricyclic antidepressants [Cassano et al 1988].

New serotonin-uptake inhibitors were also effective for treating panic disorders [Den Boer et al 1987, 1988]. It seems likely that the drugs which prominently affect the serotonergic system are more effective in panic disorders than those drugs which affect the noradrenergic system. The selective, reversible, Monoamine-A inhibitors, moclobemide and brofaromine also appeared to be effective for treating panic disorders and were without the side-effects of the classical, non-selective MAOI, [Garcia-Doreguardo et al 1991; Berger et al 1991].

In the last few years, it has become evident that benzodiazepines, namely alprazolam, may be effective in blocking panic attacks and anticipatory anxiety [Deltito 1991; Balestrieri 1989].

There are still very limited data available on the intermediate- and long-term secondary pharmacological treatment of panic disorders. A study in which imipramine and alprazolam were used indicated that during treatment for 8 months, the therapeutic effect was maintained without development any serious side-effects or a need for any increase in the dose [Curtis 1991].

It is advisable to recommend treatment for a minimum of 12 months to limit the chances of a relapse. Mavissakalian & Peril [1992] reported that 75% of patients with panic

disorder and agoraphobia who had shown marked and stable response to 6 months of acute treatment with imipramine relapsed within 6 months of discontinuing the drug. One year maintenance treatment with the antidepressant proved to have protective effects against relapse.

Long-term treatment is especially indicated in patients in whom there is a poor long-term prognosis based on for example, co-morbidity in the sense of mood disorder, personality disorder, extreme avoidance behaviour and/or serious social limitations. These patients may benefit from a flexible integration of pharmacological and cognitive-behaviourial treatment [Katschnig 1991; Pollack 1990].

Investigations into prevention of relapse in unipolar depressions have provided data which may also be successfully used to treat patients with panic disorders.

It seems likely that the best way to either prevent or to lower the frequency of relapse is to maintain the same dose of medication on which the patients initially improved. In depressive patients, the prognosis was improved further with psychotherapy [Kupfer et al 1991].

When a potent benzodiazepine is used in the treatment of panic disorder, it is recommended to slowly taper-off this medication in 3-6 months and every symptom thatarises during the tapering-off should be carefully evaluated because not only could the initial symptoms of panic disorder recur, but there may be a case for withdrawal symptomatology which may require a different approach. There is some evidence that slow, partial tapering-off of medication, namely benzodiazepine, helps to prevent relapse and to maintain the therapeutic benefit [Ballinger 1991].

Cognitive-behavior therapy was also effective in the treatment of panic disorders with agoraphobia [Klosko et al 1990].

Uncontrolled studies showed that cognitive therapy was valuable in the treatment of panic disorder.

In three controlled studies, cognitive therapy was shown to be more effective than supportive therapy and relaxation training, but was as effective as alprazolam.

In Oxford (UK), in a clinical trial in patients with panic disorder, cognitive therapy was compared with imipramine, with intensive relaxation and with a group of patients on waiting list. Patients in the cognitive therapy group showed more improvement than others after 3 months, at the end of the psychotherapeutic treatment and after 15 months. The group of patients on waiting list did not improve significantly [Gelder et al 1991].

One session per week of exposure therapy appeared to be sufficient to obtain good results in panic disorder with agoraphobia [Chambless 1990]. For well-motivated patients who can practise self-exposure on their own, it is often sufficient to provide adequate explanation of the disorder and to prescribe medication. Cognitive therapy alone is sometimes insufficient to totally suppress panic attacks. In patients in whom anticipatory anxiety prevents self-exposure, a combinaton of medication and behaviour therapy are necessary [Klein et al 1987].

In general, the prognosis for patients suffering from panic disorder is not entirely favourable. In a recent long-term follow-up study of 2-6 years in 423 patients who were treated with medication, it appeared that 31% of the patients remained convalescent after the medication period had expired. The remainder of the patients developed episodic or mildly chronic course, whereas 18.6% of the patients continued to suffer from serious chronic panic disorder [Katschnig et al 1991].

Conclusion

The biological, genetic, personality and life events studies indicate that panic disorder is caused by a combination of biological predisposition, life events and psychological maintaining factors. The results of outcome studies indicate that the advocates of both a poor and of a bad outcome in panic disorder are correct since the outcome of panic disorder depends from a number of variables. An important prognostic factors is among others: Comorbidity with personality-, and other psychiatric disorders namely depression (see also chapter 3).

In general, more than half of the patients suffering from panic attacks and agoraphobia maintained substantial improvement, 10%-20% showed full recovery at follow-up and up to 20% remained seriously ill [Hirschfeld 1991].

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Chapter 2

CHAPTER 2. BIOLOGICAL ASPECTS OF PANIC DISORDER

Introduction

Panic disorder with or without agoraphobia is a condition determined by multiple causes with a prevalence of 1.2% to 3.8% during life. The disorder clearly occurs more frequently in women than in men. This, often invalidating disease, also has a high risk of other psychiatric disorders such as abuse of alcohol and benzodiazepine, depression and suicide[1].

In the etiology of panic disorder, as we have discussed in chapter 1, the following, among others, play an important role:
1. Genetic and biological factors[1,2] 2. Separations in the early youth[3,4] 3. Personality characteristics[5] 4. Psychosocial factors[6] 5. Recent events[7]

In this chapter, the biological-psychiatrical theories concerning the origin(s) of panic disorder are presented.

The biological aspects of panic disorder involve the participation of the noradrenergic, the serotonergic and the gamma-aminobutyric acid (GABA) systems, in addition to the role of peptides and neuro-anatomical factors.

In recent years, serotonin (5-hydroxytryptamine, 5-HT) has been at the center of research into the role of neurotransmi-tters in psychiatric disorders. There are strong indications that 5-HT is involved in several diverse psychiatric disorders including, aggression, suicide, Alzheimer's dementia, anorexia nervosa, alcoholism, depressions and anxiety disorders[8].

The function of the noradrenergic (NA) system was extensively investigated previously. The findings established the importance of the foremost nucleus of NA: the locus coeruleus in panic disorders. The discovery of the bezodiazepine/GABA receptor complex provided additional information on the role of the GABA system in anxiety disorders[45,46].

The importance of some peptides in panic disorders has only come to light in the last few years and besides etiological research, also offers possibilities for new provocation tests for panic attacks.

The possibilities of functional neuro-anatomical investigations in psychiatric disorders by means of single photon emission tomography (SPECT)- and positron emission tomography (PET)- scans have increased enormously. This lead to correlations between regional brain function and psychiatric disorder.

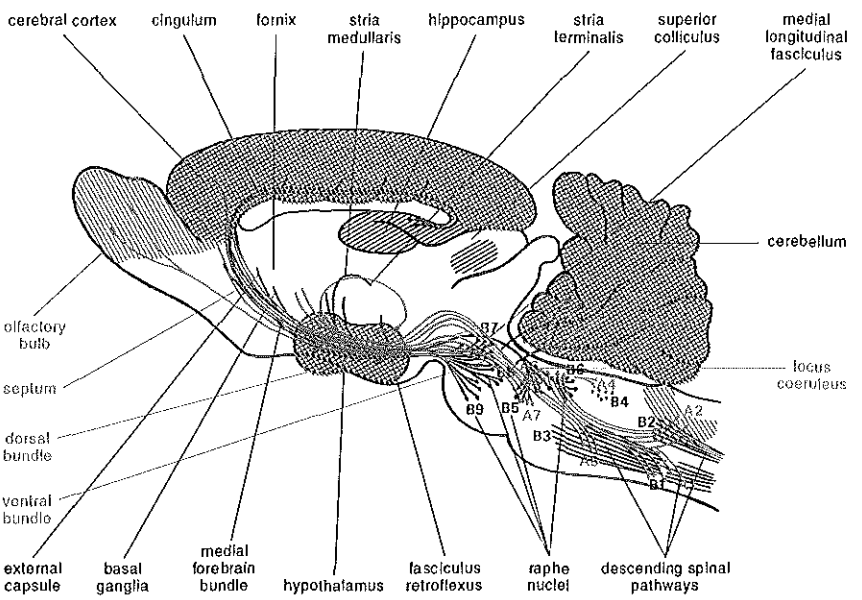
The following biological topics are dealt with in succession: The serotonergic-, noradrenergic- and GABA-theory on the origin(s) of panic disorder, the role of peptides and finally neuro-anatomical hypotheses on panic disorder.

The serotonergic hypothesis

The most important serotonergic nuclei in the brain are the dorsal and median raphe

nuclei situated in the brainstem. They have afferent and efferent connections to many parts of the brain such as the cortex, hypothalamus, thalamus, hippocampus, septum and substantia nigra (see Figure 1).

Figure 1. Major serotonin and norepinephrine neural tracts in rat brain



Note: Serotonin tracts color: red Norepinephrine tracts color: black (After Young J.A., Cohen D.J.: "The molecular biology of development", in: Basic Handbook of Child Psychiatry. New York Basic Books, 1979).

There is a close association between the serotonergic system, the dorsal raphe nuclei and the noradrenergic system, the locus coeruleus being the most important[9]. Animal studies showed that lowering of the 5-HT function resulted in decreased anxiety, whereas stimulation of the 5-HT function induced anxiety[10]. The finding that inhibitors of serotonin uptake had a therapeutic effect in patients with panic disorders strongly indicated that 5-HT also played an important role in decreasing anxiety in humans[11].

The anxiolytic effect of antidepressants is probably brought about via the down-regulation of the hypersensitive 5-HT receptors. Kahn & Van Praag postulated that over-sensitivity of some of the serotonin receptors may be a pathogenetic mechanism in panic disorder[12,13]. The down-regulation which develops upon chronic administration of antidepressants probably occurs in order to compensate the increase in 5-HT caused by these antidepressants in the synapse cleft. A short-term effect of this increase may be

responsible for the temporary worsening of the disorder during the initial weeks of treatment[14]. However, other investigators attributed the actual effect of antidepressants to an increase in the function of 5-HT[15]. There are various 5-HT receptors. Each one of these receptors has a specific pre- or post-synaptic location in the brain. The 5-HT_{1A} receptor is particularly important in panic disorder[15].

Pharmaceutical drugs such as ritanserine and buspirone (Buspar®) which act on receptors other than the 5-HT_{1A} receptor, appeared not to be effective in the treatment of panic disorders[15-17]. The exact function of the 5-HT_{1A} receptor is unclear. Hypothetically, it can be stated that an inhibitory effect on the 5-HT system via the 5-HT_{1A} receptor probably leads to anxiolytic effect, whereas over-activity in the 5-HT pathways, namely of the ascending dorsal raphe system may cause pathologic anxiety[8]. Although there is still discussion on whether there is a specific 'serotonergic disorder' which accompanies panic attacks and on the nature of this disorder (hypo- or hyper-activity), there is consensus on the fact that a number of drugs which act on the system are effective in the treatment of panic disorders. In a double-blind study in which the serotonergic-acting fluvoxamine (Fevarin®) was compared with the noradrenergic-acting maprotiline (Ludiomil®), Den Boer observed that maprotiline was considerably less effective in the treatment of panic disorder[8]. However, no differences in the affectivity for treating panic disorders were observed in a recent study in which a prominently noradrenergic-acting desipramine (Pertofran®) and largely serotonergic-acting clomipramine (Anafranil®) were compared[18].

The selectivity of these drugs and their metabolites at the levels of neurotransmitter and receptors is, however, not very high. Therefore, it is highly desirable that the investigations reported by Den Boer[8] should be repeated with drugs that have a higher selectivity for serotonergic- and noradrenergic-action.

The different hypothesis concerning the role of the serotonergic system in panic disorder have been given in table 1.

The noradrenergic hypothesis

The most important center of the central noradrenergic (NA) neurones is on the locus coeruleus (LC) which is situated at the bottom of the 4th ventricle (Figure 1). The LC receives input via many different neurotransmitter systems including serotonin, opiates, gamma-aminobutyric acid, dopamine and glycine. These modulating neurotransmitter systems probably have an inhibitory effect on the LC. In contrast, corticotrophin-releasing hormone (CRH), glutamate, purine nucleic acids, substance P and muscarinergic and cholinergic systems have an excitory effect. On the basis of these findings, besides the serotonergic system[19], the noradrenergic system also plays an important role in the integration of the adaptive reactions of the central nervous system (CNS) to stimuli from the surroundings, behavior, or physiology-attributed dysfunction of the LC may lead to the development of panic disorder[20,21].

The simplest noradrenergic theory on the origin of panic attacks goes out from an over-activity of the LC[22,23]. The theory is based on the following findings:

- Electrical stimulation of the LC in experimental animals induced behavior which could be interpreted as panic attack, whereas lesions in the LC of monkeys prevented panic attacks after electro-stimulation[23].
- The concentration of 3-methoxy-4-hydroxy-phenylglycol (MHPG), the most important metabolite of cerebral NA, correlated positively with the level of anxiety in patients with panic disorder[24,25].
- Drugs such as yohimbine, a pre-synaptical-acting α_2-receptor antagonist which increase the activity of NA cells in the LC appeared to have an anxiogenic effect. Administration of yohimbine led to an increase in the level of MHPG in the blood[26].
- Drugs such as clonidine (Dixarit®), an α_2-receptor antagonist with an inhibitory effect on the LC via pre- or post-synaptic α_2-receptors appeared to be able to partially block panic attacks[20]. Clonidine decreased the secretion of MHPG more in patients suffering from panic disorder than those in a control group.
- Chronic administration of drugs, tricyclic antidepressants and inhibitors of monoamine oxidase, led to a reduction in the central noradrenergic turnover and a decrease in the activity of the LC[28]. Both tricyclic antidepressants and monoamine oxidase inhibitors appeared to be effective in the treatment of panic disorder[29,30].

The noradrenergic theory is not without controversies. Gorman et al[31] have summarized the points of criticism:

- The effect of yohimbine was not specifically examined in a population of patients with panic disorder, but in a population of psychiatric patients with diverse disorders[31].
- It was reported that the findings by Redmond et al[23] in monkeys were not panic attacks, but concerned arousal[32].
- The investigation by Charney et al[25] in which they observed differences in response to yohimbine administered in a group of patients with panic disorder and to a group of controls was criticized because only a sub-group of patients with more than two panic attacks per week showed a significantly higher increase in the level of MHPG after yohimbine than in the control group. It also appeared that the investigation was not reproducible.
- Imipramine blocked panic attacks. But imipramine had no effect on yohimbine-induced anxiety and only made it worse[33].
- Buspirone stimulated the LC, but did not have any panic attack-provocating properties. It can, however, increase anxiety if given at high doses[33,34].
- Increase in the level of MHPG was not observed in patients with panic attacks which were induced by infusion of lactate[34] and inhalation or exposure to carbon dioxide (CO_2) in vivo for phobic stimuli.
- Electrical stimulation of the LC in humans did not produce panic reactions[36].

Den Boer[37] mentioned the following additional points of criticism on the noradrenergic hypothesis:

- The values for the levels of catecholamines in the plasma, the urine and the liquor in the groups of patients with panic disorder were no different to those in the control

group in most of the studies. The value for the level of MHPG in the liquor of these patients was also normal[38].

- Yohimbine did not only appear to be a noradrenergic-acting α_2-antagonist, but also acted on the serotonergic system as a 5-HT agonist of pre-synaptic receptors and on the dopaminergic system[39,40]. The anxiogenic effect of yohimbine, therefore, could not be exclusively attributed to its antagonistic action on the α_2-receptor, but could also have been due to its action on the 5-HT system.

In addition, it was also confusing that in individuals who were pretreated with alprazolam (Xanax^R), yohimbine overload led to less anxiety, but pretreatment with imipramine offered no protection.

Kahn & Van Praag[12] discussed the problem of the noradrenergic post-synaptic α_2-receptor function as follows:

- The response of growth hormone to clonidine was reduced in patients with panic disorder which indicated a decreased post-synaptic α_2-receptor sensitivity in these patients. The marked decrease in blood pressure after clonidine administration, however, actually indicated an increased sensitivity of the post-synaptic α_2-receptor.

The 'simple' hypothesis of over-activity of the LC via, for example, lowered pre-synaptic α_2-receptor activity[43], therefore, surely does not explain all the findings. It is more likely that there is a sub-group of patients with panic disorder in whom the regulation of their NA function is abnormal[2]. Possibly, CO_2 also plays a role in the development of a panic attack: there is a group of patients whose reaction to inhalation of CO_2 is a panic attack. The brain of these patients may be over-sensitive to CO_2 or that the LC is extra stimulated by carbon dioxide[44,45].

The GABA hypothesis

The neurotransmitter gamma-aminobutyric acid (GABA) also plays an important inhibitory role in anxiety disorders[46]. Important centers of GABA-neurons are spinal cord, cerebellar cortex, nucleus caudatus, cerebral cortex, substantia nigra and the locus coeruleus. Besides noradrenergic receptors, the locus coeruleus also has a high concentration of GABA receptors. Gamma-aminobutyric acid (GABA) has inhibitory effects on among others, the locus coeruleus and on the serotonergic cells of the raphe nuclei[47]. This is an example of the manner in which the different neurotransmitter systems can affect each other.

Specific populations of benzodiazapine-binding sites have been discovered. These sites are linked with certain GABA receptors. It is likely that the action of benzodiazapines on the GABA system is executed selectively via the $GABA_A$ receptors[45,46].

Drugs such as benzodiazapine which are agonists of the GABA function have anxiolytic effect. Drugs such as pentylenetetrazol and flumazenil (Anexate^R) which are antagonists of the GABA function can cause anxiety. The agonistic effect of benzodiazapines on GABA-effect is to open the chlorine ion channels via the so-called benzodiazapine/GABA receptor complex. This causes hyperpolarization of the post-synaptic membrane of the neuron and the neural stimulation is inhibited.

The GABA hypothesis of panic disorder states that there is an abnormal benzodiazapine/ GABA complex in patients suffering from panic disorder[46].

Some investigators were of the opinion that benzodiazapines indeed decreased the anticipation anxiety in patients with panic disorder, but were not effective in blocking panic attacks[48,49]. However, at present, there is clinical proof that potent benzodiazepines such as diazepam (Valium^R), Lorazepam (Temesta^R), alprazolam (Xanax^R) and clonazepam (Rivtril^R) are effective in the treatment of patients with panic disorder[50-54].

Gamma-aminobutyric acid (GABA) is not the only naturally produced substance in the body with a high affinity for benzodiazepine receptors:
ß-carboline-3-carboxylic acid (ß-CAM) derivatives are a group of compounds with an array of biochemical and pharmacological activity. Among others, these compounds demonstrate a high affinity for centrally located benzodiazepine receptors and can act as agonists, antagonists or reverse agonists with regard to benzodiazepine receptor[55,56].
Most of the ß-CAM derivatives have an antagonistic effect on benzodiazepines. Antagonistically acting ß-CAM produced anxiety and stress reactions in rhesus monkeys[55,57].

In humans, administration of carboline monomethylamide which is closely related to ß-CAM led to panic-like reactions[58].

Schouten[59] was the first to demonstrate a ß-carboline, norharman in human plasma. Investigations on the occurrence of ß-carbolines in groups of patients with panic disorder, in view of these data, appear to be interesting and are currently being conducted by us.

In summary it can be concluded that the neurotransmittor GABA plays an important role in panic disorder. There are however other naturally produced substances like ß carbolines, though less well investigated than GABA, who also have affinity for the benzodiazepine receptor.

The role of neuro-active peptide (Cholecystokinin) in panic disorder

Cholecystokinin (CCK) is a neuro-active peptide which occurs in several forms and has both central and peripheral action. In the brain, CCK is present in various areas such as the brainstem, the amygdala and the cortex; the hippocampus is an important center where CCK possibly interacts with the GABA system. Different types of CCK receptors have been described. Stimulation gives an excitory effect on the pyramidal neurons of the hippocampus. This effect can be completely eliminated by benzodiazepines[37]. Cholecystokininoctapeptide (CCK_8) appears to be the most common form of CCK in the central nervous system[60,61].

A difference in the number of CCK_8 receptors between patients with panic disorder and control individuals was demonstrated in clinical investigations. Panic disorder patients have fewer receptors than controls. It was also observed that intravenous administration of CCK_4 (a tetrapeptide neurotransmitter) and the commercially available pentagastrin (a pentapeptide) induced panic-like reactions in healthy volunteers and in a significantly

higher percentage in patients with panic disorder[62]. Neural pathways and receptors of CCK_4 have been identified. Intravenous use of CCK_4 for provocation test in panic disorder was observed to be safe for experiments in humans. Its effect was dose-dependent and appeared to be reliable as far as the reproducibility was concerned.

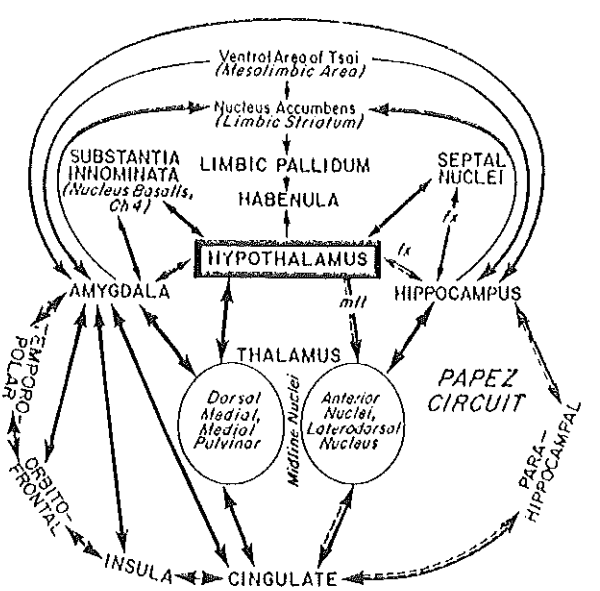
It seems likely that CCK is also important in the etiology of panic disorder. Lydiard et al[63] observed that patients with panic disorder had significantly lower concentrations of CCK_8 in cerebrospinal fluid (CSF) than a control group. They proposed the following hypotheses as an explanation:

- The sensitivity of cholecystokinin receptor is increased in patients with panic disorder. The cholecystokinin activity is lowered in order to compensate this.
- Patients with panic disorder have a decreased number of cholecystokinin receptors which is accompanied by a decreased activity of CCK_8.
- The activity of CCK_8 is decreased as compensation because of a (theoretical) increase in the activity of CCK_4.

The third hypothesis is most appealing on the basis of the provocation tests with CCK_4, but a concluding theory on how the compensation then progresses is, however, lacking.

Neuro-anatomical theories concerning panic disorder The limbic system plays a central role in human emotions including anger, excitement and anxiety. This system consists of amygdala, hippocampus, uncus, nuclei of septum and thalamus, hypothalamus and rhinencephalon wherein, among others, the gyrus para-hippocampus and gyrus cingula. The various parts of the limbic system are linked to each other (see Figure 2).

Figure 2. Limbic connections with relevance for panic disorder



Abbreviations: fx - fornix, mtt - mammillothalamic pathways. (after Mesulam: 'Neural substrates of behavior: the effects of Brain Lesions upon mental state', in: Th New harvard Guide to Psychiatry. Cambridge, Massachusetts, and London, England; Harvard University Press 1988).

A central role is set aside for the hippocampus and gyrus cingula in dealing with emotions which come from the cortex. Lesions in gyrus cingula, with links from the brainstem to frontal cortex and from the frontal cortex to the gyrus para-hippocampus, cause a decrease in the ability to experience anxiety in humans. In recent years, investigations on the imaging of brain with the aid of SPECT- and PET-scans have become possible. In such investigations, radioactive agents are injected in the body and their distribution after a certain period in the brain is mapped on the basis of the emitted radiation. These investigation techniques provide functional information on the regional activity in the brain. Patients who develop panic attacks upon infusion of lactate, showed an abnormal (increased) brain activity for consumption of blood oxygen in the para-hippocampus region, as can be shown on the PET-scan[68].

Anticipation anxiety for an electric shock in healthy volunteers increased the bilateral temporal blood flow as measured by the PET-scan[66].

In patients with panic disorder, an abnormal asymmetrical blood flow and an altered metabolism were observed in the para-hippocampal gyrus during periods without panic[67].

Gorman et al[31] classified the cerebral location corresponding with panic attacks, anticipation anxiety and avoidance behavior on the basis of neuro-anatomic findings. As a neuro-anatomical hypothesis, they proposed that panic attacks could be attributed to the stimulation of one of the three brainstem nuclei: The chemo-receptors in the extended marrow, the locus coeruleus in the pons and/or the dorsal raphe nuclei in the rostral part of the formatio dorsalis. The raphe nuclei and the chemo-receptors directly innervate the LC. According to Gorman et al[31], anticipation anxiety is rooted via the brainstem to the limbic system. Possible inhibition of the hippocampal region by the LC causes feelings of anxiety. Phobic avoidance behavior often continues to persist for a prolonged period after the stimuli have ceased. Cognitive functions are essential for this:

There are links between reticular formation-LC-limbic lobe and prefrontal cortex, via which this cognitive process may proceed. The pre-frontal cortex is that part of the brain which is most involved in learning and in dealing with complex emotions.

Associations between the autonomous presentations of panic attack with the surrounding factors and the cognitions which occur during the attack are established in the prefrontal cortex. The limbic system also modulates the emotional experiences. According to Gray et al[69,70], the information from this system, received via the thalamus or the cingula cortex is stored in the temporal horns of the brain.

In connection with this theory, it is of significant meaning that the noradrenergic system and the serotonergic system both project to the septo-hippocampal system[68].

Gray et al[69,70] meant that the ascending noradrenergic projections to the septo-hippocampal system amplified arousal. The serotonergic system with afferents from the raphe nuclei to the septo-hippocampal system probably played the same role with regards to displayed behavior. Gray et al[69] stated that drugs which reduce anxiety act on the most important noradrenergic afferents of the LC and on the serotonergic afferents of the raphe nuclei to the septo-hippocampal system (see Figure 1).

The association between the noradrenergic system and the serotonergic system was also stressed in the study by Asnai et al[71]. They tested the serotonergic system and the adrenergic system of patients with panic disorder and depression and of control individuals by overloading them with m-chlorophen-ylpiperzine (a 5-HT agonist), desipramine and a noradrenergic agonist. These authors concluded that the noradrenergic system and serotonergic system did not function independently of each other, but that there may be a common noradrenergic and serotonergic disorder in patients with panic attacks and those suffering from depression.

Conclusions

None of the theories discussed in this article or those mentioned in Table I can provide a single clear and sufficient explanation for the origin of panic disorder.

Table I Biological explanations for panic disorder

1. Hypersensitivity 5-HT receptors[13]
2. Decreased serotonergic transmission[15]
3. Over-activity of noradrenergic system, namely the locus coeruleus because of decreased pre-synaptic a_2-receptor activity[43]
4. Sub-groups of patients with panic disorder as a result of an abnormal regulation of their NA function[2]
5. Abnormal benzodiazepine/GABA complex[46]
6. Abnormal concentration of ß-carboline[59]
7. Over-sensitivity for carbon dioxide[45]
8. Abnormal cholecystokinin activity[63]
9. Common noradrenergic/serotonergic disorder[71]
10. Dysfunctional septo-hippocampal system[21]

Its biological pathogenesis remains unknown. As behavior and cognitions may depend on several functional brain regions it is likely that psychiatric disorders can be caused by different brain abnormalities. By no means have all neuro-transmitter systems yet been investigated. The development of new selective receptor agonists and antagonists may possibly accelerate the elucidation of the process(es) which underlie the biological abnormalities in patients with panic disorder[2].

As mentioned in the introduction, besides the biological factors, there are many other factors that are important in the development of panic disorder. It is not unlikely that an

integrated bio-psychosocial model of cause will qualify as an important model for explanation. Alf et al[72] provide an example: According to him an inborn predisposition for an accelerated triggering of the Locus coeruleus and/or an (for example, through experience of separation in early childhood) increased susceptibility caused by events in life would decrease the threshold for the occurrence of paroxysmal anxiety states.

In these panic disorder patients, rapid vegetative physical complaints develop as a result of psychological and/or biological factors. These complaints may be misinterpreted as catastrophic which then may lead to panic attacks.

Inborn predisposition / susceptibility + stress ↠ anxiety ↠ somatic complaints + misinterpretation ↠ panic attack

According to Alf et al[72], the further development of avoidance behavior, hypochondriasis, addiction or anticipation anxiety would depend for a major part on the personality structure of the involved individual.

In a more elaborate psychophysiological model (Ehlers & Margraf[73]) panic anxiety is described as an outcome of a positive feedback loop. In this model multitude of factors are integrated and bodily and/of cognitive changes may serve to trigger panic attacks.

At this moment we do not have a biological marker, nor a psychological profile, to characterize the patients with panic disorder.

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Chapter 3

CHAPTER 3. COMORBIDITY BETWEEN PANIC DISORDER AND MAJOR DEPRESSION: MODELS AND CONCEPTS OF THE PRESENT INVESTIGATION

This chapter focusses on the comorbidity of panic disorder with depression, its prevalence, hypothesized causes and relevant factors. As we have seen in the previous chapters panic disorder with or without avoidance behavior is a fairly frequently occurring psychiatric disorder. It has a prevalence of 2% to 4% during life and often follows a chronic recurrent course [Katherndahl & Realini, 1993]. This percentage is clearly lower than that for depression (6% to 8%) and represents only a relatively small percentage of all the anxiety disorders wich has a 15 % prevalence during life [Pasnau & Bystritsky, 1994] (see table I).

Table I. Prevalence of anxiety and depression during life

Mood disorders	%	Anxiety disorders	%
Major depressieve episode		Panic disorder	2
Any episode	6	Panic symptoms	10
Unipolar only	5	Phobias	13
Bipolar	1	Any anxiety disorder	15
Dysthymia			
Without major depression	2		
Any affective disorder	8		

Source: Pasnau & Bystritsky, 1994.

The concept of co-morbidity stands for every other clinical diagnosis which was made, or may occur during the clinical course of a patient with the index diagnosis under investigation [Feinsein, 1970].

A number of recent clinical studies have drawn attention to co-morbidity between panic disorder and major depression.

Aronson [1986] cited the figures ranging from 39% to 75% from different studies in his discussion on the co-morbidity percentages between panic disorder and depression.

Stein et al [1990a] reported a figure of 63% for lifetime depression in patients with panic disorder.

Breier et al [1986] observed that 68% of their patients with panic disorder and agoraphobia satisfied the criteria for either suffering, or for having suffered from major depres-sion. However, 35% of the patients had depressive episodes which could be regarded as secondary to the agoraphobia.

The risk of an existing panic disorder in patients with major depression is 18.8 times higher than that which may be expected on the basis of chance alone [Boyd et al, 1984]. Wetzler & Katz [1989] and Huyser [1993] reported that the percentage of anxiety symptomatology in patients with major depression was higher than the percentage of depressive symptoms in patients with panic disorder.

Psychiatric disorders including panic disorder and depression disorders also occur in positive association with other frequently occurring psychiatric disorders such as generalized anxiety disorder, social phobia, obsessive-compulsive disorder, somatic disorders and substance abuse [Maser & Cloninger, 1990].

Co-morbidity of panic disorder with rare psychiatric disorders such as winter depression [Halle & Dilsaver, 1993] and alexithymia [Parker et al, 1993] have also been reported. However, negative associations such as that between anxiety disorders and anti-social personality disorders also do occur.

In epidemiological and clinical studies, the relationship between panic disorder and depression can be investigated in two ways:

1. As the concomitant occurrence of well-defined diseases such as panic disorder or major depression according to DSM-IV criteria; a categorical classification.
2. As the correlation and co-variance of depression and panic disorder on dimensional rating scales such as the Symptom Check-List (SCL-90).

Hiller et al [1989] compared the extent of overlap between the anxiety and depressive disorders at symptom-, syndrome-, and diagnostic levels.

The degree of overlap was observed to be the highest at symptom level, whereas it was the lowest at the diagnostic level. The diagnostic process is based on symptoms and syndromes wich are usually combined for a diagnosis. If symptoms tend to be correlated they are said to form a common syndrom. Different from the diagnostic classification, wich also has other criteria as prognosis or severity characteristics, a syndrome classification provides a quantitative approach to a number of symptoms.

Hiller et al [1989] stated that the investigator must decide on the psychopathologic level at which the investigated groups would be differentiated:

If diagnosis is chosen as a criterium for classification, a part of the overlap between the disorders at symptom level is certainly lost, but the chance of demonstrating a significant difference between clinical presentations with differing psychopathology is increased.

Whether specific symptoms can be used as predictors of the diagnostic and/or syndrome overlap between panic- and depressive disorders has not yet been adequately investigated.

It is clinically observed, on the one hand, that daily variations in the mood, early awakening and psychomotor retardation occur very rarely in anxiety disorders, whereas on the other hand, severe agoraphobia, depersonalization, derealization and distortions of sensory perception occur frequently in panic disorders but not in depressions [Pasnau & Bystritsky 1994].

Factors of comorbidity between panic disorder and depression

Several factors are important in the etiology of the co-morbidity between panic disorder and depressions. These are:

1. **Gender of the patient**
   Scheibe & Albus [1992] reported that co-morbidity between panic disorder and depression was much higher in women (79.5%) than in men (20.5%). In addition, women had a higher tendency for avoidance behavior and showed more generalized anxiety.
2. **The duration of the illness**
   The chance of developing a secondary depression in patients suffering from panic disorder correlated positively with the length of the period during which the patient suffered from panic disorder [Lesser et al, 1988; Argyle & Roth, 1989].
   It is possible that having panic attacks for prolonged periods which is often accompanied by the development of avoidance behavior and demoralization may lead to depression [Sheehan & Sheehan, 1982]. However, in a recent study [Stein et al, 1990a], it appeared that severity, duration and degree of avoidance behavior were not significant predictors for the development of major depression in patients suffering from panic disorder.
3. **Genetic burden**
   Genetic studies have indicated that panic disorders and depression show a partial etiological overlap [Torgensen, 1990].
   Children of depressive parents are both "at high risk" for depression as well as for anxiety disorders. Children of parents with anxiety disorder also have a higher risk for anxiety disorders and for depression [Weissman, 1990].
   On the basis of a recent large study of the genetic factors in panic disorder and major depression, Weissman et al [1993] stated that panic disorder and major depression were distinguishable disorders which occurred together in relatives of patients in both groups more often than was to be expected on the basis of chance alone and that panic disorder accompanied by major depression was not a separate independent disorder, but was a genetically heterogeneous patientgroup.
4. **Co-morbidity with social phobia and generalized anxiety disorder**
   The incidence of major depression is significantly higher in patients suffering from panic disorder accompanied by social phobia or generalized anxiety than in patients without social phobia or generalized anxiety disorder [Stein et al 1990^{b}].

Theoretical models

A number of theoretical models have been constructed which can explain the simultaneous occurrence of panic- and depressive complaints.
Francis [1992] described five models:

1. **A continuum model**
   Anxiety and depression must be localized on the same continuum and be based on a common pathogenesis. According to this hypothesis, co-morbidity merely reflects an artificial separation of a complex syndrome into different components.
   This hypothesis is similar with the 'variant hypothesis' of Aronson [1987] and the unitary model of Stravrakani & Vargo [1986].
2. **The model of separate well defined concomitant syndromes**
   This co-morbidity hypothesis does recognize that there is overlap between anxiety disorders including panic disorder and depression. The categorical differences which are lost in a continuum model are preserved. Anxiety- and depression disorders are regarded as occurring so frequently that the two concomitant diagnoses coincide merely on the basis of change.
3. **Predisposition model**
   Anxiety and in particular panic disorders mostly preceded depressive disorders indicating that anxiety disorder may be a predisposing factor in the development of depression. This predisposition may proceed for example via a psychological pathway, such as secondary depression in patients with panic disorder wich results from demoralization [Sheehan & Sheehan, 1982].
   It is also conceivable that a biological abnormality responsible for panic disorder (e.g., high level of a neurotransmittor) might evolve into another biological abnormality (e.g., down-regulation of receptors in the same system) that might be responsible for depressive disorder.
4. **Overlap due to definition**
   The correlation between panic and depression may be partially artificial because of the overlap between the items that are used to define panic disorder and depression. It is possible that in the DSM IV, complex syndromes have been classified in very narrowly described categories which are so closely related that they often occur at the same time.
5. **A combined model**
   In this model, in addition to diagnostic categories for depression and panic disorders, the generalized mood disorders are also included for patients presenting with mixed features of both anxiety and depression. This agrees with the 'general neurotic syndrome' of Tyer [1984]. Tyer pleaded for the presence of this syndrome in individuals with chronic symptoms of anxiety and depression and specific personality characteristics such as excessive timidity, low self-confidence, dependence on others and tendency to avoid anxiety-inducing situations. This group of patients had alternating exacerbations of complaints which at one time fitted in with anxiety disorder and then again with depression. Tyer [1984] spoke of this group of patients as:

"In reality they may represent the same person wearing different clothes".
This concept also called "mixed anxiety and depressive disorder" is supported among others by the findings of Clayten et al [1991], Angst & Dobler-Mikolan [1985] and Barlow et al [1986].
Janet [1909] too, in his concept of the psychasthenia in which there is partial dissociation ("abaissement du niveau mental"), loss of the highest integrative functions and reduced awareness of the reality described a model that showed similarities with the "General Neurotic Syndrome" as formulated by Tyrer.
The psychasthenia described by Janet encompassed patients with, among others, phobias, other anxiety disorders and obsessive-compulsive complaints [for review see: Gray, 1978].

6. **Another explanation model** for the occurrence of panic disorder and depressive complaints at the same time is partial development of multiple psychopathology.
A high percentage of adult patients with panic disorder and agoraphobia appeared to have school phobias and separation anxiety as a child. Later in life, beginning in adolescence, they often suffered from social phobia and their panic attacks appeared to have been frequently preceded by mono-symptomatic autonomous disorders such as hyperventilation, palpitations and trembling. Panic attacks in turn were preceded by anticipation anxiety and avoidance behavior, whereas depression and demoralization were seen as the end phases in the development of the psychopathology [Deltito et al, 1991]. This model may be seen as a variation of the predisposition model as described under 3.

Introduction to our own investigations

In these investigations, a multi-dimensional approach at the similarities and the differences between patients with panic disorder, patients with major depression, patients with major depression and panic disorder and a reference group of healthy individuals was undertaken.

This was done on the basis of the model of an unitary hypothesis of comorbidity in wich panic disorder and major depression result from a common biological substrate and in wich psychological factors as defense organisation or coping strategies determine whether a panic disorder or depression occurs.

The three diagnostic groups were compared and the patient group as a whole was also compared with the healthy reference group concerning the following:
- Symptoms - Defense mechanisms - Coping mechanisms - Biochemical parameters

Response to adequate psychiatric treatment was determined in the three patient groups, and the influece of psychiatric treatment on defense mechanisms, coping strategies and biochemical parameters. These variables and its relationship with the patientgroup under study will be shortly described below.

Symptoms

Symptoms of the patients with major depression and with panic disorder show a certain amount of overlap as mentioned in the introduction of this chapter on co-morbidity of panic disorder with major depression. This overlap was confirmed recently once again by Huyser [1993] in the investigations on symptomatology of depression disorder and anxiety disorder and in our own study on symptomatology of in-patients suffering from major depression or panic disorder [Timmerman et al. 1994]. From a recent study [Timmerman et al. 1995] it could be concluded that panic attacks show a characteristic symptomatology which may be regarded as reproducible as indicated also by the results of various studies in which diverse groups of patients with panic disorder were evaluated for symptomatology at different moments using different evaluation tools.

This symptomatology occurs in addition to the feeling of panic, and encompasses somatic anxiety equivalents such as dizziness, chest discomfort, tachycardia, sweating and trembling.

Defense mechanisms

The use of defense mechanisms is an involuntary adaptation to intra-psychological and/or external stress directed at diminishing this stress.

Use of defense mechanisms mostly alters the perception on the internal and external reality and is an integrated psychodynamic process.

Historically, the defense mechanisms were first described by Sigmund Freud [1894]. He described 5 important properties of defense mechanisms. These were: 1. Defense is an important way to deal with feelings and instincts. 2. Defence is unconscious. 3. Defense mechanisms can be distinguished from each other. 4. Although often characteristic for serious psychiatric disorders, defense mechanisms are reversible. 5. Defense may be adaptive as well as pathologic.

Freud's daughter Anna elaborated the concept of defense mechanisms in her standard work 'The Ego and Mechanisms of Defense' [1937]. Later, she pointed out the importance of the chronology in the development of the defense organization. Some defense mechanisms such as denial and projection are normal in childhood, but may lead to psychopathology at an advanced age. Vaillant [1988] divided defense mechanisms into psychotic defense, immature defense, neurotic defense and adult defense. (Table 1)

Table 1. Structure of the defense organization[1]

PSYCHOTIC DEFENSE:	Denial
	Distortion
IMMATURE DEFENSE:	Passive aggression
	Acting out
	Dissociation
	Projection

	Autistic phantasies
	Devaluation
	Splitting
NEUROTIC DEFENSE:	Intellectualization
	Repression
	Reaction formation
	Postponement
	Somatization
	Undoing
	Rationalization
MATURE DEFENSE:	Oppression
	Altruism
	Sublimation
	Humor

[1]After Vaillant GE: Defense Mechanisms in: The New Harvard Guide of Psychiatry Cambridge: Harvard University Press [1988].

His division in psychotic and neurotic defenses is suggestive for a correlation between defense mechanism and psychopathology.

Remarkably, very little is known on the relationship between defense organization and psychiatric illnesses such as panic disorder and major depression.

In an investigation into defense organization, Bond & Vaillant [1986] observed that there was no correlation between symptom disorders and defense organization in any of the 74 clinical and ambulant psychiatric patients with various diagnoses as rated with the Bond Defense Style Questionnaire (DSQ). Patients with major depression in this investigation appeared to be very similar to the control group as far defense organization was concerned. The other groups of patients showed more immature defense organization than the control individuals. Bond & Vaillant [1986] stated that defense organization and psychiatric diagnoses were two independent variables and pleaded for a separate axis in the DSM in which defense orga-nization was to be classified.

Pollock & Andrews [1989] observed that ambulant psychiatric patients with anxiety disorder appeared to use other more immature defense mechanisms as rated with the DSQ than a control group. It appeared that within the group of patients with anxiety disorder distinction according to diagnosis and apparent use of defense mechanisms was possible:

Patients with panic disorder with or without agoraphobia appeared to use displacement, somatization and reaction formation as the main defense mechanisms, whereas patients with obsessive-compulsive complaints as a whole did not use "humor", but instead used undoing, projection and acting out as the most apparent defense mechanisms. Similar to the obsessive-compulsive group of patients, patients with social phobia did not use

humor as defense mechanism, but did use displacement and devaluation. Pollock & Andrews [1989] investigated only patients suffering from anxiety disorder. They did not study patients with major depression.

Bloch et al [1993] used the Defense Mechanism Rating Scale to compare the defense mechanism organization in a group of patients with panic disorder with that in a group of patients suffering from an early primary dysthymic disorder - a milder form of depression compared to major depression. The patients with dysthymic disorder made more use of defense mechanisms: "projection, acting out, passive aggression, hypochondriasis, devaluation and projective identification." The patients with panic disorder apparently used neurotic defense mechanisms: "reaction formation and undoing" more often.

No comparison between the patient populations and a control group of reasonable size was either reported by Akkerman et al [1992] or by Bloch et al [1993]. However, this was done by Andrews et al [1989]. They compared a group of patients with panic disorder with a control group, but observed no differences in the defense organization.

An extensive emperical study using the Defense Mechanism Inventory (DMI) was undertaken in diverse groups of healthy volunteers, however only to a very limited extent in psychiatric patients [Ihilevich & Gleser, 1986].

Application of the DMI in patients with "anxiety complaints", anxiety appeared to be possitively correlated to neurotic defenses as " denial, repression, reaction formation and intellectualization".

To date, only a single study has been reported in which a group of (clinical) patients suffering from depression was directly compared with a group of control individuals using the DMI. In that study, it appeared that depressive men were more inclined to use internalized defense, whereas depressive women were inclined to use more externalized defense than controls [Margo et al, 1993].

In another investigation of depressive patients, it appeared that these patients very often made use of the defense me-chanism: Turning aggression against self [Ihilevich & Gleser 1986]. This was in agreement with that to be expected on grounds of psychoanalytical theory [Freud 1894].

In an earlier pilot study by our own research group in patients suffering from panic disorder, it became evident that patients with panic disorder apparently used defense mechanis-ms such as denial, reaction formation and turning aggression against self in a larger extent than a control group of volunteers [Timmerman et al, 1994].

The results of the relationship between symptom disorder and defense organization are summarized in Table 2 and show that no firm conclusion about the relationship between defense mechanisms and psychiatric diseases as panic disorder and major depression can be drawn. Studys of patients with panic disorder-major depression comorbidity are lacking.

Table 2. Symptom disorder and defense mechanisms

Authors	*Symptom disorder*	*Defensemechanisms*
-Pollock et al [1989]	Anxiety disorder	Postponement, somatization reaction formation
-Akkerman et al [1992]	Major depression	Immature defense
-Bloch et al [1993]	Panic disorder	Reaction formation undoing
-Andrews et al [1989]	Panic disorder	No difference as compared to controls
-Margo et al [1993]	Major depression	Less intellectualization as compared to controls
-Ihilevich et al [1986]	Major depression	More turning aggression against self as compared to controls
-Timmerman et al [1994]	Panic disorder	More denial, reaction formation and turning aggression against self as compared to controls

The course of defense mechanisms during treatment remains unknown, with the exception of the investigations by Akkerman et al [1992]. Akkerman et al investigated the course of defense mechanisms during the therapy of patient with major depression using the Defense Style Questionnaire. There was no change in the use of neurotic or adult defense mechanisms during therapy, whereas the use of immature defense mechanisms was decreased.

In other studies, a control group was often lacking or non-validated rating scales had been used.

Coping

According to Lazarus' transactional model of stress, an event is regarded as stressful if an individual's psychological well-being is threatened [Lazarus & Folkman, 1984].

The concept of coping is defined as a form of problem-solving whereby the individual's well-being is at stake and the individual is unable to fall back onto existing routine skills and possibilities.

Coping is then also seen as 'personality in action under stress' [Troop, 1994]. Two important ways of coping can be distinguished:

1. Problem-focused coping via altering the disturbed relationship between individual and surrounding. Problem-solving and seeking help from others belong to this strategy.
2. Emotion-focused coping by regulating the disturbed relation without dealing with the cause, but through intra-psychological processes for example, denial and use of other reactions such as passively hoping that things will change, blaming oneself and avoiding social contact [Kleber & Brom, 1992]. Palliations via, for example, excessive smoking, alcohol usage and drugs abuse are also included here [Schreurs 1984].

Traditionally, coping is seen as a personality trait [Troop, 1994]. Other authors view coping as determined by the situation [Bifulco & Brown, 1994].

Andrews [1991] stated in a theoretical model that *general* vulnerability for anxiety disorders and depressions was determined by a high level of 'trait' anxiety with poor coping and that *specific* susceptibility for certain psychiatric disorders was related to psychodynamic factors. Trait anxiety is seen as the strongest determinant for the development of psychiatric symptoms within these two factor theory of neurosis. Similar to Andrews [1991], Rosenbaum [1980] stated that effective coping can protect the individual against enviromental-, cognitive- and biological threats which may otherwise lead to depression and anxiety. The 'vulnerability' model assumes that coping style is a relatively stable aspect of one's personality.

Roy-Byrne et al [1992] investigated the differences in the coping mechanisms that were used by three groups of patients with panic disorder with or without avoidance behavior. In this study there were panic disorder patients with comorbidity with major depression and personality disorders. The shift from problem-targeted to emotion-targeted coping was strongly correlated with the degree of severity of the symptomatology which was observed but not to the psychiatric diagnoses of the patients. Coping strategy appeared to be state dependent. The severity of underlying stress appeared in this investigation to be a more important predictor for the way of indicated coping than the psychiatric diagnoses. This stress-dependence of coping-strategy was in contrast to the theory by Rosenbaum [1980] who viewed coping as a stable personality-related (trait) aspect.

In the investigations by Roy-Byrne et al [1992] the diagnosis: panic disorder, depression and panic disorder with depression had no correlation to specific coping mechanisms. Whether the-re were also correlations between copingstrategy and defense organization was investigated by Schreurs [1987]. He found no clear correlations between defense organization and coping-strategy that was used. Ihilevich & Gleser [1991] did observe

correlations between defense organization and coping-strategy. It appears that individuals with a high tendency for repression, denial and reaction formation inclined towards avoidance, with those individuals whose main defense mechanism is principalization (intellectualisation) used in particular calming thoughts as coping-strategy, whereas those who turned aggression against self incline towards pessimism. Ihilevich & Gleser suggest that defense organisation and coping strategy add to each other.

Biochemical levels and psychopathology

Recent studies have shown that lowered serotonergic function is characteristic for some forms of depression, suicides and panic disorder [Ball & Whybrow, 1993; Timmerman, 1984]

Serotonin is derived from the amino acid tryptophan via 5-hydroxytryptophan (5-HT). Serotonin is mainly stored in thrombocytes.

Tryptophan is for the largest part bound to plasma albumin. In addition, there are free fractions of serotonin and tryptophan in the blood. The concentrations of these agents in thrombocytes and blood give an indication on the functioning of the serotonergic system. Only free tryptophan can cross the blood/brain barrier. The transport occurs via a carrier protein. However, for the binding to this carrier, there is competition with other large neutral amino acids (LNAA) and tyrosine.

The ratio of tryptophan and other amino acids in the plasma reflects the amount of tryptophan available for serotonin synthesis in the central nervous system [Timmerman, 1984].

Tyrosine is the precursor of noradrenaline and dopamine. Just like serotonin, these two monoamines are also thought to be important in the pathology of depression and panic disorder [Green & Costain, 1981] (see also chapter 2). Tyrosine is also for a major part bound to plasma protein and has to compete with other LNAA and tryptophan for transport through the blood/brain barrier to the brain.

In previous investigations in a group of patients with depression, we observed significantly lowered ratios of tryptophan/LNAA and tyrosine/LNAA in the plasma [Møller et al, 1986]. The neurotransmitter serotonin is involved in a large number of diverse psychiatric disorders including anxiety disorders and depression [Den Boer et al, 1987]. At the same time, there appears to be a link between the serotonergic system on the one hand and disorders of the impulse control in the sense of suicidal and aggressive impulse breakthroughs on the other hand. The functioning of the serotonergic system can be measured among others via its metabolite 5-hydroxyindoleacetic acid (5-HIAA), the level of which correlated negatively with suicide and with aggression [Asberg et al, 1976; Brown et al, 1979]. Further, in a study of our own group [Timmerman et al, 1994], it appeared that serotonin (5-HT) in blood platelets was positively correlated with subjectively experienced anxiety which fitted in with the theory which states that stimulation of the serotonergic function can induce anxiety [Kahn et al, 1992].

On the basis of the observed correlations between the serotonergic system with aggression and suicide one may speculate that this system is coupled to "aggression". The freudian hypothesis of suicide implies that aggression is targeted at the self instead of at the outside world, by using other psychological defense mechanisms.

Not only serotonin might be associated with psychological entities as e.g. defense mechanisms, agression and anxiety: ß carbolines or harmala alkaloids are of special interest since they show a spectrum of biochemical and pharmacological activities including inhibition of MAO-A, competitive inhibition of serotonin uptake, binding to benzodiazepine and opiate receptors and very likely action on dopamine receptors in preclinical studies. The · carbolines have been recognized as aromatic alkaloids of wich norharman can be detected in very low concentrations in human plasma and in several organs of the rat [for review see: van Gelderen et al, 1994].

Most of the known ß carbolines are anxiogenic, though some of the ß carbolines have anxiolytic properties. In a previous pilot study [Timmerman et al, 1994] in patients suffering from panic disorder, it was noted that their norharman, a ß carboline with similar activity as a benzodiazepine in rats, was negatively correlated with the defense mechanisms of principalization and repression and was positively correlated with coping-strategie palliation. Norharman was not a trait marker for anxiety: no correlation was observed between plasma norharman and level of anxiety.

Response to therapy, coping and defense organization

The most frequently used therapies for treating depression and panic disorder are: psycho-pharmaceutical drugs and psychotherapy [Timmerman & Pepplinkhuizen, 1993]. There are a large number of psycho-pharmaceutical drugs which are effective in the treatment of panic disorder and depression. However clomipramine is the only drug that has been officially registered in 1991 in the Netherlands for treating depression as well as panic disorder [Modigh et al, 1992]. Therefore clomipramine was chosen for the treatment of each of the patients in our study. Another advantage of choosing clomipramine was the possibility of determining the plasma concentrations of clomipramine and its active metabolite which offered the possibility to assess the therapy compliance of the patients.

Very little is known about the course of coping and defense mechanisms in patients with major depression and/or panic disorder after adequate treatment. Hoffart & Martinsen [1993] observed in their study that problem-focused coping and wishful thinking as measured on a "wishful thinking scale" in clinical psychiatric patients with agoraphobia and with major depression disminished and mainly behaved as a state phenomenon after treatment for 1 year. The agoraphobic patients, with or without depression, had before treatment a lower level of seeking social support than purely major depressed patients. This difference was not reducible to differences in the level of psychopathology before treatment. The seeking social support scores increased after treatment with the remission of symptoms and correlated well across assessments. Akkerman et al [1992], using the

Defense Style Questionnaire, investigated the course of immature defence mechanisms during the treatment of patients with major depression. During treatment, there was no change in the use of neurotic or adult defense mechanisms, whereas the use of immature defense mechanisms decreased.

Aim of the current investigations

Comorbidity between panic disorder and depression is, sofar, an unexplained phenomenon in psychiatry.

We studied this question from the standpoint of the unitairy hypothesis of panic disorder and depression in wich these disorders may share a common biological substrate and in wich other factors, in general conceptualized as psychological factors, determine and shape pathology.

Secondly, the inter-correlations between the different psychological and biochemical parameters were studied and finally the effect of combined drugs- and psychotherapy on symptomatology, defense organization, coping-strategy and biochemical parameters in the group of patients was investigated.

Chapter 4

CHAPTER 4. DESIGN OF THE STUDY

Patients

The patient investigation was conducted at the out-patient psychiatry department of a general hospital "Het Drechtsteden-ziekenhuis, locatie Refaja". At the out-patient department of psychiatry, in the period 1991-1993, 30 new patients suffering from a single episode or recurrent episodes of major depression (DSM-III-R 296.2, 296.3) were selected on time of referal. A minimum of 30 patients suffering from panic disorder with or without avoidance behavior (DSM-III-R 300.21, 300.00) were also recruited. In the DSM-III-R it is possible to establish the diagnosis of panic disorder as second axis I diagnosis in the group of patients primarily suffering from major depression and major depression as the second diagnosis in the group of patients suffering from panic disorder.

Exclusion criteria

Psychiatric disorders, including dysthymia, other than major depression or panic disorder. Depression with severe agitation, serious tendency for suicide, or psychotic symptomatology, severe sleep disorders, epilepsy, organic mental disorders, alcoholism or drug abuse during the last 5 years, thyroid diseases, liver diseases, bone-marrow suppression, allergy or hypersensitivity for clomipramine, glaucoma, urine retention, hypertension, hypotension, clinically relevant cardiovascular complaints, significant abnormalities in ECG and EEG, abnormal clinically relevant chemical/biochemical laboratory findings, clinically relevant kidney disease and pregnancy & lactation. Patients had to be free of somatic medication.

In addition, a **reference group** consisting of 54 healthy volunteers aged 18-65 years from the hospital personnel was formed. This reference group was screened for psychopathology using the SCL-90. Individuals from the reference group had a SCL-90 total score (NEU) which was similar to or lower than the average score of the standardized groups for men and women from the Dutch population.

Procedure

Psychiatric diagnosis were made by three experienced psychiatrists using to Munich Diagnostic Checklist.

Prior to treatment, the following questionnaires had to be completed in connection with psychiatric diagnostic, symptomatology, coping and defense (see for details under Questionnaires).

- Munich Diagnostic Check-List (MDCL)
- Hamilton Rating Scale for Depression (HRSD)
- Symptom Check-List (SCL-90)

- Utrechtse Coping-List (UCL)
- Defense Mechanism Inventory (DMI)

Previous history on the total duration of the illness and of the current episodes was registered. Three groups of patients were formed on the basis of Munich Diagnostic Checklist (MDCL) (see also Questionnaires):

1. Panic disorder with or without avoidance behavior
2. Major depression with or without melancholia
3. Major depression and panic disorder

Informed consent

Patients were only enrolled into this study after written informed consent had been obtained. Both the patients and their general practitioners were informed in writing as to the aim and the method of the investigation.

Prior to participation in this study, a *wash-out period* of 10 days, applied in as many patients as possible, during which no psycho-pharmaceutical drugs were used was preferred. Before starting the study, blood from the patients was screened for the use of tricyclic antidepressants.

Both the groups of patients suffering from major depression and from panic disorder were treated with clomipramine. Their clomipramine blood levels were also monitored. It was intented to treat every patient with a 150 mg dose of clomipramine.

The questionnaires mentioned above were repeated 6 months after starting treatment and at the eventual follow-up. The UCL, DMI and SCL-90 were self-rating scales which were filled in by the patients at 9.00 a.m. at the out-patient department of psychiatry. The completed questionnaires were checked by a trained secretary at the out-patient department of psychiatry.

Thereafter, a semi-structured interview took place during which the MDCL and HRSD were filled in by one of the three psychiatrists, to confirm diagnosis and severity of illness.

Previous history on the total duration of the illness and of the current episodes was registered by the investigator.

Biochemical assesment

Blood was investigated with particular regards to the previously mentioned parameters: serotonin in platelets, serotonin in blood, serotonin in plasma, norharman, tryptophan, tyrosi-ne-tryptophan ratio and tyrosine ratio. Thirty (3 x 10) ml blood was taken from each patient for determining the levels of serotonin in blood, plasma and thrombocytes, amino acids, norharman and clomipramine. Blood was taken at 8.00 a.m. and repeated 6 and 9 months after starting treatment. The bloodanalyses were conducted at the Erasmus University of Rotterdam laboratory of the Section Pathophysiology of Behavior. The biochemical methods for analyses that were used are published elsewhere [Fekkes & Bode 1993].

The treatment with clomipramine was conducted according to an increasing dose schedule, whereby a dose of 150 mg clomipramine was reached within 3 weeks of treatment. Blood levels of clomipramine were determined to check therapy compliance by the patients.

Treatment

In addition to treatment with clomipramine [Modigh et al, 1992], patients suffering from depression as well as those suffering from panic disorder were also given psychothera-peutic counselling in the form of cognitive therapy [Sokol et al, 1989]. In the first 6 months of treatment, patients participated in at least 10 sessions of cognitive therapy.

In patients with panic disorder, attention was given to incorrect cognitions mostly cognitions of catastrophic nature. Irrational beliefs concerning self-image, future and feelings of guilt were also dealt with in patients with depression. In cases of avoidance behavior, the patient was encouraged to exposure themself to threatening situations.

Questionnaires

In this investigation the patients were examined by the scores on the Symptom Check-list 90 (SCL-90) - a dimensional self-rating scale.

The clinical psychiatric diagnosis was established with the Munich Diagnostic Check-List (MDCL) - an operationalization of the DSM-III-R criteria.

The defense organization of the patients and references were measured using the Defense Mechanisms Inventory (DMI) [Gleser & Jhilevich, 1969; Jhilevich & Gleser, 1986].

The coping strategies in patients and reference group were determined with the Utrechtse Coping-List (UCL), [Schreurs, 1987] that is a satisfactorily validated scale in the Netherlands for compiling an inventory of coping.
Details of the instruments are presented below.

The Munich Diagnostic Check-list (MDCL)

The Munich Diagnostic Check-list (MDCL) [Hiller et al, 1987] was used in order to operationalize the diagnostics in patients with major depression and/or panic disorder.

The MDCL is an extensive tool which contains 33 of the most occurring DSM-III-R-diagnoses and was developed as a check-list version from the structured clinical interview (SCID) compiled by Spitzer & William [1987].

In panic disorder, among others, symptoms which occur during the panic attack, avoidance behavior in certain situations, and the severity of the panic attacks and of the avoidance behavior are scored on the MDCL. Thus, besides a qualitative function, the MDCL also has quantitative aspects.

In major depression the following are distinguished: 1st episode, recurrence, severity and satisfying or not satisfying the criteria for melancholia.

Symptomatology

The *Symptom Check-list (SCL-90)* is a multi-dimensional complaints list based on self-evaluation by the patient. The check-list was developed by Derogatis et al [1973] and has 8 sub-scales:

1. Agoraphobia (AGO)
2. Anxiety (ANG)
3. Depression (DEP)
4 Somatic complaints (SOM)
5. Inadequacy to think and act (IN)
6. Distrust and inter-personal sensitivity (SEN)
7. Hostility (HOS)
8. Sleep problems (SLA)

The total score of the SCL-90 'psycho-neuroticism' can be regarded as a measure for psychological and physical (un) well-being. The SCL-90 can be used in 3 ways:

1. As screening tool (e.g in order to assess the type and the level of psychopathology in a population).
2. As an overall measure of the severity of a psychiatric disorder.
3. As a multi-dimensional measure for specific psychopathology.

In general, the SCL-90 provides a valid measure for overall severity of symptomatology, has a satisfactory convergent validity (a high correlation with other measuring tools which measured the same construct) and a relatively high divergent validity (a low correlation with assesment instruments which measure a different construct). This was valid both for the anxiety- as well as the depression-scales [Beck et al, 1992]. In the Netherlands, the original factor structure of the SCL-90 could not be established. The distribution of items over the scales in the Dutch version was, therefore, changed with respect to the American version [Arrindell & Ettema, 1986]. The anxiety and phobia anxiety sub-scales were identical, but the depression scale had in addition, items 3, 19, 50 and 51, whereas item 79 in the depression scale was omitted. However, Koeter [1992] used both the Dutch as well as the original version of the SCL-90 and observed that there were no differences in the outcome on the depression scale. Koeter [1992] in a study in 134 psychiatric out-patients observed that patients with depression (according to DSM-III) on the average scored higher on the SCL-90 depression scale than patients with DSM-III anxiety disorder or those without a DSM-III diagnosis. There was no difference between the average scores of patients with DSM-III depression disorder and those with co-morbid depression and anxiety. Patients with anxiety disorder (according to DSM-III) had significantly higher SCL-90 phobic anxiety and anxiety scale scores as compared with patients without DSM-III diagnosis or a DSM-III depression disorder.

Koeter [1992] reported that the SCL-90 depression, anxiety and phobic anxiety scales were both categorical and dimensional measures of specific psychopathology.

It can be concluded that the SCL-90 was intended for use in ambulant psychiatric patients. The SCL-90 has a high sensitivity, but caution is recommended with regards to its specificity, especially for individual diagnostics [Arrindell et al, 1986].

Defense mechanisms

The defense organization of the patients and healthy volunteers was investigated using the *Defense Mechanisms Inventory* (DMI), [Gleser & Ihilevich, 1969; Ihilevich & Gleser 1986].

The DMI provides those under investigation with ten short descriptions of possible conflict situations. Each description is followed by four multiple choice questions. A validated Dutch translation version was used [Passchier & Verhage, 1986]. Those under investigation were asked to cross the answer which fitted in the best with their actual behavior, with the behavior they displayed in fantasy, their thoughts and feelings and the answer which was least applicable. The five possible answers after each question corresponded with five important groups of defense mechanisms. These groups were designed on theoretical and practical grounds:

1. Turning against object (TAO). It involves: 'Attack on an object that caused real or supposed external frustration.
   Identification with the aggressor and postponement fall in this category.
2. Projection (PRO). Projection means the justification of aggression by attributing the hostile intentions or customs to an external object.
3. Principalization (PRN). Principalizing copes with the reality by explaining it with rational or pseudo-rational constructions so as to avoid the personal meaning of the encountered threat in this manner. This category includes, among others, isolation and intellectualization.
4. Turning against self (TAS). This defense consists of targeting aggression to oneself, punish oneself and blame oneself.
5. Reversal (REV). Present oneself in an unsuited neutral manner, or to react in a positive manner to a frustration or a threat. This includes the classic defense mechanisms: repression, denial and reaction formation.

Following June et al [1983], we used a sixth scale for repression (REP). This scale is made up by the subtraction of (TAO + PRO) from (PRN + REV) in order to obtain a continuum in which externally targeted defense is balanced by an internally targeted focus.

The reliability and the validity of the DMI in a Dutch translation version was investigated by Passchier & Verhage [1986]. They stated that psychometric characteristics of the Dutch DMI version were satisfactory for investigational purposes, although the reliability and validity in males is less then in women.

Coping

Coping of patients and healthy volunteers was investigated using the *Utrechtse Coping List* (UCL), [Schreurs et al, 1984]. The UCL was compiled to quantify concrete behavior patterns and mental attitudes in confronting problems or unpleasant events. The UCL has 47 short descriptions of ways to deal with problems or unpleasant events.

For every item, those under investigation were asked to indicate in which manner they seldom or never, often or very often reacted. The psychometric qualitys as validity and reliability are sufficient [Schreurs, 1987]. The UCL has 7 sub-scales:

1. A; active problem solving: to take time to investigate the situation, go to work purposefully, solve the problem confidently.
2. P; palliative coping: seek distractions, feel better by smoking, drinking or relaxation.
3. V; postpone and avoid.
4. S; seek social support: seek help, discuss the problem with someone.
5. D; depressive syndrome: overwhelmed by the situation and unable to turn the tide. self-withdrawal.
6. E; expression of emotions.
7. C; reassuring cognitions: such as "everyone has an off day once", "after rain comes sunshine", self-encouraging.

In the next chapters we will discuss the results of the investigations.
Each chapter consists of an introduction in relation to the aims of the study, statistics, results and discussion.

Chapter 5

CHAPTER 5. BASELINE CHARACTERISTICS

5.1 Introduction

In the following chapters the groups of psychiatric patients with panic disorder, depression and panic disorder & depression are compared with the reference group (volunteers from the hospital personnel) and standard groups. The setup of the investigation is discussed in details in chapter 4. The central question in this investigation was whether there is a central biologically determined disorder in patients suffering from panic disorder and/or depression, whereby differences in defense organization and coping strategies possibly determine whether a patient develops panic disorder or depression.

A description of the biographical and the psychopathological details and drop outs is presented in this chapter. In the following chapters, differences between the patient groups as a whole, reference group, standard groups and the three patient groups mutually were investigated using the Symptom Check-List-90 (SCL-90), Utrechtse Coping List (UCL), Defense Mechanism Inventory (DMI) and biochemical variables. (See chapter 4 for a description of the psychological rating scales with their standard groups).

The biochemical values were separated at entry into those in blood samples from patients not on medication and those from patients under medication. The biochemical concentrations of serotonin in blood platelets (thrombocytes), in blood, in plasma and tryptophan, tyrosine and norharman as well as the so called tryptophan and tyrosine ratios in groups of patients and the reference group are presented.

5.2 Subjects, biographical and psychopathological characteristics

The group of patients consisted of a total of 74 patients of which 27 (16 women and 11 men) suffered from panic disorder, 36 (20 women and 16 men) suffered from depression and 11 (8 women and 3 men) suffered from panic disorder and depression. The average age of the patients was 41.8 years with a standard deviation of 11.7 years.

The reference group consisted of 54 (22 women and 32 men) healthy volunteers recruited from the hospital personnel. Their average age was 32.7 years with a standard deviation of 8.3 years.

For the composition of the standard groups of the SCL-90, UCL and DMI see chapter 3 and 4; in our study we made use of transformed (T) scores (see chapter 6) for comparison of patient-, and reference groups with standard groups.

A description on the differences between the diagnostic categories of the patients according to the duration of their illness is given in Table 1.

Table 1. Total duration of psychiatric disorder (years)

Diagnosis	mean	std.dev.	median
Panic disorder	12.3	10.9	8.5
Depression	8.0	9.2	4.0
Panic + Depr.	6.4	7.0	4.0

The patients with panic disorder had a much longer total duration of their illness than patients with panic disorder and depression or those suffering from depression only. In Table 2, the duration of the current episode of the illness in the patients in the three diagnostic groups is given. It was noticed that the duration of complaints in the group of patients with co-morbid depression and panic disorder was much longer than in the other two patient groups.

Table 2. Number of patients (percentage) classified according to duration of the present episode

Duration	0-3	3-12	12-36	>36 months
Diagnosis:				
Panic disorder	30.4	30.4	30.4	8.7
Depression	41.2	29.4	29.4	-
Panic + Depr.	45.5	9.1	18.2	27.3

The most important results obtained using the MUNICH DIAGNOSTIC CHECK-LIST (MDCL), a DSM III-R checklist on diagnosis [Hiller et al, 1989], are shown in Table 3.

Table 3. Munich Diagnostic Checklist

Diagnosis:	Panic disorder (n=27)	Depression (n=36)	Panic+ Depression (n=11)
Severity of Panic attacks:			
– mild / moderate	70.4%	–	54.6%
– severe	29.6%	–	45.5%
Melancholia	–	25%	20%
Severity of Agoraphobia:			
– mild / moderate	62.9%	–	80%
– severe	14.8%	–	20%

In the PANIC DISORDER patients a first time panic disorder was suffered by 41% of the patients. Eighty percent of the panic disorder patients suffered from agoraphobia, 30 % from severe panic attacks.

In the group of patients with DEPRESSION, 25% of the patients satisfied the criteria of Melancholia, 47 % of the patients in this group suffered from a first episode of depression.

In the group of patients with DEPRESSION & PANIC DISORDER, 20% of the patients satisfied the criteria of Melancholia and 46 % of the patients suffered from severe panic attacks. In this patient group with depression and panic disorder, all patients were agoraphobic.

A first episode of panic attacks was suffered by 63% of the patients and one could speak of a first episode of depression in 36% of the patients.

5.3 Drop-outs

Patients (N=7) who dropped out within the first 4 weeks of the treatment were distinguished from those patients (N=16) who dropped out after 4 weeks of treatment since an effect of the therapy can be expected after such a period.

A total of 13 patients (17.5%) discontinued therapy due to adverse side-effects of clomipramine. In the other patients the main reason for discontinuation of the therapy was lack of succes of the treatment [Timmerman et al, 1995[2]].

In the group of patients with PANIC DISORDER & DEPRESSION, two patients dropped out after more than 4 weeks of treatment. In one case it was due to adverse side-effects of clomipramine and in the other case it was because of a lack of consensus with the treating physician.

In the group of patients with PANIC DISORDER, one patient dropped out within 4 weeks of treatment (after additional inquiry, it appeared that this patient refused medication) and five patients dropped out after 4 weeks of treatment. Three dropped out because of adverse side-effects and lack of response, one because of adverse side-effects only and one because of hepatological disturbances.

In the group of patients with DEPRESSION, six patients dropped out within 4 weeks of treatment. Nine patients dropped out between 4 weeks and 6 months of treatment. One patient refused medication, five because of adverse side-effects, two because of adverse side-effects and lack of response, five because of lack of response and in two patients treatment could not be evaluated because they had moved away during the period of therapy.

It appeared that there was no difference between the severity of the psychiatric disorder in the group of patients who discontinued therapy as compared with the group of patients who continued therapy expressed as total SCL-90 score psycho-neuroticism (SCL NEU) before starting therapy. In the group of patients continuing therapy, the total SCL score was 231 ± 58 before commencing therapy. In the group of drop-outs, the total SCL score was 231 ± 69 (the difference was not significant, P= .99 two tailed).

Drop-outs are discussed further elsewhere [Timmerman et al, 1995[2]].

5.4 Discussion

The percentage of co-morbid panic disorder and major depression was reported to vary between 25% and 40% in different studies [reviewed by Pasnau & Bytrisky, 1994]. This percentage was lower in our study (15%). This could have been because our study focussed on ambulant patients. In general, the complaints in these patients were less severe than those in a clinical population. Co-morbidity was observed, however, in those patients in whom the complaints were severe [Fawcett, 1988].

In our study, a subgroup of patients (27%) with co-morbidity had a very prolonged duration of their current episode of complaints; longer than 3 years. This is in agreement with the findings reported by Argyle et al [1989] who noted that patients with a prolonged duration of illness showed more co-morbidity. Moreover, all patients with co-morbid panic disorder/major depression had agoraphobic complaints. This was not the case in groups of patients without co-morbidity.

Notably patients with panic disorder came later into psychiatric treatment than depressed patients. It is not clear whether this is because of agoraphobia of the panic disorder patients, or because of other reasons.

The drop-out rate of 31% in this study was slightly higher than 23% reported in a previous double-blind study [Timmerman et al, 1994[2]] in which two serotonin uptake inhibitors were investigated in the same setting in ambulant patients suffering from depression. However, 31% drop-out in our study was much lower than the 56% drop-out that was reported by Johnston et al [1988] in a double-blind study for 8 weeks in which clomipramine was investigated in women suffering from agoraphobia. It is possible that

the percentage of drop-outs in our study was lower, because the patients were offered open treatment which reduced their uncertainty and because of the combination with psychotherapy. Johnston et al [1988] in their study also increased the dose of clomipramine to a higher maximum (300 mg/day) which may have led to adverse side-effects in more patients and more drop-outs. However, the average daily dose used by them was 82.8 mg which was lower than that used in our study.

Chapter 6

CHAPTER 6. PSYCHIATRIC PATIENTS: PROFILE AT BASELINE

6.1 Introduction

The central question of the studies described in this chapter was whether defense organization, coping strategies and biochemical parameters of the patient group consisting of patients with panic disorder and/or depression differ from a reference group (see also chapter 3 and 4).

In the investigations on baseline values, it had to be initially established whether the reference group and the patient group could be distinguished from each other at the level of psychological complaints, using the SCL-90. The scores of the SCL-90 were then compared with those from a norm group from the Dutch population. The genders were separated in doing so.

With the Utrechtse Coping-list (UCL), it was investigated whether the use of the coping strategies in the patient group as a whole was different from that in the reference and standard groups.

The defense organization in the patient group and in the reference group were mutually compared and compared with that of a standard group using the Defense Mechanism Inventory (DMI). More detailed descriptions of SCL-90, UCL and DMI are presented in chapter 4.

It was subsequently investigated whether there were any biochemical differences between the patient group and the reference group. The levels of norharman, levels of serotonin in the blood, plasma and in thrombocytes, concentrations of amino acids: tryptophan, tyrosine and the ratios of tryptophan and tyrosine as compared with other amino acids were all investigated.

Relations of tyrosine and tryptophan will be analysed as compared with other large neutral amino acids in the patient group and in the reference group. The levels of norharman and serotonin will be correlated to the psychiatric disorder (see also chapter 4). For biochemical evaluations, the patients were divided into those using psychopharmaceutical drugs such as tricyclic antidepressants and patients not on such medication.

6.2 Method of statistical analysis

The mean and the 95% confidence interval (C.I.) of the raw scores of SCL-90, UCL and DMI of the reference group and the patient group as a total at baseline and after therapy for six and nine months are shown in Table 4. (Appendix)

First for comparability, especially to visual presentation, the SCL-90 scores of the standard group were transformed into a T score with a mean of 50 and a standard deviation of 10. The SCL-90, UCL and DMI scores of the patient group and the reference group were transformed and compared with the in the above mentioned manner transformed scores of the standard group.

The results are shown in the Tables and the Graphs.

The T scores of SCL-90, UCL and DMI are given with 95% confidence intervals. Likewise the biochemical values are presented as means with 95 % confidence intervals in the different patient groups and the reference group. (table 6)

In the subsequent step, Fisher's linear discriminant analysis for independent samples was used to identify psychological and biochemical variables which were relevant in contributing towards distinguishing the patient group from the reference group. Significant discriminant functions at 0.05 level only were maintained in the model. For testing X^2 was used. In addition the correlations of the individual predictive variables and the linear discriminant function were presented. After discriminant analysis, to test for stability, a cross-validation was performed on a changing one-fifth of the cases. The results were presented in the form of 'pooled' results of the classifications of the 5 cross-validations.

As a measure of performance of the analysis the percentage correctly classified was calculated.

6.3 Results

The mean and the 95% confidence interval of the raw scores of DMI, UCL and SCL-90 of the reference group and the patient group as a total at baseline are shown in Table 4 (see appendix).

In Table 5 the transformed scores as 95% confidence intervals of SCL-90, UCL and DMI in the patient group and in the reference group are shown.

Table 5. Baseline values in patients and reference (T scores compared with normgroupes)

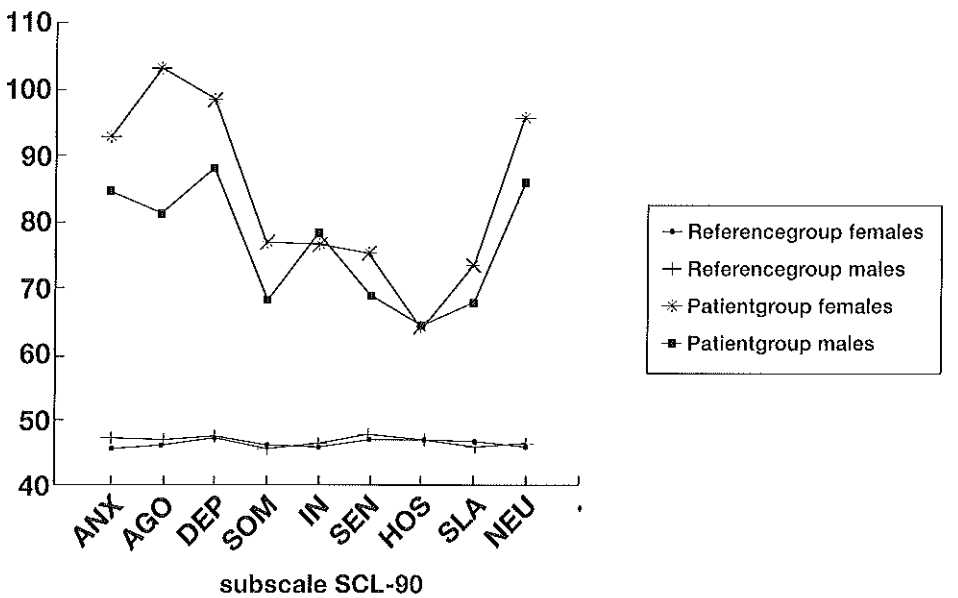
	Reference (n=54)		Patients (n=74)	
	mean	CI[1]	mean	CI[1]
SCL subscale				
ANX	46.2	44.9; 47.5	89.4	84.6; 94.2
AGO	46.3	44.9; 46.9	94.2	85.7; 102.7
DEP	47.3	45.8; 48.9	94.5	88.9; 100.1
SOM	45.9	44.7; 47.1	73.3	69.6; 77.1
IN	46.1	44.7; 47.5	77.2	73.1; 81.2
SEN	47.3	45.3; 48.3	72.6	67.7; 77.7
HOS	47.1	45.9; 48.3	64.0	59.6; 68.4
SLA	46.2	45.0; 47.6	71.2	67.4; 75.0
NEU	46.0	44.5; 47.6	91.7	86.5; 96.8
UCL subscale				
A	49.0	46.4; 51.7	39.5	37.1; 41.8
P	54.4	51.4; 57.2	56.9	54.4; 59.3
V	47.8	46.2; 49.5	60.6	57.8; 63.4
UCL-S	59.0	56.0; 62.0	55.3	52.0; 58.5
D	48.0	46.0; 50.1	78.9	69.9; 75.9
E	51.0	48.7; 53.4	48.0	44.7; 51.4
G	49.8	47.1; 52.4	48.9	46.8; 51.0
DMI subscale				
TAO	54.5	51.8; 57.1	48.9	46.3; 51.5
PRO	52.7	50.3; 55.1	52.1	49.8; 54.3
INT	53.4	50.9; 55.8	46.3	43.9; 48.7
TAS	42.8	39.8; 45.8	56.0	53.1; 59.0
REV	46.2	44.1; 48.4	48.1	45.6; 50.5

[1] CI = 95% confidence interval of the mean

The scores in the reference group appeared to be lower than those in the patient group on all scales of SCL-90. In Figure 1, a graphic presentation of the transformed scores of SCL-90 in the patient group as a whole and those in the reference group is given.

This was done separately for men and women.

Figure 1. Transformed baseline values in the patientgroup and the referencegroup



There were differences between the scores in men and women, whereby the women had higher scores on all sub-scales of the SCL-90 with the exception of inadequacy to think and act (IN) and hostility (HOS).

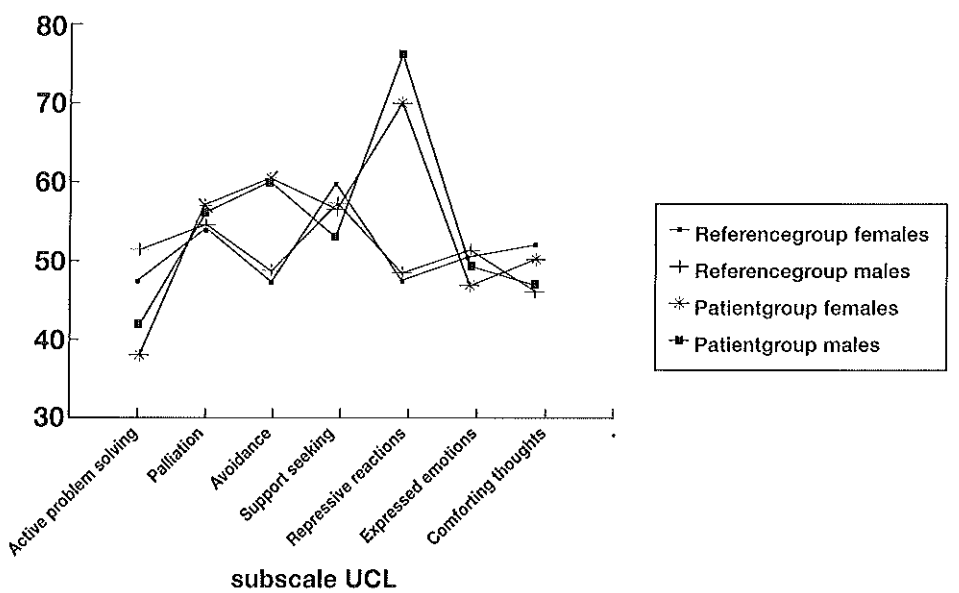
The differences between the genders were the highest on the scales: anxiety (ANX), agoraphobia (AGO), depression (DEP) and the total score psycho-neuroticism (NEU).

In Table 5, it can also be seen that the mean and 95% confidence interval of UCL scores in the patient group were higher than those in the reference group on the following scales: avoidance (UCL-V) and depressive reaction pattern (UCL-D).

In comparison with the standard group, the patient group had an increased tendency towards palliative coping (UCL-P). The patients had lower scores on active problem solving (UCL-A) as compared with the standard group and the reference group.

A graphic presentation of the transformed UCL scores in the patient group and the reference group as compared with the standard group is given in Figure 2. It is clear from this Figure that there were no important differences between the UCL scores of men and women in the patient group and the man and women in the reference group.

Figure 2. Transformed baseline values in the patientgroup and the referencegroup

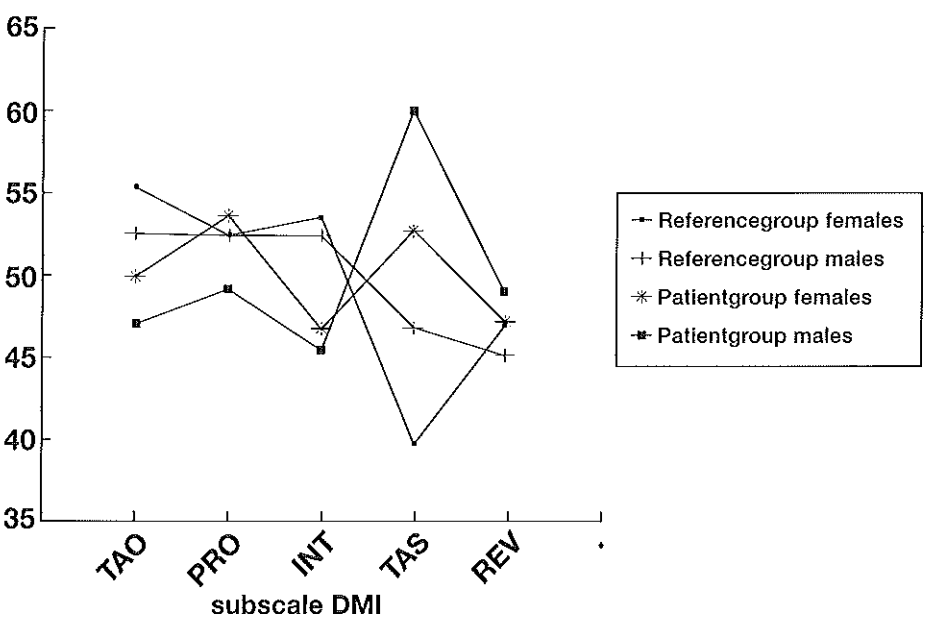


In the UCL, the reference group had a similar score profile to that in the standard group with the exception of a higher score on the sub-scale seeking social support (UCL-S).

Table 5 shows the results of the patient group as a whole and the reference group on the DMI. The patient group scored higher on turning aggression against self (TAS) and lower on turning aggression against others (TAO) and intellectualization (INT) than the reference group.

A graphic subdivision of the DMI scores for both men and women and the scores of the reference group are presented in Figure 3.

Figure 3. Transformed baseline values in the patientgroup and the referencegroup



Males scored higher on turning aggression against self than women. Gender had no other important influence on the DMI scores. The scores in the reference group were not different from those in the standard group with the exception of turning aggression against self (TAS) which was lower in the reference group.

The biochemical values in the reference group, in the medication free patient group and in the patient group as a whole at baseline are given in Table 6.

Table 6. Baseline biochemical values in patients and reference

		Reference (n=27)	Medication free patients (n=30)	Patients with medication (n=36)	All patients (n=66)
Ser[1] in plasma (10^{-9} mol/l)	mean CI[2]	14.2 7.8 ; 20.7	15.5 10.4 ; 20.6	7.6 5.1 ; 10.1	11.2 8.4 ; 14.0
Ser in platelets (10^{-9}mol/ $10E^{9}$ pl)	mean CI	3.6 3.2; 4.0	3.5 3.1; 4.0	1.1 0.2; 2.0	2.9 2.4; 3.4
Ser in blood (10-9 mol/l)	mean CI	957.7 815.9; 1099.6	820.5 682.4; 958.6	131.4 26.3; 236.5	547.7 414.2; 681.2
Norharman (10-12 mol/l)	mean CI	0.45 0.37; 0.53	0.49 0.31; 0.59	0.53 0.40; 0.65	0.51 0.42; 0.60
Tyrosin (10-6 mol/l)	mean CI	67.1 59.0; 75.3	63.9 55.4; 72.4	60.4 55.9; 64.9	61.9 57.5; 66.3
Tyrosin ratio	mean CI	11.4 10.3; 12.4	10.7 9.99; 11.5	11.3 10.6; 12.0	11.0 10.4; 11.6
Tryptophan (10-6 mol/l)	mean CI	52.8 48.5; 57.0	49.9 45.6; 54.2	41.9 39.1; 44.7	45.3 42.7; 47.9
Tryptophan ratio	mean CI	8.9 8.2; 9.6	8.6 7.8; 9.5	7.5 7.1; 7.9	8.0 7.5; 8.5

[1] Serotonin

[2] CI = 95% confidence interval of the mean.

There were no differences between the reference group and the patient group not on medication. The baseline levels of serotonin in the thrombocytes, plasma and in the blood of the clomipramine treated patients were lower than in the patients not on medication. The same was also true for the tryptophan levels in this group. The differences in the biochemical values between the patient groups with and without medication will be discussed in more details in chapter 10. It was investigated with discriminant analysis whether it was possible to distinguish between the patient group and the reference group on the basis of psychological and biochemical variables. The difference was adjusted for age and gender.

A discriminant analysis was than performed on the SCL-90, UCL and DMI in the patient group and the reference group (Table 7).

Table 7. Discriminant analyses on psychological variables at baseline; patients versus reference

Canonical corr.	X2	DF	P
0.86	159.20	7	0.0001

Correlation between psychological variables and discriminant score:

SCL-ANX	0.77
SCL-NEU	0.75
SCL-DEP	0.72
SCL-IN	0.66
UCL-D	0.65
SCL-SLA	0.60
SCL-SOM	0.54
SCL-SEN	0.49
SCL-AGO	0.40

Cases correctly classified: 94%

The sensitivity, the specificity, the true positive predictive value and the true negative predictive value of the discriminant analyses are given in Table 8.

Table 8. Patientgroup compared with referencegroup at baseline. Prediction based on discriminant analyses

Subscale	C.C.* (%)	sens[1] (%)	spec[2] (%)	true pos[3] (%)	true neg[4] (%)
SCLANX	85.9	98.2	77.0	75.7	98.3
SCLAGO	78.1	100.0	62.2	65.9	100.0
SCLDEP	88.3	98.2	81.1	79.1	98.4
SCLSOM	86.7	100.0	77.0	76.1	100.0
SCLIN	87.5	100.0	78.4	77.2	100.0
SCLSEN	75.0	92.6	62.2	64.1	92.0
SCLHOS	76.6	94.4	63.5	65.4	94.0
SCLSLA	81.3	94.4	71.6	70.8	94.6
SCLNEU	89.8	98.2	83.8	81.5	98.4
UCL-A	68.8	63.0	73.0	63.0	73.0
UCL-P	53.9	66.7	51.4	46.3	62.3
UCL-V	74.2	90.7	62.2	63.6	90.2
UCL-S	57.0	46.3	64.9	49.0	62.3
UCL-D	84.4	92.6	78.4	75.8	93.6
UCL-E	59.4	44.4	70.3	52.2	63.4
UCL-G	51.6	46.3	55.4	43.1	58.6
DMITAO	59.2	65.4	55.4	50.8	69.5
DMIPRO	52.4	59.6	47.3	44.3	62.5
DMIINT	63.5	65.4	62.2	54.8	71.9
DMITAS	72.2	75.0	70.3	63.9	80.0
DMIREV	54.0	51.9	55.4	45.9	62.1

* C.C.= Correctly Classified (%)

[1] sensitivity

[2] specificity

[3] True positive predictability

[4] True negative predictability

Positive predicted value means these proportion of patients with positive results or tests, negative predictive value gives the predictive value of a negative test or post-test likelihood of no disease. Sensitivity indicates the percentage of patients with true positive test results, specificity the percentage of patients with true negative test results [Sackett, 1983].

It appeared that it was possible to establish a valid distinction between the patient group and the reference group on the basis of psychological variables. A correct classification was obtained in 94% of the cases.

The best predictors for the patient group or the reference group were not only the SCL-90 sub-scales, but also the coping scales Avoidance (UCL-V), Depressive reactions (UCL-D) and the defense scale Turning Against Self (DMI-TAS) result in a higher than 70% hit.

The discriminant analysis of the biochemical parameters in the reference group and the those at baseline in the patient group not on medication showed that the plasma tyrosine ratio in the patient group was lower than in the reference group.

A correct distinction between the patients and the reference group was possible on the basis of the biochemical variables in 68% of the cases (Table 9).

Table 9. Discriminant analyses on biochemical data at baseline; patients versus reference group

Canonical corr.	X^2	DF	P
0.40	9.26	3	0.05

Correlation between biochemical variables and discriminant score:

Tyrosine ratio	-.031
Tryptophane ratio	-0.21
Norharman	0.16
Plasma serotonin	-0.11
Tyrosine	-0.04
Thrombocyt serotonin	-0.03
Tryptophane	-0.01

Cases correctly classified: 68%

The results of discriminant analyses after cross validation show that as far as the distinction between the patient population as a whole and the reference group on the basis of psychological parameters (SCL-90, UCL and DMI) was concerned, the model obtained via the discriminant analysis appeared to be stable - a correct classification in 75% of the cases:

Discriminant analyses after *cross validation* on psychological values in the patient group and references at baseline:

Sample[1]	Psychol. variables (n. correctly classified)		
1	n=27	(23)	
2	n=25	(23)	
3	n=24	(23)	
4	n=24	(23)	
5	n=24	(19)	
Total correctly classified			
	111	(75 %)	

[1] Cross-validation was performed on a changing one-fifth of the cases

The model on the basis of biochemical parameters was not robust - there was a drop in correct classification of 26% from the cases after cross-validation.

Discriminant analyses after *cross validation* on biochemical values in the patient group versus the reference group at baseline:

Sample[1]	Biochem. variables (n. correctly classified)		
1	n=10	(5)	
2	n=11	(4)	
3	n=13	(5)	
4	n= 9	(7)	
5	n=13	(7)	
Total correctly classified:			
	28	(50 %)	

[1] Cross-validation was performed on a changing one-fifth of the cases

6.4 Discussion

As compared with the standard group of psychiatric out-patients [Arrindell & Ettema, 1986], the patient population investigated by us had **SCL-90** scores ranging from higher than average to high as far as men were concerned and average as far as the women were concerned.

On the basis of this findings, it can be established that in the group of patients investigated, one could speak of an average to severe psychiatric symptomatology as compared with other psychiatric out-patients.

The reference group recruited by us from the hospital staff appeared to have less complaints on the SCL-90 than the standard group recruited from the Dutch population (Figure 1). This could have been due to the fact that the reference group consisted of a selection of working individuals, all hospital staff members and comparatively young (see also chapter 5).

The complaints in the patient group were higher than those in the standard group and in the reference group on each SCL-90 sub-scale.

The scores of the **UCL** showed that the patient group indicated a manner of coping which may be considered as inadequate and whereby in comparison with the reference group more use was made of palliation, avoidance and reaction with a depressive reaction pattern, whereas active problem solving was used less by the patients. Our findings agreed with those reported by Roy-Byrne et al [1992], who observed that patients with panic disorders and/or major depression reported to use coping that was less directed towards problem solving.

High scores on avoidance and on depressive reaction pattern in the UCL may be inherent to the psychiatric problems of the patients. Whether this is true might be derived from the inter-correlation between UCL and the severity of the psychiatric complaints (see chapter 8) and from the possible changes in coping strategies after adequate treatment (see chapter 12).

On the **DMI** the patient group distinguished itself clearly from the reference group and the standard group in defense organization, whereby patients made frequenter use of more non-adult defense mechanisms:
Projection and turning against self, but less use was made of the defense mechanisms intellectualization and turning against others (Table 4). This is in agreement with the findings reported by Pollack et al [1989] who investigated a group of ambulant patients with anxiety disorder and with those reported by Akkerman et al [1992] who investigated defense organization in patients suffering from major depression and with the findings of a previous study [Timmerman et al, 1994]. However, in the studies by Pollack et al [1989] and Akkerman et al [1992] appropriate control groups were not investigated (see also chapter 3). In contrast with our study Andrews et al [1989] did not observed differences in the psychological defense organization of patients with panic disorder compared with a reference group.

Margo et al, [1993] in her study in depressed patients using the DMI observed that women with depression were more likely to use externalizing defenses and depressed men were more likely to use internalizing defenses than their respective nondepressed comparison groups for example: men had a higher tendency towards turning against self than the standard group in the studies reported by Gleser & Ihilevich [1986]. Margo et al, [1993] reported that the use of optimistic defense such as reversal and intellectualization were more frequent used in controls. Both defense mechanisms have a purpose in suppressing negative feelings and in creating a feeling of well-being. In our study, similar to Margo et al, [1993], we also observed that men showed more use of turning agression against self and less use of intellectualization than in the standard group. Women used projection more, but the use of turning agression against others by women and reversal by men and women was similar to that in the standard groups.

The discriminant analysis showed that a large number of psychological factors contribute in distinguishing reference group from patient group.

The highest sensitivity and specificity for the distinction between reference group and patients was observed in the SCL-90 scales. Severity of the symptomatology provided thus a better distinction between the two groups than differences in defense organization or coping strategy. Nevertheless one of our central questions: Patients with panic disorder and/or depression have a deviant defense organization and use of coping strategies compared with a reference group was confirmed in our investigations.

Biochemical measures

We found differences between tyrosine-, and tryptophan ratio of patients with panic disorder and/or depression and this ratio's in the reference group with lower values in the patient group. This is in line with the supposed function of the aminoacids tryptophan and tyrosine: Tyrosine is the precursor of (nor)adrenaline & dopamine and tryptophan is the precursor of serotonin. Besides the neurotransmitters noradrenaline and dopamine, serotonin probably also plays an important role in the etiology of depression [Green & Costain, 1981]. There is competition between the precursors of the neurotransmitters and other large amino acids for transport through the blood/brain barrier (see for more details: chapter 3).

The distinction between the patient group and the reference group was less prominent on basis of biochemical parameters than on basis of psychological factors, especially after cross validation. However sixty eight percent of the patients could still be correctly classified on basis of the biochemical parameters (Table 9). The unstable results with discriminant analyses after cross validation on the biochemical variables were possibly caused by the small size of the medication free patient group.

In this distinction besides the tyrosine ratio (the ratio between tyrosine and other amino acids in plasma which compete for transport to the brain) the tryptophan ratio was important. This agrees with our biochemical hypotheses presented in the introduction chapter 3 that the aminoacids tyrosine and tryptophan may play a role in the development of panic disorder and depression. There were no differences in the levels of norharman and serotonin in the plasma, thrombocytes and blood in the patient group and the reference group. This is similar to our findings in a pilot study in patients with panic disorder [Timmerman et al, 1994].

Table 4. **Psychological variables in patients and referencegroup at baseline, 6 and 9 months**

		Baseline		6 months	9 months
		Referencegroup (n=54)	Patients (n=74)	Patients (n=51)	Patients (n=26)
DMITAO	mean	39.6	34.2	35.2	38.0
	CI[1])	37.0; 42.2	31.8; 36.6	32.4; 38.0	33.4; 42.6
DMIPRO	mean	38.9	38.5	37.7	37.7
	CI	37.1; 40.7	36.9; 40.1	35.7; 39.7	35.3; 40.1
DMIINT	mean	48.7	44.0	45.7	45.3
	CI	47.1; 50.3	42.4; 45.6	43.7; 47.7	43.1; 47.5
DMITAS	mean	35.1	43.6	39.7	36.5
	CI	33.1; 37.1	41.6; 45.6	37.7; 41.7	33.3; 39.7
DMIREV	mean	37.8	39.7	41.7	42.4
	CI	35.8; 39.8	37.5; 41.9	38.9; 44.5	38.4; 46.4
DMIREP	mean	8.0	11.0	14.5	12.0
	CI	1.4; 14.6	4.6; 17.4	6.5; 22.5	0.6; 23.4
UCL-A	mean	18.1	14.6	14.9	16.0
	CI	17.1; 19.1	13.8; 15.4	14.1; 15.7	14.6; 17.4
UCL-P	mean	17.0	17.8	17.4	17.8
	CI	15.8; 18.2	16.8; 18.8	16.4; 18.4	16.4; 19.2
UCL-V	mean	14.0	18.2	16.8	15.6
	CI	13.4; 14.6	17.2; 19.2	15.8; 17.8	14.0; 17.2
UCL-S	mean	13.8	12.5	11.7	12.2
	CI	12,8; 14.8	11.5; 13.5	10.9; 12.5	11.0; 13.4
UCL-D	mean	9.9	17.2	13.5	12.4
	CI	9.3; 10.5	16.2; 18.2	12.5; 14.5	11.2; 13.6
UCL-E	mean	6.4	5.8	5.7	5.8
	CI	6.0; 6.8	5.2; 6.4	5.1; 6.3	5.2; 6.4

Table 4. Psychological variables in patients and referencegroup at baseline, 6 and 9 months (continued)

		Baseline		6 months	9 months
		Referencegroup (n=54)	Patients (n=74)	Patients (n=51)	Patients (n=26)
UCL-G	mean	11.6	11.2	11.7	12.1
	CI	10.8; 12.4	10.6; 11.8	10.9; 12.5	11.1; 13.1
SCLANX	mean	11.3	30.0	19.3	15.5
	CI	10.7; 11.9	27.8; 32.2	17.3; 21.3	13.3; 17.7
SCLAGO	mean	7.1	17.2	10.9	9.4
	CI	6.1; 8.1	15.4; 19.0	9.5; 12.3	8.2; 10.6
SCLDEP	mean	18.9	48.7	30.6	26.8
	CI	17.7; 20.1	45.1; 52.3	30.2; 31.0	22.4; 31.2
SCLSOM	mean	14.1	29.9	21.0	18.6
	CI	13.3; 14.9	27.7; 32.1	18.8; 23.2	15.2; 22.0
SCLIN	mean	11.2	25.7	18.9	16.2
	CI	10.6; 11.8	23.7; 27.7	16.9; 20.9	13.4; 19.0
SCLSEN	mean	22.8	40.0	29.6	26.5
	CI	21.4; 24.2	36.6; 43.4	26.0; 33.2	23.3; 29.7
SCLHOS	mean	6.8	11.0	8.5	8.7
	CI	6.4; 7.2	9.8; 12.2	7.5; 9.5	7.5; 9.9
SCLSLA	mean	3.6	9.7	5.5	5.0
	CI	3.2; 4.0	8.7; 10.7	4.7; 6.3	4.3; 5.8
SCLRES	mean	10.1	18.8	14.7	12.5
	CI	9.7; 10.5	17.2; 20.4	13.1; 16.3	10.7; 14.3
SCLNEU	mean	105.9	230.9	158.8	139.2
	CI	101.3; 110.5	216.7; 245.1	143.6; 174.0	12.1; 157.4
SCLPAN	mean	10.9	25.7	17.4	14.6
	CI	10.1; 11.7	23.9; 27.5	16.0; 18.8	12.6; 16.6

[1] CI = 95% Confidence interval

Chapter 7

CHAPTER 7. DISTINCTION BETWEEN THE PATIENT GROUPS WITH PANIC DISORDER AND/OR DEPRESSION ON PSYCHOLOGICAL AND BIOCHEMICAL VARIABLES

7.1 Introduction

In the study described in this chapter, the extent to which the three patient groups with panic disorder, depression and panic disorder & depression could be distinguished from each other on the basis of psychological and biochemical parameters was investigated.

The central question in this chapter was whether one could speak of a unitary etiology in panic disorder and major depres-sion which lies in a single basic biological affliction. If this was the case, then it could be expected that patients with major depression and/or panic disorder could be distinguished from each other on the basis of symptomatology and possibly on the basis of defense organization and coping, but not on differences in biological parameters. Firstly, it was investigated whether it was possible to distinguish between patient groups with depression and panic disorder on the basis of characteristic symptomatology of panic attacks using the "panic score" that was designed by us on the basis of SCL-90 items. This was done since the SCL-90 was developed in the 1970s, an era in which the concept of panic disorder was not yet clearly described and frequently went masked under the hyperventilation syndrome. Therefore the SCL-90 lacked a subscale for the measurement of panic disorder. The panic score of the SCL-90 (PAN) designed by us consisted of the in table 10 mentioned items which are identical to 10 of the 13 symptoms of a panic attack according to the DSM III-R [Timmerman et al, 1995[3]].

Table 10. Items of the SCL-90 for the DSM III-R diagnosis panic disorder

Items:	004	Dizziness
	012	Pain in chest/heart region
	017	Trembling
	039	Palpitations
	040	Nausea or stomach distress
	048	Shortness of breath
	049	Warm/cold flushes
	059	Thought of death or dying
	072	Attacks of anxiety or panic
	086	Thoughts/images of anxiety nature

The next step was a comparison on symptoms, defense organisation, and coping strategy between the three different patient groups with panic disorder, depression and panic disorder & depression. The last step is a comparison of the biochemical profiles between the three patient groups.

7.2 Statistical analysis

The transformation to the standard group was conducted as described in chapter 6. The scores of SCL-90, UCL and DMI in the three patient groups are given as mean and the 95% confidence interval of the mean in Tables 11,12 and 13 and graphically in Figures 4,5, and 6.

The internal consistency as a measure of reliability of the panic scale designed was estimated with Cronbach standardized alpha. Subsequently it was examined whether the separate items could *distinguish* between patients with panic disorder and those with depression (diagnosis according to the DSM III-R criteria and MDCL). [Timmerman et al, 1995[3]].

Using the fishers' mutiple linear discriminant analysis, with corrections for age and gender, the extent to which the three patient groups mutually differed from each other on sub-scales of the SCL, UCL and DMI together and on the biochemical variables were investigated. The following step was a cross validation of the discriminant analysis to see how robust our model is. This method of statistical analysis was described in chapter 6.

7.3 Results

Psychopathology;

The T-scores of the sub-scales of the SCL-90 of the reference -group, patients with panic disorder, patients with depression and patients with panic disorder & depression are shown in table 11. Mean and 95% confidence intervals of the mean in these groups transformed to the standard group of the sub—scores and total score (NEU) of the SCL-90 are mentioned in this table.

Table 11. Baseline values on the SCL-90[1]) in three patientgroups and in referencegroup

	Dep & pan		Depression		Panic		Reference	
SCL-subs	mean	95% CI[2])	mean	95% CI	mean	95% CI	mean	95% CI
ANX	101.0	92.7 10.4	86.5	79.9 93.3	88.6	79.9 97.3	46.2	44.9 47.5
AGO	109.5	86.5 132.4	83.4	72.3 94.5	102.6	88.5 116.7	46.3	45.8 46.9
DEP	106.4	93.4 119.3	100.0	93.1 106.9	82.3	72.6 92.0	47.3	45.7 48.9

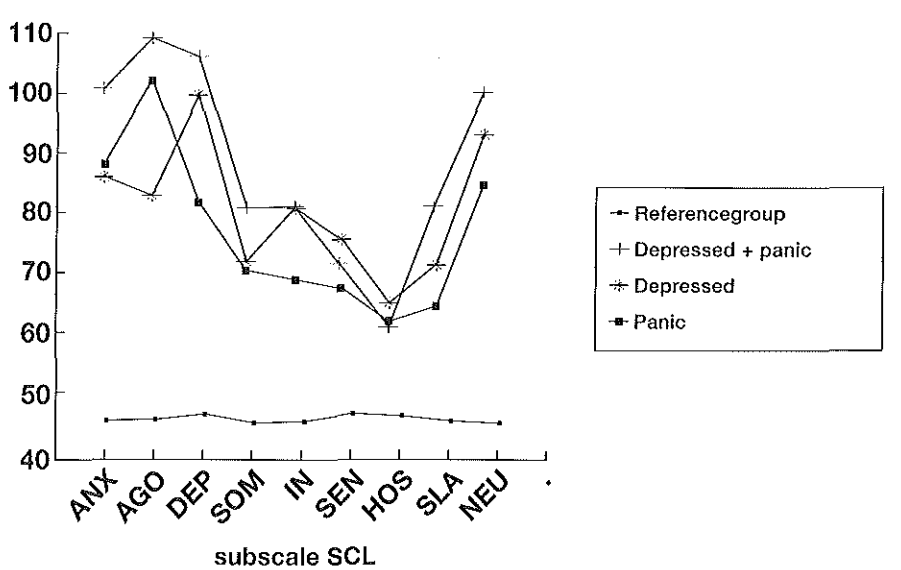
Table 11. Baseline values on the SCL-90[1]) in three patientgroups and in referencegroup (continued)

	Dep & pan		Depression		Panic		Reference	
SOM	81.5	70.9 92.1	72.5	67.3 77.7	71.1	65.0 77.2	45.9	44.7 47.1
IN	81.6	72.8 90.5	81.4	75.6 87.3	69.6	63.2 76.1	46.1	44.7 47.4
SEN	71.8	57.3 86.3	76.2	68.9 83.6	68.2	60.5 75.9	47.3	45.3 49.3
HOS	61.8	53.8 69.8	65.7	58.8 72.5	62.5	55.1 69.9	47.1	45.9 48.3
SLA	82.7	77.2 88.3	72.1	66.5 77.8	65.2	59.3 71.2	46.3	45.0 47.6
NEU	100.6	88.3 112.7	93.7	86.5 100.8	85.4	76.8 94.0	46.0	44.5 47.6

[1]) T-scores compared with normgroup;
[2]) CI = 95% Confidence interval

The scores of all sub-scales of SCL-90 in all the three patient groups were significantly higher than those in the reference group, whereby the group of patients with co-morbid major depression and panic disorder achieved the highest total score in the SCL-90 followed by the group of patients with major depression.

Figure 4. Transformed baseline values in the patientgroup and the referencegroup



The *profile* of the scores of the SCL-90 in all the three patient groups was highly similar (Figure 4) with the scores of agoraphobia in the group of patients with depression being lower than those in the other two patient groups. The scores of depression were higher than those in the patient group with panic disorder.

In an explorative study the *total score* of the designed panic scale expressed as the sum of the scores of the different items provided a significant distinction between patients with depression and those with panic disorder ($P<0.05$). The results are given in more detail elsewere [Timmerman et al, 1995[3]]. The items 12 (pain in chest/heart region), item 48 (shortness of breath) and item 72 (anxiety or panic attacks) significantly distinguished between patients with panic disorder and those with depression.

Coping:

The scores of the sub-scales of the UCL are shown in Table 12.

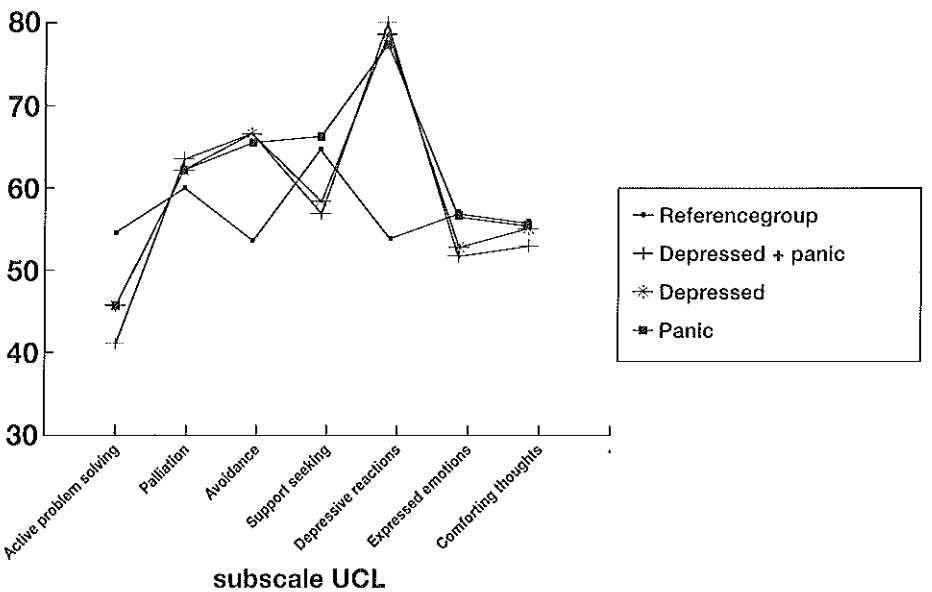
Table 12. Baseline values on the UCL[1]) in three different patientgroups and in referencegroup

	Dep & pan		Depression		Panic		Reference	
UCL-subs	mean	95% CI[2])	mean	95% CI	mean	95% CI	mean	95% CI
UCL-A	35.8	31.4 40.3	40.1	36.8 43.4	40.2	35.7 44.6	49.0	46.4 51.7
UCL-P	57.9	52.9 62.9	56.7	53.4 60.1	56.6	51.8 61.4	54.4	51.5 57.2
UCL-V	61.1	54.5 67.6	60.9	56.2 65.7	59.9	56.2 63.5	47.8	46.2 49.5
UCL-S	51.1	46.0 56.2	52.6	47.8 57.4	60.6	55.1 66.1	59.0	56.0 62.0
UCL-D	74.4	67.5 81.2	73.2	69.1 77.3	71.9	66.1 77.6	48.0	45.9 50.1
UCL-E	45.7	37.4 54.0	46.8	41.8 51.9	50.6	45.2 56.0	51.0	48.6 53.4
UCL-G	46.9	43.7 50.1	49.1	45.9 52.3	49.5	45.8 53.2	49.8	47.1 52.4

[1]) T-scores compared with normgroup;
[2]) CI = 95% Confidence interval

A graphic presentation of the results of the UCL in the three patient groups as compared with the standard group is depicted in Figure 5.

Figure 5. Transformed baseline values in the three patientgroup and the referencegroup



These three groups had an almost identical profile with the exception of a higher score on coping strategy seeking support (UCL-S) in the patient group with panic disorder.

Defense mechanisms:

The psychological defense organization as determined with the Defense Mechanism Inventory (DMI) in patients with major depression, panic disorder and panic disorder with major depression are shown in Table 13.

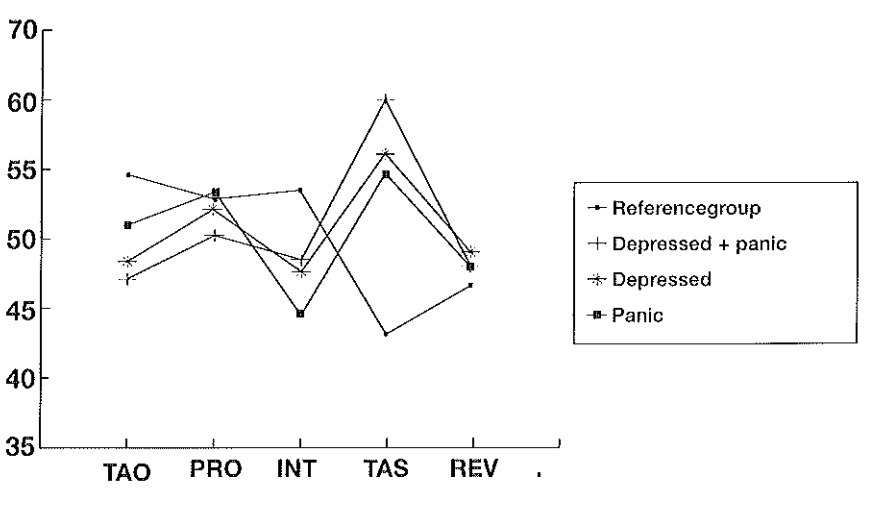
Table 13. Baseline values on the DMI[1]) in three different patientgroups and in referencegroup

	Dep & pan		Depression		Panic		Referencegroup	
DMI-subs	mean	95% CI[2])	mean	95% CI	mean	95% CI	mean	95% CI
TAO	46.9	41.6 52.2	48.1	45.0 51.3	50.8	45.5 56.1	54.5	51.8 57.1
PRO	50.0	44.2 55.8	51.9	49.1 54.7	53.2	48.8 57.5	52.7	50.3 55.1
INT	48.1	44.5 51.6	47.3	43.8 50.8	44.2	39.9 48.5	53.4	50.9 55.8
TAS	59.8	51.0 68.6	55.9	52.2 59.7	54.6	49.2 60.0	42.8	39.8 45.8
REV	47.6	42.4 52.7	48.7	45.3 52.0	47.5	42.8 52.2	46.2	44.1 48.4

[1]) T-scores compared with normgroup [2]) CI = 95% Confidence interval

A graphic presentation of the results of the DMI in the three patient groups is depicted in Figure 6. The three patient groups had a very similar profile.

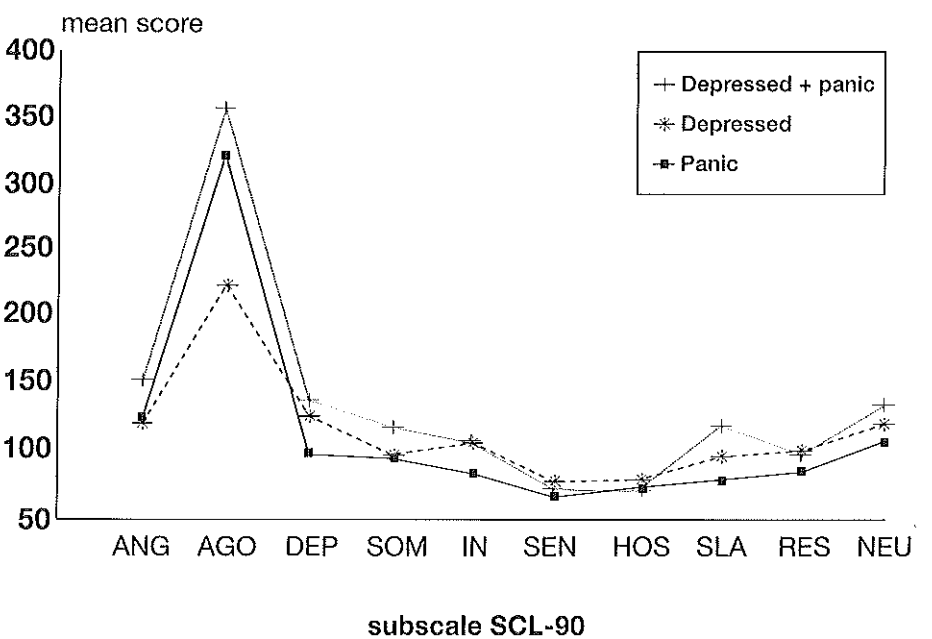
Figure 6. Transformed baseline values in the patientgroup and the referencegroup



The high scores of the patients on the defense mechanisms turning against self (TAS) and the low scores of itellectua-lization (INT) were noticeable. Patients with depression had a lower tendency towards turning agression to ohers (TAO) than those in the standard and reference group.

The *SCL-90* scores in the three patient groups transformed to the reference group are shown in Figure 7.

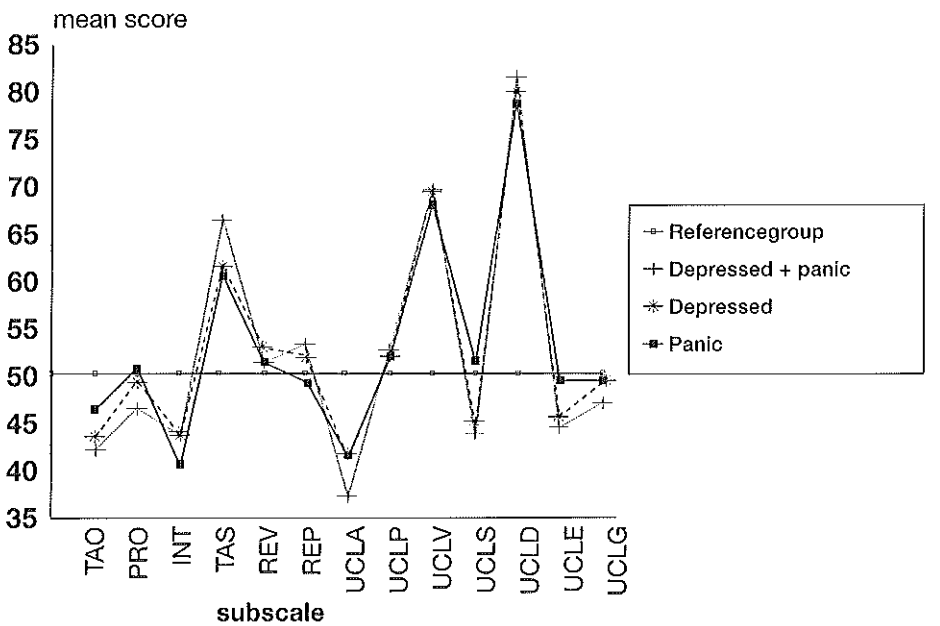
Figure 7. Transformed baseline values in the three patientgroups *)



Transformed to referencegroup

The transformed UCL and DMI scores of the three patient groups are shown in Figure 8. An almost identical pattern in the three patient groups was once again obvious.

Figure 8. Transformed baseline values in the three patientgroup and the referencegroup



The extent to which the three patient groups differed from each other in the sub-scales of the SCL-90, UCL and DMI individually and together was investigated using multiple linear **discriminant analysis** (see table 14).

Table 14. Discriminant analysis on psychological variables at baseline; three patient groups compared

Canonical corr.	X2	DF	P
0.68	49.20	12	0.05

Correlation between psychological variables and discriminant score

SCL-DEP	0.39	DMI-REV	-0.33
SCL-AGO	-0.27	SCL-RES	0.27
UCL-D	0.23	UCL-V	0.22
DMI-PRO	0.20	SCL-HOS	0.20
SCL-IN	0.20	UCL-E	0.19
DMI-REP	-0.18	SCL-SEN	0.18
SCL-NEU	0.18	DMI-TAS	0.15
SCL-ANG	-0.49		

Cases correctly classified: 68%

In Table 15 a classification scheme based on the discriminant analysis is presented. In this scheme, percentage correctly classified, sensitivity and true predictive value in the three patient groups on the basis of psychological variables are shown.

Table 15. Discriminant analysis on SCL-90, UCL and DMI in the three patientgroups at baseline

Scales	% Hit	% Sensitivity			% True positive predictive value		
Subs.		DP[1]	D[2]	P[3]	DP	D	P
SCLANX	36.5	63.6	52.8	3.7	21.9	54.3	14.3
SCLAGO	50.0	54.6	72.2	18.5	22.2	63.4	83.3
SCLDEP	43.2	63.6	22.2	63.0	24.1	50.0	58.6
SCLSOM	33.8	45.5	8.3	63.0	17.9	60.0	41.5
SCLIN	35.1	54.6	11.1	59.3	19.4	40.0	48.5
SCLSEN	47.3	0	50.0	63.0	0	54.6	46.0
SCLHOS	32.4	63.6	36.1	14.8	14.9	59.1	80.0
SCLSLA	33.8	54.6	13.9	51.9	24.0	29.4	43.8
SCLNEU	32.4	54.6	8.3	55.6	18.8	37.5	44.1
UCL-A	27.0	63.6	0	48.2	18.0	0	37.1
UCL-P	27.0	63.6	0	48.2	18.4	0	36.1
UCL-V	29.7	54.6	0	59.3	17.7	0	40.0
UCL-S	324	45.5	8.3	59.3	15.6	30.0	50.0
UCL-D	28.4	54.6	0	55.6	26.7	0	39.5
UCL-E	27.0	63.6	0	48.2	17.5	0	38.2
UCL-G	28.4	72.7	0	48.2	19.5	0	39.4
DMITAO	28.4	45.5	5.6	51.9	15.2	50.0	37.8
DMIPRO	33.8	54.6	11.1	55.6	20.7	66.7	38.5
DMIINT	31.1	72.7	5.6	48.2	21.6	40.0	40.6
DMITAS	41.9	45.5	27.8	59.3	20.8	62.5	47.1
DMIREV	46.0	0	52.8	55.6	0	50.0	41.7

[1] DP: Depression & Panic [2] D: Depression [3] P: Panic

In 68% of the cases, it was possible to correctly predict the group to which the patient belonged to on the basis of psycho-logical variables. For the distinction, the scores of the SCL-90 sub-scales depression, agoraphobia, anxiety and sensitivity made significant contributions. The model provided by discriminant analyses provided to be moderately stable after crossvalidation: Discriminant analyses *after cross validation* on psychological values in the three patientgroups at baseline

Sample[1]	Psychol. variables (n. correctly classified)		
1 n=17	(8)	2 n=15	(6)
3 n=15	(7)	4 n=14	(6)
5 n=14	(7)		

Total correctly classified 34 (46 %)

[1] Cross-validation was performed on a changing one-fifth of the cases

In Table 16, the raw biochemical values at baseline in the three patient groups who were not on medication are given as mean and 95% confidence interval. No differences between these three groups were observed except for a low norharman concentration in patients with panic disorder and a higher tyrosin concentration in the depressed patients.

Table 16. Baseline biochemical values in medicationfree patient groups

	Depression & Panic (n=15)		Panic (n=11)		Depression (n=5)	
Patientgroup	mean	95% CI	mean	95% CI	mean	95% CI
5HT[1] thrombo's	3.56	2.74 4.38	3.36	0.74 5.98	3.61	1.09 5.13
Norharman	0.55	0 1.61	0.30	0 0.84	0.59	0 1.41
Tryptophane	44.40	33.12 55.68	49.64	28.22 71.06	52.00	22.44 81.56
Tryptophane ratio	9.48	4.04 14.92	9.39	4.09 14.69	7.74	3.76 11.72
Tyrosin	54.80	6.92 102.62	56.18	31.38 92.74	73.21	22.45 123.97
Tyrosin ratio	10.94	6.54 15.34	10.08	6.40 13.86	11.10	4.48 17.72
5HT blood	900.72	329.19 1472.15	896.71	151.23 1615.19	748.27	0 1571.87

[1] 5HT = serotonin

For the discriminant analysis of the biochemical parameters, only the values obtained using blood samples from patients (N=31) who were not on medication at entry into the study were used.

The values of the different biochemical parameters who contributed significantly after discriminant analysis between the three patient groups are given in Table 17.

Table 17. Discriminant analysis at baseline: three patient groups compared on biochemical variables

Canonical corr.	X^2	DF	P
0.64	15.70	6	0.02

Correlation between biochemical factors and discriminantscore	
Norharman	0.45
Tryptophan ratio	-0.32
Tryptophan	-0.18

Cases correctly classified: 62%

The levels of norharman distinguished the three patient groups from each other. In patients with panic disorder, the level of norharman was lower than that in the other two patient groups.

A correct classification in one of the three patient groups was possible in 62% of the cases on the basis of biochemical variables. Besides norharman, the tryptophan ratio and tryptophan also contributed in distinguishing between the three patient groups.

Cross-validation of biochemical parameters provided a correct classification in 30% of the patients:

Discriminant analyses after cross validation on biochemical values in three patientgroups at baseline:

Sample[1]	Biochemical variables (n. correctly classified)		
1	n=6	(3)	
2	n=6	(3)	
3	n=7	(2)	
4	n=6	(1)	
5	n=8	(1)	

Total correctly classified 10 (30 %)

[1] Cross-validation was performed on a changing one-fifth of the cases

The limited stability derived after cross-validation was probably caused by the small size of the groups.

7.4 Discussion

In previous research we found that the patient groups with depression and panic disorder were clearly distinguished from each other at the level of symptoms using the panic scale that was designed by us on the basis of **SCL-90** items and with the SCL-90 scales: anxiety (ANG), agoraphobia (AGO), and depression (DEP) [Timmerman et al,1995[3]]. However, it was not possible to distinguish clearly between the three patient groups on the basis of defense organization or indicated use of coping strategy. Defense organization and coping strategy appeared not to be correlated with the three different types of psychiatric disorder.

However, as was expected on the basis of the literature, patients with depression had a higher tendency to turn aggression to self than patients with panic disorder as measured with the **DMI** Turning Agression against Self (TAS) scale [Ihelevich & Gleser, 1986; Margo et al, 1993].

Patients with co-morbid panic disorder and depression made less use of mature [according to the classification by Vaillant, 1988] defense mechanisms such as Reversal (REV, Intellectualization (INT) and tended less towards active problem solving (UCL-A).

Similar to that observed in our study, Roy-Byrne et al [1992] also reported that there were no differences in the indicated use of **coping strategy** between patients with panic disorder and depression.

However, Hoffart & Martinsen [1993], in their investigation in 95 patients with depression, depression and agoraphobia and with agoraphobia only observed that patients with only agoraphobia and depression-, and with agoraphobia sought less social support and tended more towards wishful thinking than patients suffering from depression. These authors suggested that agoraphobia was associated with more maladaptive coping than was the case in patients with depression. Agoraphobia seemed to be a more severely disabled subgroup of patients with panic disorder.

The number of patients correctly classified on the basis of psychological parameters using discriminant analysis was 68%. A table 15 shows this percentage was negatively influenced by the patient group with co-morbid depression and panic disorder. A correct classification in this group was only possible in 36% of the cases. The significant factors which contributed in distinguishing the groups were symptom clusters, but not the differences in coping strategy or defense organization.

In discriminant analysis on the biochemical values, the patient group with panic disorder distinguished itself from the other two patient groups and the reference group by a lower concentration of norharman. This differed from the findings of a previous study [Timmerman et al, 1994[1]] in which there were no differences in the levels of norharman in patients with panic disorder and a reference group, but does fit in well with the possible activity of norharman as a benzodiazepine receptor agonist [Van Gelderen et al, 1994]. A decrease in this agonistic function could possibly lead to an increased anxiety. However,

the group of patients suffering from panic disorder without medication at baseline was rather small (11 patients) and the level of norharman in the patient group with co-morbid panic disorder and depression did not differ from that in the reference group. Investigations on the levels of norharman in a larger group of patients with panic disorder would, therefore, also be warranted.

We observed no significant differences between the levels of serotonin in the plasma and thrombocytes in patients not on medication and those in the reference group. This is in disagreement with the findings of Hanh Le Quan-Bui et al [1984] who observed that the levels of serotonin in the plasm of patients with major depression were clearly reduced indicating that there was a dysfunctional serotonergic system in panic disorder and major depression. It is also in contrast with the observations in our earlier investigations [Timmerman et al, 19941], where no relationship between the levels of serotonin in thrombocytes and anxiety was observed. (A further discussion on the inter-dependence between biochemical and psychological parameters is presented in chapter 11).

Similar to the discriminant analysis of the psychological parameters, the percentage of correctly classified patients on the basis of biochemical parameters using discriminant analysis was negatively influenced by the group of patients with comorbid panic disorder and depression. Sixty two percent of the cases were correctly classified whereby norharman was the most important distinguishing factor. (table 17)

It was *concluded* that the model provided by discriminant analysis in which the patient groups and the reference groups were distinguished from each other with the help of psychological and biochemical differences was stable, but possibly because of their limited size, the three patient groups could not be distinguished clearly from each other.

There was a lack of specificity of different defense mechanisms and coping strategies between patients with panic disorder and major depression which supported the unitary hypothesis of the two disorders on a psychological level [Lapierre & Hamilton, 1993]. This fits with the idea that co-morbidity arises as a consequence of the lack of specificity of different defense mechanisms for particular types of personality and its disorders [Maser & Cloninger, 1990].

The unity between panic disorder and depression that was observed from a psychological point of view was not observed from the biochemical profile: The biochemical data suggest that the small patient group with the diagnosis panic disorder have a lower norharman plasma level than the two other patient groups. It is possible that biological factors determine which psychiatric disorder, panic disorder or depression occur. This was in agreement with recent genetic studies in which panic disorder and depression emerged as separate illnesses [Weissman et al, 1994] and with the Kraepelinian biomedical theory in which each psychiatric disease is believed to have specific genetic and neurobiological antecedents.

Chapter 8

CHAPTER 8. INTERDEPENDENCE OF PSYCHOLOGICAL CHARACTERISTICS

8.1 Introduction

The inter-correlation between the coping strategies and defense mechanisms, operationalized in the sub-scales of UCL and DMI, were investigated in the reference group and in the patient group as a whole prior to commencing therapy in order to gain further insight into the relationship between the psychological variables. In addition, it was also examined whether there were differences in inter-correlations between the patient group and the reference group. The inter-correlations between the bioche-mical variables and the psychological variables were also investigated in the reference group and the patient group without medication. These are discussed in chapter 11.

8.2 Statistical method

The inter-correlations of the sub-scales of DMI and UCL in the patient group at baseline and in the reference group were estimated (Pearson product moment correlation coefficient) and were adjusted for age and gender. The significant inter-correlations with their 95 % confidence interval between the DMI and UCL scales in the patient group and the reference group have been determined ($p < 0.05$, two tailed T-test)

8.3 Results

Only the substantial inter-correlations between DMI and UCL scales in the patient group are shown in Table 18 (appendices) and, separately for patients and reference group in Table 21. (Table 21 presents in addition the biochemical concentrations with their intercorrelations of the patients who were medication-free at baseline)
See for Table 21 chapter 11

In the **DMI** the direction of significant association in the patient group and reference group were similar. Between the scales of the DMI and UCL, in the patient group, positive associations were observed between projection and expression of emotions. Negative correlations were observed between intellectualization and depressive reactions and expression of emotions.

No significant correlations between UCL and DMI scales were noted in the reference group.

Concerning the **UCL** we observed a positive correlation between palliation (P) and depressive reactions (D) in the reference group but a negative association in the patient group. In the patient group the correlation between avoidance (A) and social support seeking was also negative in contrast with the reference group. Moreover, we found a negative association between depressive reactions (D) and reassuring thoughts (G) in the patient group while their associations in the reference group were positive.

In the reference group, we did not observe any negative correlations mutually between any of the UCL scales.

8.4 Discussion

Schreurs [1987] investigated the inter-correlations between the **UCL** scales in 1200 employees of the Dutch Railways Association. Similar to that observed in our investigations in the reference group, he also observed a positive correlation between avoidance and depressive reactions, between seeking support and depressive reactions and positive correlations between palliation and almost all other UCL scales. Schreurs [1987] also observed a positive association between expression of emotions and palliation. This association, although not significant, was also positive in our reference group. Schreurs [1987] concluded that all scales apparently contained an element for the avoidance of the problem and for the regulation of aroused tension.

In contrast with the reference group, the patient group, showed negative correlations between reassuring thoughts and depressive reactions, and between avoidance and seeking support.

It appeared from table 4 (Chapter 6) that the patients used less adequate coping mechanisms such as seeking support and reassuring thoughts than those in the reference group. The other associations between the coping strategies in the patient group and in the reference group were similarly directed and there were only quantitative differences in the degree of association. More significant associations regarding the UCL were being noted within the patient group.

As far as the **DMI** was concerned, the findings in the reference group were very similar to those reported for the standard group in the literature: Passchier & Verhage [1986] reported the same inter-correlations in their investigations in Dutch controls.

Similar to Ihilevich & Gleser [1986], we also observed a positive correlation between turning aggression against others and projection in the reference group. Further, Ihilevich & Gleser [1986] observed a positive correlation between reversal and intellectualization. Reversal and intellectualization also correlated positively in our reference group.

Freud had already established that these two defense mechanisms were functionally linked when he described the disconnection of thoughts and feelings as a form of repression [1962]. Since the elimination of unpleasant emotions from the consciousness is common in both intellectualization and reversal, they often occur together in the same individual.

Negative correlations were observed between turning aggression against others and reversal, between projection and reversal and between intellectualization and turning aggression against others and projection.

These negative correlations observed in the reference group also corroborated those reported in the standard group by Ihilevich & Gleser [1986].

The same positive and negative correlations between the defense mechanisms as those in the reference group were also observed in our patient group, whereby there were only quantitative differences between the reference group and the patient group. In the reference

group, we did observe a few significant correlations between UCL and DMI scales. In his investigations, Schreurs [1987] concluded that there was no clear relationship between UCL and DMI and that both scales indeed measured a different construct namely coping and defense. However, we observed a positive correlation between intellectualization and active problem solving in the patient group. Both were considered as adequate intra-psychological processes for solving problems (see chapter 3). We observed moderate negative associations between intellectualization and depressive reactions and expression of emotions in the patient group. It is possible that intellectualization gives some protection against depressive reactions. However the confidence interval is rather large.

In *conclusion*, it can be stated that there were quantitative differences in the intercorrelations in UCL and DMI in the reference group and the patient group, but that the direction of the associations in these two groups was identical.

Concerning coping these quantitative differences in correlations between the patient group and the reference group involved the strategies avoidance and depressive reactions which were possibly correlated with the symptomatology of the psychiatric disorder. If these coping strategies preexist to psychiatric disease we expect them to be mainly trait dependent and not much change in the indicated use of these coping strategies after therapy is likely to occur. In chapter 9 we will investigate whether this is the case.

Table 18. Substantial partial[1] correlations between psychological variables, adjusted for gender and age (N=74)

Turning agression against others (DMITAO)			
	r[2]	95% CI[3]	
DMIPRO	.62	.46	.74
DMIINT	-.63	-.75	-.50
DMIREV	-.68	-.79	-.53
DMIREP	-.91	-.94	-.86
SCLHOS	.35	.13	.54
SCLIN	.24	.01	.44

1) Two-tailed
2) Pearson product-moment correlation coefficient
3) Confidence Interval

Projection (DMIPRO)			
	r	95% CI	
DMITAS	-.40	-.58	-.19
DMIINT	-.48	-.58	-.19
DMIREV	-.70	-.80	-.56
DMIREP	-.83	-.89	-.74
SCLHOS	.24	.01	.44
UCL-E	.40	.19	.58
UCL-P	.25	.02	.45

Table 18. Substantial partial[1)] correlations between psychological variables, adjusted for gender and age (N=74) (continued)

Intellectualisation (DMIINT)			
	r	95% CI	
DMIREV	.38	. 17	.56
DMIREP	.72	.59	.81
UCL-A	.35	.13	.54
UCL-D	-.37	-.55	-.15
UCL-E	-.31	-.50	-.09
SCLANX	-.33	-.52	-.11
SCLIN	-.37	-.55	-.15
SCLSEN	-.35	-.54	-.13
SCLHOS	-.30	-.49	-.08
SCLNEU	-.36	-.54	-.14
SCLDEP	-.25	-.45	-.02

Turning agression against self (DMITAS)			
	r	95% CI	
DMIREP	.26	.03	.46
SCLDEP	.29	.07	.49

Table 18. Substantial partial[1] correlations between psychological variables, adjusted for gender and age (N=74) (continued)

Reversal (DMIREV)			
	r	95% CI	
DMIREP	.85	.77	.90
SCLDEP	-.25	-.45	-.02
SCLIN	-.24	-.44	-.01

Repression (DMIREP)			
	r	95% CI	
SCLIN	-.28	-.48	-.06
SCLSEN	-.24	-.44	-.01
SCLHOS	-.34	-.53	-.12
SCLNEU	-.24	-.44	-.01

Palliation (UCL-P)			
	r	95% CI	
UCL-E	.28	.06	.48
UCL-G	.45	.25	.62

Table 18. Substantial partial[1)] correlations between psychological variables, adjusted for gender and age (N=74) (continued)

Active problem solving (UCL-A)			
	r	95% CI	
UCL-P	.27	.04	.47
UCL-V	-.28	-.48	-.06
UCL-D	-.32	-.51	-.10
UCL-G	.48	.28	.64
SCLANX	-.31	-.50	-.09
SCLAGO	-24	-.44	-.01
SCLDEP	-.24	-.44	-.01
SCLIN	-.36	-.54	-.14
SCLNEU	-.25	-.45	-.02
SCLPAN	-.33	-.52	-.11

Avoidance (UCL-V)			
	r	95% CI	
UCL-D	.38	.17	.56
SCLDEP	.28	.06	.48
SCLNEU	.28	.06	.48
SCLIN	.41	.20	.58

Table 18. Substantial partial[1] correlations between psychological variables, adjusted for gender and age (N=74) (continued)

Seeking support (UCL-S)			
	r	95% CI	
UCL-D	.36	.14	.54
UCL-E	.58	.41	.71
SCLAGO	.30	.08	.49

Depressive reactions (UCL-D)			
	r	95% CI	
UCL-E	.41	.20	.58
UCL-G	-.33	-.52	-.11
SCLANX	.58	.41	.71
SCLAGO	.40	.19	.58
SCLDEP	.63	.47	.75
SCLSOM	.54	.36	.68
SCLIN	.63	.47	.75
SCLSEN	.61	.44	.74
SCLHOS	.41	.20	.58
SCLSLA	.49	.29	.65
SCLNEU	.74	.62	.83
SCLPAN	.55	.37	.69

Table 18. Substantial partial[1] correlations between psychological variables, adjusted for gender and age (N=74) (continued)

Expressed emotions (UCL-E)			
	r	95% CI	
SCLIN	.35	.13	.54
SCLSEN	.41	.20	.58
SCLHOS	.65	.50	.76
SCLNEU	.32	.10	.51

Chapter 9

CHAPTER 9. EVALUATION OF THE CHANGES IN PSYCHIATRIC PATIENTS AFTER THERAPY AND THREE MONTHS LATER

9.1 Introduction

In the study described in this chapter we investigated whether there were changes in the scores of SCL-90, UCL and DMI during the treatment of psychiatric patients with a combination of antidepressants and cognitive therapy, and if so wich direction those changes had.

Moreover, we also examined whether any changes persisted after medication therapy was discontinued. This was carried out by measuring the symptomatology of the patients with the SCL-90, and in the stability of defense organization and coping strategies by the scores of DMI and UCL after 6 months of therapy (the moment on wich a subgroup of the patients decided to stop their therapy) and at follow-up, three months later.

We expected that the SCL-90 scores would decline with successful therapy, but that scores of DMI and UCL will not change considerably since we expect them to reflect more trait than state aspects of the patients and not highly prone to changes.

It was also examined which of the three patient groups showed the strongest effect of therapy as measured in SCL-90, and if there were differences between the three patient groups concerning coping and defense mechanisms after combined psychotherapeutic and clomipramine therapy.

9.2 Method of statistical analysis

The changes in the psychological sub-scales were expressed as mean and 95 % confidence interval of the mean and are shown in Table 4. (see chapter 6)

Missing values are estimated by the method of predicted mean matching [Little, 1988].

By estimating missing values no empty cells will be present wich is necessary condition for a repeated measurement design. The number of cases will not be diminished and consequently the power of statistical analyses will be higher and the number of cases will be equal for all analyses[1].

Next the regression analysis was performed on all individual variables after the missing values had been substituted (Slaets [1994]) as follows;

First the variables were standardized at T0 and T6. Then the three psychiatric groups were coded by two dummy variables (codes 1 and 2). The subgroup depression became linear dependent and as a consequence eliminated from the analyses.

The regression analysis was performed with both the dummy coded variables and the baseline measurements corrected for age and sexe as independent (predictive) variables. Finally the standardized regression coefficient (beta) and the standard error of beta for the baseline measurements and the psychiatric subgroups at six months were estimated (Table 19)[2].

1) To that aim, a regression analysis was performed for the missing value at T6 with T6 predicted variable and T0, age and gender as predictive variables.
The derived estimated value for T6 from the analysis was compared with that case that had this estimated value or that was close to it. Subsequently, the missing value at T6 was substituted by the observed value for the last named case. The same method was used for the missing value at T0.
2) The standard regression coefficient can be interpretated as follows:
The higher the regression coefficient of the predictor variable, the higher the association with the outcome variable. If the beta is negative than a high value implies that the outcome value is related negatively with the standerdized predictor variable. For example: A beta of .50 means that an increase of the predictor variable with one point yields an expected increase of .50 on the outcome variable measured at T=6 months. If beta is -.50 than the expected value on the outcome variable will decrease with .50.

9.3 Results

After six months of therapy, there was still a group of 51 patients in the study. From this group, 26 patients wanted to discontinue their medication at that moment. This group of 26 patients was evaluated again three months after discontinuing their medication.

The mean scores and their 95 % confidence interval of SCL-90, UCL and DMI in the two different patient groups, (those who wanted to stop their medication and those who wanted to continue their medication after six months of treatment), are shown in Table 4. In the SCL-90, scores of all sub-scales had decreased between baseline and six months as can be seen in the 95 % confidence interval. The highest decrease was in the SCL-90 scales anxiety (ANX), depression (DEP), panic (PAN), sleep disorders (SLA) and psycho-neuroticism (NEU). The mean SCL psycho-neuroticism score (NEU), a frequently used indicator for an overall therapeutic effect was reduced further during the period six months-nine months from 158.82 to 139.23.

A further analysis (not included in this thesis) revealed that there were no significant differences on SCL, UCL and DMI scores and biochemical values between the dropouts, the patient group who stopped therapy after six months and those patients who were included in the follow-up investigations. We concluded that the dropouts were random.

From the UCL scales avoidance (V) and depressive reactions (D) decreased the most. There were hardly any other changes in the UCL scales.

In the DMI small increasements were noted in turning agression against others (TAO), reversal (REV) and repression (REP). Turning aggression against self (TAS) was decreased.

It was noticeable that changes in psychological parameters at six months, had mostly taken root at the follow-up after nine months. This was especially true for the effect on the symptomatology.

Regression analysis showed that the psychiatric subgroup appeared not to be an important factor in the outcome of the different coping and defense scales at six months. The subgroup panic disorder & depression however did have the smal-lest therapeutic response as revealed by SCL-90 NEU score.

Table 19. Differential qualities of diagnostic catagories[1] (adjusted for age and gender), on outcome after six months of treatment

	Depression and panic		Panic	
	Beta	SE Beta	Beta	SE Beta
DMITAO	0.14	0.21	0.57	0.21
DMIPRO	0.14	0.25	0.31	0.25
DMIINT	0.26	0.29	0.29	0.29
DMITAS	- 0.22	0.23	0.66	0.23
DMIREV	0.36	0.22	0.31	0.22
DMIREP	0.19	0.21	0.53	0.21
UCL-A	- 0.01	0.29	0.39	0.29
UCL-P	0.62	0.13	- 0.14	0.28
UCL-V	0.45	0.31	- 0.07	0.31
UCL-S	0.06	0.30	0.49	0.31
UCL-D	0.20	0.28	0.16	0.29
UCL-E	0.17	0.24	0.45	0.24
UCL-G	0.13	0.31	0.27	0.31
SCLANX	0.66	0.28	- 0.24	0.28
SCLAGO	0.10	0.29	0.06	0.29
SCLDEP	0.16	0.33	0.14	0.33
SCLSOM	0.69	0.22	- 0.07	0.22
SCLIN	0.20	0.32	0.22	0.32
SCLSEN	0.55	0.23	0.05	0.23
SCLHOS	0.57	0.24	0.11	0.24
SCLSLA	0.65	0.31	- 0.20	0.30
SCLRES	0.70	0.24	- 0.14	0.24
SCLNEU	0.83	0.26	- 0.33	0.26
SCLPAN	0.53	0.25	- 0.02	0.24

[1]adjusted for corresponding baseline variables

9.4 Discussion

As was expected, the pattern of complaints in patients with panic disorder and/or major depression as measured with the **SCL-90** altered considerably during combined treatment with clomipramine and cognitive therapy. Although, the therapeutic effect in all three patient groups in this open trial was high, it was observed that the patient group with co-morbid panic disorder and major depression showed lower response to therapy at six months than the other diagnostic groups as measured by the SCL Psycho-neuroticism (NEU) which is an overall measure for psychological distress.

This was in agreement with the findings by Albus & Scheibe [1992] who reported that patients with co-morbid panic disorder and major depression showed a poor response to therapy (see also chapter 3).

Probably consists the comorbid group of more severe ill patients. Improvement was reached after six months of treatment and continued to persist at follow-up at nine months in the group of patients who discontinued their medication after six months. In **coping style** the most notably changes, diminishments, were in avoidance and depressive reaction pattern. Of the defense mechanisms only turning agression to self decreased markedly. Although moderately the scores of the DMI- and the UCL scales in the patients had changed in the direction of those in the standard groups.

Further, it appeared that it was not relevant to which diagnostic group the patients belonged to for the outcome on the different scales of the UCL and DMI.

On the basis of this, one can state that the changes in the style of coping and indicated defense mechanisms were not dependent on having a specific psychiatric disorder in the sense of panic disorder or major depression or both. The lack of specificity was in line with the findings by Bond & Vaillant [1986] who found that DSM III diagnosis could not predict defense style.

The use of coping strategies such as depressive reactions and avoidance was probably partially related to the presence of depression and/or panic disorder symptomatology at baseline. A large number of our patients with panic disorder had also agoraphobia which implied avoidance (see also: chapter 5). On the basis of our findings of the lack of considerable change in UCL scores, we might concluded that coping is mainly a stable trait. Traditionally, coping was seen as a trait characteristic [Troop, 1994]. This is also is in agreement with the hypothesis by Andrews [1991] who stated that general vulnerability for anxiety disorders and depression was determined by a high level of trait anxiety and poor coping.

On the basis of their investigations in thirty in-patients with agoraphobia and/or depression who were treated with psychotherapy (exposure and insight providing psychotherapy) for thirteen weeks, Hoffart & Martinsen [1993] observed that while the coping strategies active problem solving and wishful thinking behaved mainly as state phenomena, avoidance behaved predominantly as a trait phenomenon. Seeking social support had both trait and state phenomenon. The results of this study however are tentative because off the small sample size.

In this study of Hoffart & Martinsen, a high level of seeking social support predicted a favorable therapeutic result. This is in agreement with the outcomes of life-stress research which pointed out that the presence of social support forms a buffer against the occurrence and recurrence of psychological disorders [Surtees, 1980].

It was noticeable that of the **defense mechanisms**, reversal (REV) and turning agression against others (TAO) increased, although insignificantly and turning against self (TAS) decreased. This suggest that during therapy, patients tend to direct aggression less at themselves, but more towards others. Therefore, it can be stated that psychological defense probably is partly state determined, which idea is in agreement with Freud's original ideas [1986].

Since a part of the TAS question refers to depressive feelings and mood it is, however, possible that the TAS scores in patients form an epiphenomenon of psychopathology, especially depression.

After six months of therapy (the moment of discontinuation of the medication and cognitive therapy), the level of repression (REP) was increased insignificantly compared with the baseline value, but repression diminished again at follow-up three months later. After therapy the patient group had changed in defense organization in the direction of those in the reference group.

In disagreement with Akkerman [1992], who observed no changes after therapy in neurotic defense mechanisms, we observed that the use of mature defense mechanisms (PRN) was increased after the therapy. Projection, however, which is an immature defense mechanism, decreased during the therapy, wich was in accordance with the results of the study by Akkerman [1992]. Most of these changes were statistically not significant, so these conclusions als tentative.

In this study we made use of a comparatively small patient group especially at our follow-up investigations. Since we did not used a placebo control group we cannot rule out that the changes found in our patient group are sponteneous. However, most patients had their illness during quite a long time (see chapter 5) wich makes that sponteneous remission seems unlikely.

Chapter 10

CHAPTER 10. DISTINCTION BETWEEN PATIENTS ON MEDICATION AND THOSE NOT ON MEDICATION AT BASELINE

10.1 Introduction

In this study, all patients who did and who did not use antidepressants as medication at baseline were included. A limited number (n=43) of patients were put on medication with clomipramine before the analysis of their blood samples were done. For ethical reasons, the clinical severity of the psychiatric condition of the patients in such cases received priority above the setup of the study. The use of medication as far as the tricyclic antidepressants were concerned was checked by determining the blood levels. In the studies described in this chapter, it was investigated whether there were differences in the psychological and the biochemical parameters at baseline between these two groups of patients.

If there were no differences between the psychological variables in the two patient groups, then it would be justified to study the two different patient groups combined in these respects. We expected that there would be differences between the biochemical parameters in the two patient groups because of the influence of clomipramine.

10.2 Statistical analysis

Mean scores with standard deviation of sub-scales of SCL-90, DMI and UCL in the patients group on medication (n=43) and the patient group not on medication (n=31) at baseline were compared. It was investigated wether there were significant differences between the two patient groups with the Wilcoxon test.

It was also investigated whether there was a difference in the severity of the psychopathology between the two patient groups on the basis of the SCL-90 total score (NEU). The mean score with 95 % confidence interval of the biochemical variables in the two patient groups were also compared (table 6).

10.3 Results

The mean scores on the psycholgical measures with standard deviation in the group of patients who did and did not use tricyclic antidepressants are given in Table 20.

Table 20. Comparison between patients with and without use of tricyclic antidepressants at baseline

	Medicationfree (n=31)		Medication (n=43)	
	Mean	Sd	Mean	Sd
DMITAO	35.4	10.7	33.4	10.3
DMIPRO	41.0	5.4	36.6	6.7
DMIINT	42.7	7.1	44.9	6.2
DMITAS	43.1	7.6	44.0	8.6
DMIREV	37.9	7.8	41.1	10.1
DMIREP	4.3	25.7	15.9	28.2
UCL-A	14.8	3.7	14.4	3.8
UCL-P	18.6	4.1	17.2	3.8
UCL-V	18.5	4.5	18.0	3.8
UCL-S	13.0	4.3	12.2	4.1
UCL-D	17.5	4.2	17.0	3.7
UCL-E	5.9	2.5	5.8	2.5
UCL-G	11.7	2.7	10.9	2.0
SCLANX	30.5	9.0	29.6	9.3
SCLAGO	17.6	6.9	16.9	8.4
SCLDEP	48.0	15.9	49.2	15.3
SCLSOM	29.5	9.1	30.1	9.6
SCLIN	26.2	8.6	25.3	8.0
SCLSEN	42.5	14.5	38.3	15.1
SCLHOS	10.7	4.1	11.2	5.3
SCLSLA	9.4	4.4	9.9	3.7
SCLRES	18.7	6.4	18.9	6.6
SCLNEU	233.1	60.6	229.3	62.1
SCLPAN	26.1	7.4	25.4	7.4

There were only small nonsignificant differences between these two patient groups. The biochemical values in these two patient groups are shown in Table 6. (see Appendix)

The serotonin level in thrombocytes was lower in the group of patients who used antidepressants. Also the tryptophan and levels of serotonin in the blood and plasma were decreased in these patients.

There were no significant differences in the other biochemical parameters between the two patient groups .

10.4 Discussion

A majority of the patients were still on the tricyclic antidepressant clomipramine at the first blood sampling.

Regarding the complaints (SCL-90), copingstrategies (UCL) and defense mechanisms (DMI) scores at baseline were almost identical in the two patient groups as was expected. Therefore it is unnecessary to distinguish between patients who still used clomipramine and those who did not at entry into the study.

It is known that antidepressants (e.g. clomipramine) influence the level of serotonin in the blood, plasma and thrombocytes of the patients. The levels of serotonin in the blood, plasma and thrombocytes of patients who used these antidepressants were lower than those in patients who did not use antidepressants and than those in the reference group.

This effect can be attributed to the fact that clomipramine has a strong influence on the serotonergic system by inhibiting the uptake of serotonin. Previous investigations using selective inhibitor of serotonin uptake, citalopram had the same effect on the levels of serotonin in the blood and thrombocytes (the levels of serotonin in the plasma were not investigated in that study) [Timmerman et al, 1987].

Our findings were in contrast to the investigations reported by Hanh Le Quan-Bui et al [1984] who observed that treatment with tricyclic antidepressants had no effect on the levels of serotonin in the plasma and in the thrombocytes of patients with major depression. However, these authors did not mention the type of antidepressants that were used for treatment. It may well be that they had used antidepressants such as maprotiline which had either only a slight effect or no effect at all on the serotonergic system.

Sarrias et al [1987] conducted a study with clomipramine in eighteen patients with melancholia and observed that the level of serotonin in thrombocytes strongly decreased during the therapy, but that there was no change in the level of serotonin in the plasma.

These authors concluded that there were different pools of plasma- and thrombocyte serotonin. Since in our study serotonin in plasma decreased as well, we were unable to confirm this conclusion.

Besides a significant negative influence on the levels of serotonin in thrombocytes, blood and plasma, the use of clomipramine also appeared to be associated with a low level of tryptophan, a precursor of serotonin in the patients, and with a low tryptophan ratio, the reason for which remains unknown.

One could speculate that the use of clomipramine causes enzyme-induction in the liver with activation of tryptophan pyrrolase whereby degradation of tryptophan is increased. However, this explanation is less likely because low doses of antidepressants already inhibit this enzyme [Bradawy & Evans, 1981].

Other explanations for a decrease in the level of tryptophan in the plasma is an increased uptake of free tryptophan by brain tissue possibly in combination with the shift of albumin-bound tryptophan towards free tryptophan by the tricyclic antidepressant [Thomas et al, 1987], or decreased absorbtion of tryptophan from the gastrointestinal tract.

The use of clomipramine had no significant influence on the baseline levels of norharman and tyrosine.

Table 6. Baseline biochemical values in patients and reference

		Reference (n=27)	Medication free patients (n=30)	Patients with medication (n=36)	All patients (n=66)
Ser[1] in plasma (10^{-9} mol/l)	mean CI[2]	14.2 7.8 ; 20.7	15.5 10.4 ; 20.6	7.6 5.1 ; 10.1	11.2 8.4 ; 14.0
Ser in platelets (10^{-9}mol/ $10E^{9}$ pl)	mean CI	3.6 3.2; 4.0	3.5 3.1; 4.0	1.1 0.2; 2.0	2.9 2.4; 3.4
Ser in blood (10-9 mol/l)	mean CI	957.7 815.9; 1099.6	820.5 682.4; 958.6	131.4 26.3; 236.5	547.7 414.2; 681.2
Norharman (10-12 mol/l)	mean CI	0.45 0.37; 0.53	0.49 0.31; 0.59	0.53 0.40; 0.65	0.51 0.42; 0.60
Tyrosin (10-6 mol/l)	mean CI	67.1 59.0; 75.3	63.9 55.4; 72.4	60.4 55.9; 64.9	61.9 57.5; 66.3
Tyrosin ratio	mean CI	11.4 10.3; 12.4	10.7 9.99; 11.5	11.3 10.6; 12.0	11.0 10.4; 11.6
Tryptophan (10-6 mol/l)	mean CI	52.8 48.5; 57.0	49.9 45.6; 54.2	41.9 39.1; 44.7	45.3 42.7; 47.9
Tryptophan ratio	mean CI	8.9 8.2; 9.6	8.6 7.8; 9.5	7.5 7.1; 7.9	8.0 7.5; 8.5

[1] Serotonin

[2] 95% Confidence interval of the mean.

Chapter 11

CHAPTER 11. RELATIONSHIP BETWEEN PSYCHOLOGICAL AND BIOCHEMICAL VALUES AT BASELINE: AN EXPLORATION

11.1 Introduction

Van Praag [1995] states that the Kraepelinian experience in which behavior disorders were regarded as discrete illnesses such as major depression or panic disorder yielded a wealth of interesting data in biological psychiatric investigations, but failed to provide a single noteworthy specificity for diagnosis. He stated that nosological concepts were not the end-point for the diagnosis, but were just a beginning.

According to this the next step is the dismantling of the hypothetical syndrome into its various components including psychological (dys)functions. Van Praag [1995] expected that these two-tailed diagnosis would lead to a shift from a nosological to a multi-functional orientation, whereby psycho-pharmaceuticals directed more at the complaints instead of the diagnosis could be prescribed.

In our earlier investigations into the relationship between biochemical parameters, presentation of psychiatric illness and psychological dysfunctions, we observed in agreement with the view of Van Praag [1995] that norharman was not correlated with a psychiatric illness (panic disorder), but to psychological dysfunctions in the sense of indicated defense organization and coping strategies [Timmerman et al, 1994[1]].

In the study described in this chapter, relationships between biochemical parameters and psychological parameters at baseline in patients not on medication and the reference group were investigated.

The questions were whether there were any correlations between biochemical variables and psychological dysfunctions and whether there was a difference between these correlations in the patient group and the reference group.

11.2 Statistical method

Partial inter-correlations of psychological and biochemical parameters that were estimated at baseline in patient group not on medication and in the reference group were adjusted for age and gender. These partial inter-correlations, were presented including a 95% confidence interval and are shown in table 21 (see appendices) and, in summary, in table 21[a].

11.3 Results

Since the psychological variables at baseline in patient group not on medication did not essentially differ from those in the patient group on medication (chapter 10), the inter- cor-relations between the psychological variables for this patient group are not discussed separately (see chapter 8), except for the SCL-90, not discussed earlier. Active problem solving coping (UCL-A) in the UCL scale showed a negative correlation with the severity of symptomatology (NEU) as measured in the SCL-90. Depressive reactions(UCL-D) correlated positively with all SCL-90 scales.

Some important significant inter-correlations of biochemistry and psychology in the reference group and the patient group:

DMI

Turning aggression against others (TAO) correlated negatively with serotonin in the thrombocytes and plasma in the patient group and positively in the reference group.

In the patient group, repression (REP) was correlated positively with 5-HT in thrombocytes and with tryptophan ratio.

In the reference group, repression was correlated negatively with 5-HT in thrombocytes, plasma 5-HT and with tryptophan ratio but positively with tyrosine ratio and tyrosine.

Table 21a Confidence intervals of partial correlations between serotonin in thrombo`s and in plasma with psychological variables (excerpt from table 21)

serotonin in thrombo`s[1]						
	Patients			Reference		
DMI	TAO	REP	HOS	TAO	REP	HOS
SCL	-.67	.09	-.68	.16	-.72	-.52
95% C.I.[2]	.00	.72	-.07	.75	-.11	.21

serotonin in plasma				
	Patients		Reference	
DMI	TAO	REP	TAO	REP
95% CI	-.21	-.23	.12	-.76
	-.54	.48	.73	-.20

[1] Substantial partial correlation adjusted for age and gender
[2] 95% confidence interval

UCL

From the coping mechanisms depressive reactions (D) was correlated positively with tyrosine ratio in the patient group.

However, this correlation was negative in the reference group. UCL-D also showed a negative correlation with 5HT in thrombocytes.

There were other no significant correlations between coping mechanisms and biochemical variables in the patient group.

SCL-90

In the SCL-90, we observed positive correlations between serotonin in thrombocytes and anxiety (ANX), depression (DEP) and sleep disorders (SLA) in the reference group.

The tryptophan ratio was correlated positively with anxiety. There was, however, a negative correlation between serotonin in plasma and depression (DEP) in the patient group.

Serotonin in plasma was correlated negatively with hostility (HOS) both in the patient group and to a lesser extend in the reference group.

This was also true for the correlations between hostility and tryptophan ratio.

Biochemical variables

There was a strong positive correlation between serotonin in plasma and that in blood in both the patient group and in the reference group.

Moreover, in the patient group there were positive correlations between tryptophan & tyrosine and tryptophan ratio & tyrosine ratio. In the reference group, we observed positive correlations between tryptophan & tyrosine, tyrosine & tyrosine ratio and tryptophan ratio and serotonin in thrombocytes.

11.4 Discussion.

The results of this exploration into inter-correlations between biochemical and psychological variables described in this chapter must be interpreted with caution because of the small size of the groups.

Thrombocytes have many similarities with serotonergic synaptosomes and have been used as a model for uptake of serotonin by synaptosomes [Pletcher, 1981]. In our patients, serotonin in thrombocytes appeared to be negatively correlated with parameters of aggression and positively with levels of repression and denial. The negative correlation between serotonin in thrombocytes and turning aggression against others, depression (DEP) and hostility (HOS) and between serotonin in plasma and tryptophan with HOS in our patient group supported the suggested coupling between aggression and depression with a low functioning serotonergic system [Brown et al, 1979; Much-Seler et al, 1983; Van Praag, 1991]. The correlations between biochemical variables with symptoms as hostility support the hypothesis by Van Praag [1991] in which he stated that biochemical parameters were not correlated with the presentations of psychiatric illnesses, but were correlated with behavior. The patient group differed highly from the reference group in the coupling of these serotonergic parameters with psychological parameters which pleads for a relationship between these biological parameters and psychological dysfunctions.

In our previous study [Timmerman et al, 1994] we observed negative correlations between norharman and intellectualization (INT) and repression (REP) and positive correlations between norharman and palliation (UCL-P). In this present study however, we observed no significant correlations between norharman and defense organization or coping mechanisms in the patient group. On the basis of these results it is unlikely that norharman reflects intra-psychological processes such as defense and coping.

In the patient group, we observed that repression (REP) and reversal (REV) were negatively correlated with the amino acid tyrosine and with the ratios of tyrosine and tryptophan as compared with other large neutral amino acids.

Our findings are compatible with a function of tyrosine, since tyrosine, the precursor of dopamine, is a neurotransmitter which has a possible positive correlation with novelty seeking and impulsiveness [reviewed by Glas, 1991].

We suggest that patients with high novelty seeking and impulsiveness seem to be less likely to make frequent use of repression and reversal.

Problem solving coping (UCL-A) showed a (nonsignificant) negative correlation with the severity of symptomatology (NEU) as measured in the SCL-90 in the patient group. Depressive reactions correlated positively with all SCL-90 scales.

This was in agreement with the findings reported by Roy-Byrne et al [1992] who observed that level of "distress" in patients with panic disorder and/or depression was a strong predictor for the use of less problem solving but more emotionally directed coping.

Though our patient sample was rather small and the ranges in the confidence intervals large a tentative conclusion of in this chapter may be, that though we did not found a correlation between a specific psychiatric disorder and a biochemical substrate (see chapter 7), we did found (negative) corrrelations between various agression parameters and serotonin in thrombocytes.

Table 21. Substantial[1] partial correlations between psychological- and biochemical variables adjusted for age and gender in referencegroup and in at baseline medicationfree patients

Turning agression against others (DMITAO)							
REFERENCEGROUP (n=49)					MEDICATIONFREE PATIENTS (n=31)		
	corr	95% CI			corr	95% CI	
DMIPRO	.48	.23	.67	DMIPRO	.52	.21	.74
DMIINT	-.68	-.80	-.49	DMIINT	-.60	-.79	-.31
DMITAS	-.36	-.58	-.09	DMITAS	-.54	-.75	-.23
DMIREV	-.75	-.85	-.59	DMIREV	-.62	-.80	-.34
DMIREP	-.90	-.94	-.83	DMIREP	-.88	-.94	-.77
HTP [2]	.51	.16	.75	HTP	-.38	-.67	.004
HPP [3]	.48	.12	.73	HPP	-.21	-.54	.16

[1] two tailed [2] serotonin in platelets; [3] serotonin in plasma.

Projection (DMIPRO)							
REFERENCEGROUP (n=49)					MEDICATIONFREE PATIENTS (n=31)		
	corr	95% CI			corr	95% CI	
DMIINT	-.49	-.68	-.24	DMIINT	-.50	-.73	-.18
DMITAS	-.46	-.66	-.21	DMITAS	-.22	-.53	.15
DMIREV	-.58	-.74	-.36	DMIREV	-.73	-.86	-.50
DMIREP	-.73	-.84	-.57	DMIREP	-.80	-.90	-.61
UCL-S	.10	-.19	.40	UCL-S	.47	.13	.70
UCL-E	0	-.28	.28	UCL-E	.51	.19	.73
TPR [4]	.53	.19	.76	TPR	-.42	-.68	-.07
TYR [5]	-.36	-.65	.03	TYR	.47	.13	.71

[4] tryptophan ratio; [5] tyrosin

Table 21. Substantial[1)] partial correlations between psychological- and biochemical variables adjusted for age and gender in referencegroup and in at baseline medicationfree patients (continued)

Intellectualisation (DMIINT)							
REFERENCEGROUP (n=49)					MEDICATIONFREE PATIENTS (n=31)			
	corr	95% CI				corr	95% CI	
DMIREV	.56	.33	.73		DMIREV	.40	.05	.66
DMIREP	.81	.69	.89		DMIREP	.75	.54	.87
UCL-A	.08	-.20	.36		UCL-A	.51	.19	.73
UCL-D	-.33	-.56	-.05		UCL-D	-.36	-.62	.02
SCLRES	.04	-.24	.32		SCLRES	-.38	-.65	-.03
TPR	-.45	-.71	-.09		TPR	.06	-.31	.41
TYR	.44	.07	.700		TYR	-.33	-.62	.04
HPP	-.47	-.72	-.11		HPP	.13	-.24	.47

Turning agression against self (DMITAS)							
REFERENCEGROUP (n=49)				MEDICATIONFREE PATIENTS (n=31)			
	corr	95% CI			corr	95% CI	
UCL-A	-.32	-.55	-.04	UCL-A	-.47	-.70	-.13
UCL-V	.37	.10	.59	UCL-V	.10	-.27	.44
SCLDEP	.31	.03	.54	SCLDEP	.26	-.11	.56
SCLSOM	.32	.04	.55	SCLSOM	-.01	-.36	.35

Table 21. Substantial[1] partial correlations between psychological-, and biochemical variables adjusted for age and gender in referencegroup and in at baseline medicationfree patients (continued)

Reversal (DMIREV)							
REFERENCEGROUP (n=49)					MEDICATIONFREE PATIENTS (n=31)			
	corr	95% CI				corr	95% CI	
DMIREP	.88	.79	.93		DMIREP	.84	.68	.92
HTP	-.45	-.71	-.09		HTP	.56	.24	.79
TPR	-.33	-.63	.05		TPR	.37	.02	.65
TYR	.09	-.05	.63		TYR	-.63	-.81	-.34
TRR[6]	-.32	-.30	.46		TRR	-.39	-.65	-.03
HPP	-.57	-.78	-.24		HPP	.10	-.27	.44

[6] Tyrision ratio

Repression (DMIREP)							
REFERENCEGROUP (n=49)				MEDICATIONFREE PATIENTS (n=31)			
	corr	95% CI			corr	95% CI	
HTP	-.47	-.72	-.11	HTP	.46	.09	.72
TPR	-.43	-.69	-.05	TPR	.32	-.05	.61
TYR	.41	.04	.68	TYR	-.54	-.75	-.22
TRR	.24	-.16	.57	TRR	-.39	-.65	-.03
HPP	-.54	-.76	-.20	HPP	.14	-.23	.48

Table 21. Substantial[1] partial correlations between psychological-, and biochemical variables adjusted for age and gender in referencegroup and in at baseline medicationfree patients (continued)

Active problem solving (UCL-A)							
REFERENCEGROUP (n=49)					MEDICATIONFREE PATIENTS (n=31)			
	corr	95% CI				corr	95% CI	
UCL-P	.25	-.03	.49		UCL-P	.39	.04	.65
UCL-E	.08	-.20	.35		UCL-E	.37	.02	.64
UCL-G	.26	-.02	.50		UCL-G	.44	.11	.69

Palliation (UCL-P)							
REFERENCEGROUP (n=49)					MEDICATIONFREE PATIENTS (n=31)			
	corr	95% CI				corr	95% CI	
UCL-S	.50	.26	.69		UCL-S	.07	-.30	.41
UCL-D	.46	.21	.66		UCL-D	-.04	-.39	.32
UCL-G	.53	.29	.70		UCL-G	.53	.22	.75
SCLNEU	.29	.01	.53		SCLNEU	-.06	-.40	.30

Table 21. Substantial[1] partial correlations between psychological-, and biochemical variables adjusted for age and gender in referencegroup and in at baseline medicationfree patients (continued)

Avoidance (UCL-V)							
REFERENCEGROUP (n=49)					MEDICATIONFREE PATIENTS (n=31)			
	corr	95% CI				corr	95% CI	
UCL-S	.37	.10	.59		UCL-S	-.24	-.55	.12
UCL-D	.53	.29	.70		UCL-D	.39	.04	.65
SCLANX	.29	.01	.53		SCLANX	.29	-.07	.59
SCLSOM	.36	.0	.58		SCLSOM	.28	-.08	.58
SCLIN	.21	-.08	.46		SCLIN	.53	.22	.74
SCLRES	.38	.11	.60		SCLRES	.57	.27	.80
SCLNEU	.26	-.02	.50		SCLNEU	.44	.10	.69
NHP	-.45	-.71	-.08		NHP	-.33	-.63	.06

Seeking support (UCL-S)							
REFERENCEGROUP (n=49)				MEDICATIONFREE PATIENTS (n=31)			
	corr	95% CI			corr	95% CI	
UCL-D	.40	.14	.61	UCL-D	.41	.07	.67
UCL-E	.35	.08	.57	UCL-E	.71	.47	.85
SCLHOS	.36	.09	.58	SCLHOS	.20	-.17	.52
TRR	-.44	-.70	-.07	TRR	.35	-.01	.63

Table 21. Substantial[1] partial correlations between psychological-, and biochemical variables adjusted for age and gender in referencegroup and in at baseline medicationfree patients (continued)

Depressive reactions (UCL-D)							
REFERENCEGROUP (n=49)					MEDICATIONFREE PATIENTS (n=31)			
	corr	95% CI				corr	95% CI	
UCL-E	.30	.02	.53		UCL-E	.15	-.22	.48
UCL-G	.48	.23	.67		UCL-G	-.49	-.72	-.16
SCLANX	.56	.34	.73		SCLANX	.39	.04	.66
SCLDEP	.48	.24	.67		SCLDEP	.49	.16	.72
SCLSOM	.45	.20	.64		SCLSOM	.51	.19	.73
SCLIN	.36	.09	.58		SCLIN	.49	.16	.72
SCLSEN	.41	.16	.62		SCLSEN	.62	.34	.80
SCLSLA	.24	-.04	.48		SCLSLA	.41	.06	.66
SCLRES	.49	.24	.67		SCLRES	.57	.27	.77
SCLNEU	.53	.30	.70		SCLNEU	.62	.34	.80
SCLPAN	.30	-.09	.61		SCLPAN	.40	.05	.66
NHP[7]	-.64	-.82	-.35		NHP	-.29	-.60	.10
TRR	-.25	-.50	.24		TRR	.40	.05	.67
HPP	.43	.06	.70		HPP	-.43	-.69	-.08

Expressed emotions (UCL-E)							
REFERENCEGROUP (n=49)					MEDICATIONFREE PATIENTS (n=31)			
	corr	95% CI				corr	95% CI	
SCLANX	-.04	-.31	.24		SCLANX	-.43	-.69	-.05
SCLHOS	.04	-.24	.31		SCLHOS	.42	.07	.67

Table 21. Substantial[1] partial correlations between psychological-, and biochemical variables adjusted for age and gender in referencegroup and in at baseline medicationfree patients (continued)

Comforting thoughts (UCL-G)							
REFERENCEGROUP (n=49)					MEDICATIONFREE PATIENTS (n=31)			
	corr	95% CI				corr	95% CI	
SCLHOS	.36	.09	.58		SCLHOS	.20	-.17	.51
TRR	-.44	-.70	.-07		TRR	.35	-.01	.63

Anxiety (SCLANX)							
REFERENCEGROUP (n=49)					MEDICATIONFREE PATIENTS (n=31)			
	corr	95% CI				corr	95% CI	
SCLAGO	.71	.54	.82		SCLAGO	.46	.13	.70
SCLDEP	.77	.63	.86		SCLDEP	.70	.46	.84
SCLSOM	.66	.47	.79		SCLSOM	.58	.28	.78
SCLIN	.65	.46	.78		SCLIN	.44	.10	.69
SCLSEN	.68	.50	.80		SCLSEN	.41	.07	.67
SCLHOS	.41	.15	.62		SCLHOS	.13	-.24	.46
SCLSLA	.26	-.02	.50		SCLSLA	.77	.57	.88
SCLRES	.72	.55	.83		SCLRES	.46	.13	.70
SCLNEU	.86	.77	.92		SCLNEU	.74	.52	.87
SCLPAN	.78	.57	.89		SCLPAN	.85	.71	.93
TPR	.40	.02	.68		TPR	.22	-.15	.54
HPP	.54	.20	.76		HPP	-.32	-.61	.05

[1] norharman

Table 21. Substantial[1] partial correlations between psychological-, and biochemical variables adjusted for age and gender in referencegroup and in at baseline medicationfree patients (continued)

Agoraphobia (SCLAGO)							
REFERENCEGROUP (n=49)					MEDICATIONFREE PATIENTS (n=31)			
	corr	95% CI				corr	95% CI	
SCLDEP	.55	.32	.72		SCLDEP	.60	.31	.79
SCLSOM	.48	.24	.67		SCLSOM	.57	.27	.77
SCLIN	.47	.22	.66		SCLIN	.44	.10	.69
SCLSEN	.48	.24	.67		SCLSEN	.57	.27	.77
SCLRES	.60	.39	.75		SCLRES	.51	.19	.73
SCLNEU	.60	.39	.75		SCLNEU	.71	.48	.85
SCLPAN	.91	.81	.96		SCLPAN	.54	.23	.75

Depression (SCLDEP)							
REFERENCEGROUP (n=49)				MEDICATIONFREE PATIENTS (n=31)			
	corr	95% CI			corr	95% CI	
SCLSOM	.64	.44	.78	SCLSOM	.66	.40	.82
SCLIN	.63	.43	.77	SCLIN	.74	.52	.87
SCLSEN	.72	.55	.83	SCLSEN	.55	.24	.76
SCLHOS	.43	.18	.63	SCLHOS	.42	.08	.67
SCLSLA	.21	-.07	.46	SCLSLA	.57	.27	.77
SCLRES	.66	.47	.79	SCLRES	.58	.28	.78
SCLNEU	.88	.80	.93	SCLNEU	.89	.78	.95
SCLPAN	.62	.31	.81	SCLPAN	.69	.44	.84
HPP	.49	.13	.73	HPP	-.39	-.66	-.03

Table 21. **Substantial[1] partial correlations between psychological-, and biochemical variables adjusted for age and gender in referencegroup and in at baseline medicationfree patients (continued)**

Somatisation (SCLSOM)							
REFERENCEGROUP (n=49)					MEDICATIONFREE PATIENTS (n=31)			
	corr	95% CI				corr	95% CI	
SCLIN	.60	.39	.75		SCLIN	.59	.30	.78
SCLSEN	.65	.46	.79		SCLSEN	.56	.26	.76
SCLHOS	.46	.21	.65		SCLHOS	.46	.13	.70
SCLSLA	.08	-.20	.35		SCLSLA	.53	.22	.74
SCLRES	.75	.60	.85		SCLRES	.53	.22	.74
SCLNEU	.81	.69	.89		SCLNEU	.81	.64	.90
SCLPAN	.72	.47	.86		SCLPAN	.81	.64	.90

Insufficiency (SCLIN)							
REFERENCEGROUP (n=49)					MEDICATIONFREE PATIENTS (n=31)			
	corr	95% CI				corr	95% CI	
SCLSEN	.62	.42	.76		SCLSEN	.69	.44	.84
SCLHOS	.27	-.01	.51		SCLHOS	.55	.24	.76
SCLRES	.47	.22	.66		SCLRES	.65	.38	.82
SCLNEU	.75	.60	.85		SCLNEU	.82	.66	.91
SCLPAN	.74	.50	.87		SCLPAN	.46	.13	.70
TYR	.13	-.26	.49		TYR	.39	.03	.66
HPP	.17	-.22	.52		HPP	-.51	-.74	-.18

Table 21. Substantial[1] partial correlations between psychological-, and biochemical variables adjusted for age and gender in referencegroup and in at baseline medicationfree patients (continued)

Sensitivity (SCLSEN)							
REFERENCEGROUP (n=49)				MEDICATIONFREE PATIENTS (n=31)			
	corr	95% CI			corr	95% CI	
SCLHOS	.67	.48	.80	SCLHOS	.46	.13	.70
SCLRES	.79	.66	.88	SCLRES	.77	.57	.88
SCLNEU	.91	.85	.95	SCLNEU	.81	.64	.90
SCLPAN	.65	.36	.83	SCLPAN	.40	.05	.66
HPP	.20	-.19	.54	HPP	-.39	-.66	-.03

Hostility (SCLHOS)							
REFERENCEGROUP (n=49)				MEDICATIONFREE PATIENTS (n=31)			
	corr	95% CI			corr	95% CI	
SCLRES	.60	.39	.75	SCLRES	.28	-.08	.58
SCLNEU	.61	.40	.76	SCLNEU	.52	.20	.74
HTP	-.18	-.52	.21	HTP	-.39	-.68	-.003
TPR	-.02	-.40	.36	TPR	-.42	-.68	-.07

Table 21. Substantial[1] partial correlations between psychological-, and biochemical variables adjusted for age and gender in referencegroup and in at baseline medicationfree patients (continued)

Sleeping problems (SCLSLA)							
REFERENCEGROUP (n=49)					MEDICATIONFREE PATIENTS (n=31)			
	corr	95% CI				corr	95% CI	
SCLRES	.04	-.24	.31		SCLRES	.40	.05	.66
SCLNEU	.24	-.04	.48		SCLNEU	.61	.33	.79
SCLPAN	.06	-.33	.43		SCLPAN	.71	.48	.85
TPR	.19	-.20	.53		TPR	.39	.03	.66
HPP	.47	.11	.72		HPP	-.28	-.58	.09

Rest items (SCLRES)							
REFERENCEGROUP (n=49)					MEDICATIONFREE PATIENTS (n=31)			
	corr	95% CI				corr	95% CI	
SCLNEU	.85	.75	.91		SCLNEU	.77	.57	.88
SCLPAN	.64	.34	.82		SCLPAN	.47	.14	.71
TYR	0	-.38	.38		TYR	.41	.06	.67
HPP	.24	-.15	.57		HPP	-.45	-.70	-.11

Total score (SCLNEU)							
REFERENCEGROUP (n=49)					MEDICATIONFREE PATIENTS (n=31)			
	corr	95% CI				corr	95% CI	
SCLPAN	.76	.53	.88		SCLPAN	.76	.56	.88
HPP	.36	-.02	.65		HPP	-.48	-.72	-.14

Table 21. Substantial[1] partial correlations between psychological-, and biochemical variables adjusted for age and gender in referencegroup and in at baseline medicationfree patients (continued)

Serotonin in platelets (HTP)							
REFERENCEGROUP (n=49)				MEDICATIONFREE PATIENTS (n=31)			
	corr	95% CI			corr	95% CI	
HTW[8]	.85	.69	.93	HTW	.86	.71	.94

[8] Serotonin in blood

Tryptophan (TRP)							
REFERENCEGROUP (n=49)				MEDICATIONFREE PATIENTS (n=31)			
	corr	95% CI			corr	95% CI	
TPR	.28	-.11	.60	TPR	.45	.11	.70
TYR	.50	.15	.74	TYR	.65	.38	.82
TRR	-.02	-.40	.36	TRR	.43	.08	.68

Tryptophan ratio (TPR)							
REFERENCEGROUP (n=49)				MEDICATIONFREE PATIENTS (n=31)			
	corr	95% CI			corr	95% CI	
TYR	-.49	-.73	-.14	TYR	-.28	-.58	.09
HPP	.46	.10	.72	TRR	.07	-.30	.43

Table 21. Substantial[1] partial correlations between psychological-, and biochemical variables adjusted for age and gender in referencegroup and in at baseline medicationfree patients (continued)

Tyrosin (TYR)								
REFERENCEGROUP (n=49)					MEDICATIONFREE PATIENTS (n=31)			
	corr	95% CI				corr	95% CI	
TRR	.64	.34	.82		TRR	.71	.47	.85

Tyrosin ratio (TRR)								
REFERENCEGROUP (n=49)					MEDICATIONFREE PATIENTS (n=31)			
	corr	95% CI				corr	95% CI	
HPP	-.28	-.60	.11		HPP	-.46	-.71	-.11

Chapter 12

CHAPTER 12. COURSE AFTER SIX MONTHS OF TREATMENT AND ON FOLLOW UP IN THE PATIENT GROUP NOT ON MEDICATION AT BASELINE

12.1 Introduction

The group of patients not on medication at baseline was followed separately in order to obtain additional insight into the changes in the biochemical parameters during combined treatment with clomipramine and cognitive therapy. We expected that the defense organisation of the patients will be stable, trait dependent, while coping strategies of the patients might change because of cognitive therapy. After successful treatment the SCL-90 score's are presumed to decline. Clomipramine is expected to decrease the serotonin in blood and thrombocytes.

The changes in the psychological and biochemical values throughout the investigation period in this patient group were therefore measured.

12.2 Statistical method

In addition to mean and confidence interval, the results of changes in defense organisation, coping style, symptoms and biochemical variables were also measured as percentage change in T6-T0 and T9-T0. Extreme values can play a very substantial role in groups of small sizes, whereby chance plays an important role. Therefore, in order to eliminate the influence of extreme values as much as possible, a 5% trim was applied whereby the extreme values were excluded from the analysis (Table 22).

The 95 % confidence interval on the biochemical values in the reference group and in the medication free patients at baseline,after six months and after nine months is presented in table 23.

12.3 Results

The mean and the 95 % confidence interval of the mean of the results for 6 and 9 months are presented in Table 4.

Table 4. Psychological variables in patients and referencegroup at baseline, 6 and 9 months

		Baseline		6 months	9 months
		Referencegroup (n=54)	Patients (n=74)	Patients (n=51)	Patients (n=26)
DMITAO	mean	39.6	34.2	35.2	38.0
	CI[1])	37.0; 42.2	31.8; 36.6	32.4; 38.0	33.4; 42.6
DMIPRO	mean	38.9	38.5	37.7	37.7
	CI	37.1; 40.7	36.9; 40.1	35.7; 39.7	35.3; 40.1
DMIINT	mean	48.7	44.0	45.7	45.3
	CI	47.1; 50.3	42.4; 45.6	43.7; 47.7	43.1; 47.5
DMITAS	mean	35.1	43.6	39.7	36.5
	CI	33.1; 37.1	41.6; 45.6	37.7; 41.7	33.3; 39.7
DMIREV	mean	37.8	39.7	41.7	42.4
	CI	35.8; 39.8	37.5; 41.9	38.9; 44.5	38.4; 46.4
DMIREP	mean	8.0	11.0	14.5	12.0
	CI	1.4; 14.6	4.6; 17.4	6.5; 22.5	0.6; 23.4
UCL-A	mean	18.1	14.6	14.9	16.0
	CI	17.1; 19.1	13.8; 15.4	14.1; 15.7	14.6; 17.4
UCL-P	mean	17.0	17.8	17.4	17.8
	CI	15.8; 18.2	16.8; 18.8	16.4; 18.4	16.4; 19.2
UCL-V	mean	14.0	18.2	16.8	15.6
	CI	13.4; 14.6	17.2; 19.2	15.8; 17.8	14.0; 17.2
UCL-S	mean	13.8	12.5	11.7	12.2
	CI	12,8; 14.8	11.5; 13.5	10.9; 12.5	11.0; 13.4
UCL-D	mean	9.9	17.2	13.5	12.4
	CI	9.3; 10.5	16.2; 18.2	12.5; 14.5	11.2; 13.6
UCL-E	mean	6.4	5.8	5.7	5.8
	CI	6.0; 6.8	5.2; 6.4	5.1; 6.3	5.2; 6.4

Table 4. Psychological variables in patients and referencegroup at baseline, 6 and 9 months (continued)

		Baseline		6 months	9 months
		Referencegroup (n=54)	Patients (n=74)	Patients (n=51)	Patients (n=26)
UCL-G	mean	11.6	11.2	11.7	12.1
	CI	10.8; 12.4	10.6; 11.8	10.9; 12.5	11.1; 13.1
SCLANX	mean	11.3	30.0	19.3	15.5
	CI	10.7; 11.9	27.8; 32.2	17.3; 21.3	13.3; 17.7
SCLAGO	mean	7.1	17.2	10.9	9.4
	CI	6.1; 8.1	15.4; 19.0	9.5; 12.3	8.2; 10.6
SCLDEP	mean	18.9	48.7	30.6	26.8
	CI	17.7; 20.1	45.1; 52.3	30.2; 31.0	22.4; 31.2
SCLSOM	mean	14.1	29.9	21.0	18.6
	CI	13.3; 14.9	27.7; 32.1	18.8; 23.2	15.2; 22.0
SCLIN	mean	11.2	25.7	18.9	16.2
	CI	10.6; 11.8	23.7; 27.7	16.9; 20.9	13.4; 19.0
SCLSEN	mean	22.8	40.0	29.6	26.5
	CI	21.4; 24.2	36.6; 43.4	26.0; 33.2	23.3; 29.7
SCLHOS	mean	6.8	11.0	8.5	8.7
	CI	6.4; 7.2	9.8; 12.2	7.5; 9.5	7.5; 9.9
SCLSLA	mean	3.6	9.7	5.5	5.0
	CI	3.2; 4.0	8.7; 10.7	4.7; 6.3	4.3; 5.8
SCLRES	mean	10.1	18.8	14.7	12.5
	CI	9.7; 10.5	17.2; 20.4	13.1; 16.3	10.7; 14.3
SCLNEU	mean	105.9	230.9	158.8	139.2
	CI	101.3; 110.5	216.7; 245.1	143.6; 174.0	12.1; 157.4
SCLPAN	mean	10.9	25.7	17.4	14.6
	CI	10.1; 11.7	23.9; 27.5	16.0; 18.8	12.6; 16.6

[1] CI = 95% Confidence interval

Table 22 shows that application of the 5% trim did not have any major influence on the majority of the percentages of changes.

Table 22. Followup on at baseline medicationfree patients: psychological and biochemical variables

	Percentage change T0-T6				Percentage change T0-T9			
	n	mean	sem[1]	trim[2]	n	mean	sem	trim
TAO	20	10.04	7.04	9.32	14	20.01	12.51	17.72
PRO	20	-.278	3.23	-3.02	14	-9.15	4.18	-9.01
INT	20	4.32	3.16	3.44	14	4.29	5.13	2.88
TAS	20	-7.42	4.65	-5.95	14	-13.10	5.47	-12.1
REV	20	10.3	7.06	5.78	14	18.07	11.94	12.36
REP	19	-43.10	36.64	-59.80	14	-91.28	38.62	-85.65
UCLA	20	8.95	10.88	2.41	14	8.76	8.02	8.90
UCLP	20	1.33	7.01	-2.76	14	-1.03	5.32	-.66
UCLV	20	-8.81	4.80	-8.58	14	-9.10	5.08	-8.52
UCLS	20	4.16	8.04	2.64	14	-1.78	10.77	-3.69
UCLD	20	-18.69	4.66	-17.72	13	-25.82	4.37	-25.91
UCLE	20	11.27	9.91	7.58	14	-6.07	8.93	-5.26
UCLG	20	-2.94	7.18	-6.55	14	1.02	7.16	-1.05
ANG	20	-39.59	4.00	-39.41	14	-44.78	6.11	-46.17
AGO	20	-39.08	5.44	-39.13	14	-36.84	6.02	-36.52
DEP	20	-35.94	5.25	-36.56	14	-40.02	7.59	-41.45
SOM	20	-31.38	3.69	-31.03	14	-37.47	4.49	-37.8
IN	20	-32.18	4.28	-32.05	14	-37.46	5.87	-38.2

Table 22. Followup on at baseline medicationfree patients: Psychological and biochemical variables (continued)

	Percentage change T0-T6				Percentage change T0-T9			
	n	mean	sem	trim	n	mean	sem	trim
IN	20	-32.18	4.28	-32.05	14	-37.46	5.87	-38.28
SEN	20	-30.69	4.63	-30.27	14	-28.00	5.61	-27.26
HOS	20	-21.31	4.00	-21.14	14	-9.23	9.00	-9.30
SLA	20	-26.82	8.53	-27.38	14	-25.77	9.33	-28.49
RES	20	-21.12	4.86	-21.06	14	-25.34	5.28	-24.99
NEU	20	-34.93	3.82	-33.98	14	-36.99	5.24	-37.13
PAN	20	-33.65	4.13	-33.41	14	-42.90	4.61	-44.02
NHPP	17	19.93	14.71	18.80	12	6.20	22.00	.80
TRP	20	-4.67	5.14	-6.58	10	-7.04	11.02	-10.47
TRPR	20	2.49	6.61	-.89	10	3.64	11.44	.33
TYR	20	2.39	9.96	-3.77	10	.37	12.00	-1.00
TYRR	20	7.43	8.24	2.30	10	8.95	8.07	8.20
HTPR	6	-94.81	1.84	-95.17	7	-20.35	17.86	-19.82
HTW	6	-94.49	1.92	-94.84	9	255.45	192.11	199.0
HPP	20	-49.31	9.77	-52.44	13	10.29	27.58	3.10

PAN: SCL "Panic Scale";
NHPP: Norharman;
TRP: Tryptophan;
TRPR: Tryptophan ratio;
TYR: Tyrosin;
TYRR: Tyrosin ratio;
HTPR: serotonin in platelets;
HTW: serotonin in blood;
HPP: serotonin in plasma.

At baseline, 31 of the patients did not use antidepressants. Twenty of these 31 patients still participated in the study after six months (see also chapter 5). Fifteen of these 20 patients discontinued their medication after six months.

One patient was lost to follow-up, so that biochemical values at follow-up were available in 14 patients who were not on medication at baseline.

The course of the scores of the psychological sub-scale showed a decrease in all scales of the SCL-90 (Table 22). There was a modest decrease in the scales hostility (HOS: 21 %) and sleep disorders (SLA: 27 %) after six months. There was a decrease of 30% or more in the other scales of the SCL-90.

For the group who was measured after 9 months the changes were persistent after nine months with the exception of hostility. Its score increased again after stopping therapy.

The most impressive change in the DMI scores was a decrease in repression (REP), a composite scale.

From the coping strategies Depressive reactions (UCL-D) declined. The remainder of the coping scales stayed rather stable though there was a small increase in the use of adequate coping strategies as active problem solving (UCL-A) and expression of emotions (UCL-E).

The course of the biochemical values in the patient subgroup not on medication are given as raw values at baseline, at six months and at nine months together with those in the reference group in Table 23.

Table 23. Mean scores and their 95% confidence interval (CI) on biochemical variables in referencegroup and in at baseline medicationfree patients

		Baseline		Six months	Nine months
		Reference (n=27)	Medication free patients (n=30)	Medication free patients (n=21)	Medication free patients (n=13)
Ser [1] in plasma (10^{-9} mol/l)	mean CI	14.20 7.79 ; 20.61	15.50 10.44 ; 20.60	4.41 2.51 ; 6.31	10.61 7.02 ; 14.20
Ser in platelets (10^{-9}mol/ $10E^{9}$ pl)	mean CI	3.57 3.15; 3.99	3.50 3.05; 3.99	.12 0.08; 0.16	3.18 1.86; 4.50
Ser in blood (10-9 mol/l)	mean CI	957.72 815.86; 1099.58	820.47 682.35; 958.59	31.27 20.85; 41.69	905.38 541.84; 1268.92
Norharman (10-12 mol/l)	mean CI	0.45 0.37; 0.53	0.49 0.31; 0.59	0.49 0.31; 0.66	0.36 0.28; 0.43
Tyrosin (10-6 mol/l)	mean CI	67.11 58.98; 75.25	63.90 55.42; 72.38	61.38 52.30; 70.46	54.70 44.60; 64.80
Tyrosin ratio	mean CI	11.36 10.33; 12.39	10.70 9.86; 11.54	11.35 9.99; 12.71	11.36 9.77; 12.95
Tryptophan (10^{-6} mol/l)	mean CI	52.78 48.52; 57.04	49.87 45.56; 54.18	41.81 38.71; 44.91	37.90 34.87; 40.93
Tryptophan ratio	mean CI	8.89 8.22; 9.56	8.64 7.77; 9.51	7.71 7.02; 8.40	7.77 7.00; 8.54

[1] Serotonin

During the therapy, there was a decrease of more than 50% in serotonin in thrombocytes and in blood. This was due to a depletion of serotonin caused by clomipramine that was used by the patients. At nine months, an increase followed which approached the initial values. Tryptophan decreased during the therapy and in contrast to the levels of serotonin in thrombo-cytes and in blood, continued to decline for up till nine months.

12.4 Discussion

After therapy for six months and at follow-up after nine months, the psychological variables in the group of patients who did not use clomipramine at baseline were not different than those in the patient group as a whole as described in chapter 9. The first group, though small, showed a very substantial therapeutic effect as measured in the SCL-90.

In the defense organization, after six months of therapy, there were small decreases in intra-punitive mechanisms such as turning aggression against self (TAS) and an increase in turning aggression against others (TAO) and reversal (REV). The difference between acting out defence mechanisms and those defense mechanisms which are internally directed is expressed by repression (REP). By far, the biggest changes were observed in these composite scale repression (REP) which decreased by 43% during therapy for six months and by 91% after nine months. Our patient population showed more use of acting out defense mechanisms after the cognitive-, and psychopharmacological therapy. This is noteworthy since according to Juni & Yanishefsky [1983] this repression scale reflects "trait" quality more than the individual DMI scales and was determined less by situational stress.

The tendency of changes within this patient group continued for up to nine months after commencing therapy which seemed to imply a certain amount of permanence.

However, longer follow-up studies are necessary before any definite firm statements can be made.

The coping strategy depressive reactions (UCL-D) decreased six months after starting the therapy. This was probably related to the parallel changes in the symptomatology of the patients. Active problem solving (UCL-A) increased and so did the expression of emotions (UCL-E). Expression of emotions and active problem solving were regarded as adequate means of coping.

In the period six to nine months after the start of the therapy, the scores in the UCL scales with the exception of depressive reactions (UCL-D) and expression of emotions (UCL-E) showed hardly any changes.

The therapeutic effect as measured on the UCL scale depressive reactions and the course of SCL-90 scores increased further. The use of expression of emotions decreased after stopping therapy.

Though the number of patients is rather small the results of the investigations indicated that after treatment with cognitive therapy and clomipramine, the patients indicated a more problem directed coping. The changes in the scales palliative coping (UCL-P), seeking support (UCL-S) and reassuring thoughts (UCL-G) were very small. It is possible that these coping strategies reflect more trait than state characteristics. Historically, the indicated coping strategy was also seen mainly as a trait character [Troop, 1994].

The serotonergic antidepressant (clomipramine) had a clear effect on the concentrations of serotonin in the blood, plasma & thrombocytes. Clomipramine caused a depletion of serotonin. It was noticed very clearly that after stopping clomipramine at six months, the concentrations of serotonin in the blood, plasma & thrombocytes increased, but the level the serotonin precursor tryptophan did not. The finding that during treatment with tricyclic antidepressant the level of tryptophan in the plasma decreased was in agreement with that reported by Thomas et al [1987] in a study in patients with depression.

As stated before the cause of this low level of tryptophan after therapy for six and at follow up remains unknown.

The low amount of tryptophan probably leads to a reduction in the synthesis of serotonin in the brain which may lead to changes in mood and behavior as e.g. depression.

In a recent study, it appeared that reduction of tryptophan in the diet of volunteers with a positive family history of major depression could lead to depressive mood [Benkelfat et al, 1994]. Tryptophan depletion via diet restrictions also significantly increased depressive complaints in patients with obsessive-compulsive disorder as compared with controls [Barr et al, 1994]. In our patient group, there was a considerable percentage of recurrence in psychiatric complaints in the long term, more than 20% of the patients showed a relapse [Timmerman et al 1995[2]].

One can speculate that the low level of tryptophan, and to a lesser extent, the low tryptophan ratio also after stopping clomipramine possibly constitute a risk for the recurrence of psychopathology.

Prior to commencing therapy, the tyrosine ratio in the patient group as compared with that in the reference group was decreased. It is possible that the increase in the level of tyrosine in the patients reflected their recovery.

Table 23 shows that norharman increased during the therapy for six months. This increase is likely to be related to the medication therapy. While the effect of therapy between six and nine months still increased, the level of norharman decreased again.

Chapter 13

CHAPTER 13. CONCLUDING REMARKS

The basis of this thesis is the clinical observation that patients at the out-patient department of psychiatry of a general hospital sometimes present with a psychiatric profile which satisfies the criteria of panic disorder either with or without agoraphobia according to the DSM-III-R criteria, whereas at the same time, a considerable percentage of these patients also satisfy the criteria for major depression according to the same classification system. Not only did it appear that in these ambulant patients one could speak of a simultaneous presence of two clusters of psychiatric symptoms, but it also appeared that patients who initially presented for treatment in connection with a circumscribed panic disorder, at a later stage or during a new episode, no longer satisfied the criteria for panic disorder, but suffered from major depression or vice versa.

Based on these clinical observations, a search for a theoretical model to explain this so-called co-morbidity of panic disorder and major depression was undertaken. A number of theories concerning this were worked-out and are presented in chapter 3 of this thesis. In this investigation, based on these theories, it was postulated as a hypothesis that the neuro-biological substrate in patients with panic disorder and/or depression is identical and whereby a non-specific vulnerability for panic disorder and major depression develops.

The psychological defense organization and used coping strategies were assumed to be specific for the individuals and according to this hypothesis determine which symptomatology would arise in patients.

Initially, it was investigated whether the distinction of the patients suffering from panic disorder and those suffering from major depression was valid on the ground of symptomatology. In a number of studies with different set-ups, panic disorder appeared to show a very characteristic symptomatology whereby besides psychologically experienced anxiety in the sense of paroxysmal anxiety: fear of going crazy, fear of dying and depersonalization signs, also somatic symptoms such as dizziness, dyspnea, tachycardia, increased sweating and tremors were characteristic. The results of this part of our investigations were published elsewhere [Timmerman et al, 1995[1]]. It appeared that not only did panic disorder have a characteristic symptomatology, but that a valid distinction between patients suffering from panic disorder and those suffering from major depression on the basis of symptomatology as measured in the Symptom Check List-90 (SCL-90) was also possible [Timmerman et al, 1995[3]].

In the subsequent investigation (chapter 6), the extent to which defense organization and indicated coping strategies in the groups of patients differed from that in the patients in the reference- and the control groups was examined. It became clear from this investigation that the indicated defense -mechanisms in the patient group was less adult and the coping was less adequate than that in the reference- and the control groups. However, this did not answer the question whether non-adult defense organization and less effective coping stra-tegies indicated the vulnerability for the development of psychopathology or that (a period of) psychopathology induces the use of non-adult

defense - mechanisms and less effective coping strategies. Prospective investigation into the course of defense organization and indicated coping strategies was necessary in order to answer this question. We attempted to answer this question partially in the second part of the study in which the proportions of the defense organization and coping strategies in patients before treatment were compared with those after recuperation.

The important result that emerged from our study was that patients with major depression, panic disorder or panic disorder & major depression could not be distinguished from each other on the basis of indicated coping strategies and defense mechanisms (see chapter 7). This implied that there was no support for the hypothesis that there were distinct defense mechanisms and coping strategies which determined or modeled the psychiatric presentation.

In biochemical investigations, we observed some differences between the three groups of patients as compared with the reference group. The concentration of tyrosine and the tyrosine-index (the proportion of the amino acid tyrosine as compared with those of the other large neutral amino acids in the plasma) in the plasma of the group of patients was lower than that in the reference group. However, for the rest, in this investigation of limited set-up, there was insufficient evidence for the existence of a biological substrate for these psychiatric disorders. However, the patient group that qualified for further investigation was rather small because a number of patients were already on medication before first blood samples could be taken for biochemical analyses.

Within the three groups of patients, it appeared that the ß-carboline norharman provided the best distinction towards psychiatric group.

It was noteworthy hereby that the concentration of norharman in the plasma of patients with panic disorder was lower than that in patients with depression, depression & panic disorder and the reference group. Norharman is an aromatic alkaloid. In the brain of rats there were specific binding sites found with a very high affinity for norharman. Norharman and namely harman also shows a reasonably high affinity for the benzodiazepine receptor [reviewed by Van Gelderen et al, 1994]. Recent investigations showed that norharman had a strong sedative effect in rats; moreover, the norharman concentrations in the human plasma showed a circadian-rhythm. The concentration of norharman in the plasma decreases during the day.

The affinity of (nor)harman for benzodiazepine receptors and the sedative effect in rats indicated an endogenous anxiolytic activity and are certainly not in contrast to the finding that the concentration of norharman was low in patients with panic disorder. However, further investigations are necessary, especially because we did not observe any abnormalities in the concentration of norharman in the group of patients suffering from panic disorder & major depression.

In the mean time, although investigations into the biological effects of norharman in the rat have been undertaken, to date, no studies have been conducted into the biological effect of norharman and harman in humans. Longitudinal prospective studies on the concentrations of norharman and harman in the plasma of healthy volunteers and (sub)groups of psychiatric patients are therefore warranted.

In the second part of this study, possible changes in defense mechanisms and coping were investigated after combined treatment with antidepressants and cognitive therapy. The results of this part of the investigations must be interpreted with the necessary caution because of the relative small size of the patient group.

An important outcome was that defense organization measured with the Defense Mechanism Inventory (DMI) under the influence of the combined treatment changed. In particular there was a decrease in the use of the defense mechanism "turning aggression against self" in the direction of the reference group. This is in agreement with the initial ideas of S. Freud [1986] concerning defense mechanisms.

The indicated coping strategies measured with the Utrechtse Coping List (UCL) appeared to be more stable than defense -organization; this is in agreement with the ideas of Troop [1994], who saw coping chiefly as a personality trait (trait determined character). Although, the combination of medicament and cognitive therapy administered by us appeared to be successful in a large number of patients with regards to the reduction in the number of symptoms [Timmerman et al, 1994], the therapy, other then that was expected and hoped, led to no other fundamental changes in the coping strategies of the patients. Prospective long-term studies are necessary, and are being performed, in order to examine the stability of defense organization and indicated coping strategies in groups of patients and control groups.

The investigation into the relationship between the psychological and biochemical variables showed that there was a negative correlation between the concentration of serotonin in thrombocytes & plasma and aggression parameters and confirmed the previously suggested link between aggression and depression on the one hand and a low functioning serotonergic system on the other hand [Van Praag, 1991]. Treatment with clomipramine caused a depletion of serotonin in thrombocytes and prolonged treatment resulted in the lowering of its concentration in the plasma. The concentration of tryptophan in the plasma decreased during treatment with clomipramine. In contrast to the concentration serotonin in thrombocytes and plasma, the concentration of tryptophan in the plasma remained low at follow-up.

It is possible that the low concentration of tryptophan in the plasma can lead to a reduction in the synthesis of serotonin which may lead to changes in mood and behavior which can cause depression. In our view, further investigations into the relationship between the concentrations of tryptophan and possibly of tyrosine in the plasma with recurrent psychopathology are warranted.

The results of our investigations did not support the postulated unitary hypothesis for the development of panic disorder, depression and panic disorder & depression. There was some biochemical evidence for the heterogeneity between the groups of patients. In addition, there was no difference in defense and coping between the groups of patients, but there was a real noticeable evenness irrespective of the diagnosis. However, it should be noted that only a limited number of biochemical parameters in a relatively small group of patients not on any medication were investigated so that firm conclusions can not be drawn.

In addition, our findings of similar defense mechanisms and coping strategies in patients with panic disorder and/of depression als lend support to the hypothesis by Tyrer [1992] who postulated 'General Neurotic Syndrome'. In doing so, Tyrer considered a mixture of anxiety and depressive complaints with personality traits such as excessive timidity, low self confidence, avoiding anxiety-provocing situations and dependence on others, but it remains unclear what determined the sympto-matology that was in the foreground.

In our study, we noted a mixture of anxiety and depressive complaints in the symptomatology of the patients using the SCL-90. In our three groups of patients very high scores as compared with those in standardized group were observed in amongst others for the scales anxiety and depression. We also observed (using the UCL) high scores in the scale for avoidance. The scale seeking social support (also in the UCL) was only moderately increased in our groups of patients as compared with those in the standardized- and reference groups.

However, it seems likely that seeking social support, a directed active process, is different than dependence on others as meant by Tyrer.

On the basis of defense, coping and limited biochemical investigations, we were unable to find any explanatory model which could clarify as to why one patient develops panic disorder, whereas a second patient develops depression and a third patient develops both disorders.

As an explanation hypothesis, we postulate that besides a non-specific vulnerability, precipitating factors such as Life Events determine which form of psychopathology would arise.

Thus, the development of panic disorder is probably linked to separation conflicts (see chapter I), whereas depression is probably induced by powerlessness and demoralization. Further prospective investigations are imperative to test this hypothesis.

Chapter 14

HOOFDSTUK 14. CONCLUSIES EN AANBEVELINGEN

Ten grondslag aan dit proefschrift ligt de klinische observatie dat patiënten van een polikliniek Psychiatrie van een algemeen ziekenhuis zich soms presenteren met een psychiatrisch beeld dat voldoet aan de criteria voor paniekstoornis al dan niet met agorafobie volgens DSM-III-R criteria, terwijl deze patiënten tevens in een aanzienlijk percentage voldoen aan de criteria voor een depressie in engere zin volgens hetzelfde classificatie systeem. Niet alleen blijkt er bij deze ambulante patiënten zin sprake te zijn van gelijktijdig voorkomen van twee psychiatrische symptoomclusters; ook blijkt dat patiënten zich aanvankelijk onder behandeling stellen in verband met een circumscripte paniekstoornis terwijl zij in een later stadium of bij een nieuwe ziekteperiode, niet langer voldoen aan de criteria voor paniekstoornis maar lijden aan een depressie in engere zin of omgekeerd.

Op basis van deze klinische observaties werd gezocht naar een theoretisch verklaringsmodel om deze zo geheten comorbiditeit van paniekstoornis en depressie in engere zin te verklaren.

Een aantal theorieën hieromtrent wordt uitgewerkt in hoofdstuk drie van dit proefschrift. Uit deze theorieën wordt in dit onderzoek als hypothese geformuleerd dat bij patiënten met een paniekstoornis en/of depressie, het neuro-biologisch substraat voor deze aandoeningen identiek is en waarbij er een non-specifieke vulnerabiliteit ontstaat voor paniekstoornis en depressie in engere zin.
De psychologische afweerorganisatie en gebruikte copingstrategieën worden als specifiek voor de beide patiëntgroepen verondersteld en bepalen volgens deze hypothese welke symptomatologie er bij patiënten ontstaat.

Als eerste wordt onderzocht of op grond van symptomatologie het onderscheid tussen patiënten die lijden aan een paniekstoornis en een depressie in engere zin valide is. Paniekstoornis blijkt in een aantal, qua opzet uiteenlopende, studies een zeer karakteristieke symptomatologie te vertonen waarbij naast psychologisch ervaren angst in de zin van paroxysmale angst -angst om gek te worden, angst om dood te gaan-en depersonalisatie verschijnselen ook somatische symptomen als duizeligheid, dyspnoe, tachycardie, verhoogde transpiratie en tremoren karakteristiek zijn. De resultaten van dit deel van ons onderzoek zijn tevens elders gepubliceerd [Timmerman et al, 1995[1]]. Niet alleen blijkt paniekstoornis een kenmerkende symptomatologie te hebben, ook is een valide onderscheid op basis van symptomatologie, zoals gemeten op de Symptom Check List-90 (SCL-90) tussen patiënten met een paniekstoornis en patiënten met een depressie in engere zin mogelijk [zie ook Timmerman et al, 1995[3]].

In het onderzoek wordt vervolgens (beschreven in hoofdstuk zes) nagegaan in hoeverre afweerorganisatie en gehanteerde copingstrategieën in onze patiëntengroepen verschillen van een referentiegroep en controlegroepen. Daarbij wordt duidelijk dat de gehanteerde afweermechanismen in de patiëntengroep minder rijp zijn en de coping minder adequaat is dan in een referentiegroep en controlegroepen. Hiermee wordt echter geen antwoord gegeven op de vraag of onrijpe afweerorganisatie en matige copingstrategieën de vulnerabiliteit voor het ontstaan van psychopathologie geven, of dat (een periode van) psychopathologie het gebruik van onrijpe afweermechanismen en minder effectieve copingstrategieën induceert. Teneinde deze vraag te kunnen beantwoorden is prospectief onderzoek over het beloop van afweerorganisatie en gehanteerde copingstrategieën noodzakelijk. Wij trachten deze vraag, gedeeltelijk, te beantwoorden in het tweede deel van het onderzoek waarbij is nagegaan hoe de afweerorganisatie en copingstrategieën bij herstelde patiënten zich verhouden tot die van voor de behandeling.

Als belangrijk resultaat in ons onderzoek komt naar voren dat patiënten met een depressie in engere zin, paniekstoornis of paniekstoornis en depressie in engere zin zich op basis van gehanteerde copingstrategieën en afweermechanismen *niet* van elkaar laten onderscheiden (zie hoofdstuk 7). Dit impliceert dat wij geen steun vinden voor de hypothese dat er sprake is van onderscheiden afweermechanismen en copingstrategieën die het psychiatrisch beeld bepalen of vormgeven.

Bij biochemisch onderzoek vinden wij enig verschil in de drie patiëntengroepen ten opzichte van de referentiegroep: de concentratie in plasma tyrosine en de tyrosine-index (de verhouding van het aminozuur tyrosine ten opzichte van de andere grote neutrale aminozuren in plasma) is in de patiëntengroep ten opzichte van de referentiegroep verlaagd maar voor het overige zijn er in deze beperkte opzet onvoldoende aanwijzin-gen voor het al dan niet bestaan van een biologisch substraat van deze psychiatrische stoornissen. De onderzochte patiënten-groep welke in aanmerking kwam voor nadere biochemische analyse was echter klein, daar een aantal patiënten reeds vóórdat bloed kon worden afgenomen voor biochemische analyses ingesteld werd op psychofarmaca.

Binnen de drie patiëntengroepen blijkt het ß-carboline norharman het beste naar psychiatrische groep te differentiëren.

Het valt hierbij op dat patiënten met een paniekstoornis een lager plasma norharman gehalte hebben dan patiënten met een depressie, depressie en paniekstoornis dan de referentiegroep. Norharman is een aromatische stikstofverbinding die behoort tot de groep van de ß-carbolines of harmanalkoloïden. In rattehersenen zijn specifieke bindingsplaatsen voor norharman aangetoond met een zeer hoge affiniteit.

Norharman en met name harman vertonen ook een redelijk grote affiniteit voor de benzodiazepinen receptor (zie voor een overzicht Van Gelderen et al, 1994). Uit recent onderzoek blijkt norharman bij ratten een sterk sedatief effect te hebben; voorts vertonen de Norharman concentraties in het plasma bij mensen een circadiaanritme, de plasma concentratie norharman daalt gedurende de dag.

De affiniteit van (nor)harman voor benzodiazepinen receptoren en het sedatief effect bij ratten suggereert een endogeen anxiolytische werking en zijn bepaald niet strijdig met de bevinding dat norharman bij patiënten met paniekstoornis verlaagd is. Nader onderzoek is echter noodzakelijk, te meer daar wij in de patiëntengroep lijdend aan een paniekstoornis plus een depressie in engere zin een niet afwijkend norharmangehalte vinden.

Hoewel er inmiddels onderzoek is verricht naar de biologische effecten van norharman bij de rat, is er nog geen studie verricht naar het biologisch effect van norharman en harman bij de mens. Ook dient er longitudinaal prospectief onderzoek naar de norharman en harman concentratie in plasma bij gezonde vrijwilligers en (sub)groepen psychiatrische patiënten verricht te worden.

In het tweede deel van deze studie zijn mogelijke veranderingen in afweermechanismen en coping onderzocht na een gecombineerde behandeling met antidepressiva en cognitieve therapie. De uitkomsten van dit deel van het onderzoek dienen met de nodige voorzichtigheid te worden geïnterpreteerd daar het om een relatief kleine groep patiënten gaat.

Een belangrijke uitkomst is dat afweerorganisatie gemeten volgens de Defense Mechanism Inventory (DMI) onder invloed van de gecombineerde behandeling verandert. Met name vindt een afname plaats in het gebruik van het afweer mechanisme " turning against self", waardoor dit meer op het niveau van de referentie groep kom te liggen. Dit is in overeenstemming met de oorspronkelijke ideeën van S. Freud (1986) betreffende afweermechanismen.

De gehanteerde copingstrategieën gemeten met de Utrechtse Coping Lijst (UCL) blijken stabieler dan afweerorganisatie; dit komt overeen met de ideeën van Troop (1994), die coping ziet als voornamelijk een persoonlijkheids trek (trait bepaalde eigenschap). Hoewel de door ons toegepaste gecombineerde medicamenteuze en cognitieve therapie in een groot aantal patiënten succesvol voor wat betreft symptoomreductie blijkt [Timmerman et al, 1994], geeft de behandeling anders dan verwacht en gehoopt geen fundamentele veranderingen in de coping strategieën van de patiënten. Prospectief lange termijn onderzoek is nodig en wordt momenteel uitgevoerd, ten einde de stabiliteit van afweerorganisatie en gehanteerde copingstrategieën na te gaan bij controlegroepen en patiëntengroepen.

Het onderzoek naar de samenhang tussen de psychologische en biochemische variabelen laat zien dat er een negatieve correlatie is tussen de concentratie van serotonine in trombocyten en plasma en agressie parameters. Dit bevestigt de eerder gesuggereerde koppeling tussen enerzijds agressie en depressiviteit en anderzijds een laag functionerend serotoninerg systeem anderzijds (Van Praag, 1991). Clomipramine behandeling veroorzaakt een depletie van serotonine in thrombocyten en bij langere behandelduur een verlaging van het serotoninegehalte in plasma. Ook het plasma tryptofaan gehalte daalt gedurende de behandeling met clomipramine. In tegenstelling tot de serotonine in thrombocyten en plasma bleef het plasma tryptofaan ook bij follow up laag.

Het is mogelijk dat de lage concentratie aan plasma tryptofaan tot een reductie in de synthese van serotonine lijdt, hetgeen veranderingen in stemming en gedrag, zoals bijvoorbeeld depressie kan veroorzaken. Nader onderzoek naar de correlatie tussen plasma tryptofaan en mogelijk ook plasma tyrosine met recidief psychopathologie is ons inziens geïndiceerd.

Ons onderzoek geeft geen steun aan de geformuleerde unitaire hypothese voor het ontstaan van paniekstoornis, depressie, en paniekstoornis met depressie. Biochemisch zijn er enige aanwijzingen voor heterogeniteit tussen de patiëntengroepen; en bovendien is er geen onderscheid in afweer en coping tussen de patiënten groepen maar juist een opvallende gelijkvormigheid ongeacht de diagnose. Hierbij dient te worden opgemerkt dat wij slechts een beperkt aantal biochemische parameters onderzochten in relatief kleine medicatievrije groepen patiënten, zodat wij geen harde conclusies mogen trekken.

Onze bevindingen van overeenkomstige afweermechanismen en copingstrategieën bij patiënten met een paniekstoornis en/of een depressie geven dan ook steun aan de hypothese van Tyrer (1992) die een 'General Neurotic Syndrome' postuleert. Tyrer gaat hierbij uit van een mengeling van angst en depressieve klachten met persoonlijkheidskenmerken als excessieve timiditeit, laag zelfvertrouwen, vermijden van angstprovocerende situaties en afhankelijkheid van anderen, waarbij onduidelijk blijft wat de op de voorgrond staande symptomatologie bepaalt.

De gemengde angst en depressieve klachten vinden wij bij ons onderzoek naar de symptomatologie van de patiënten door middel van de SCL-90. In onze drie patiëntengroepen worden ten opzichte van normgroepen sterk verhoogde scores gevonden op onder andere de schalen angst en depressiviteit. Ook vinden wij (op de UCL) hoge scores op de schaal voor vermijding. De schaal sociale steun zoeken (eveneens van de UCL) is in onze patiëntengroepen slechts matig verhoogd ten opzichte van normgroepen en referentiegroep.

Het lijkt echter waarschijnlijk dat sociale steun zoeken, een gericht actief proces, anders is dan afhankelijkheid van anderen zoals bedoeld door Tyrer.

Op basis van afweer, coping en beperkte biochemische onderzoe-kingen vinden wij geen model waarom de ene patiënt een paniekstoornis ontwikkelt, een andere patiënt een depressie, en een volgende patiënt beide. Als verklarings hypothese postuleren wij dat naast een aspecifieke vulnerabiliteit, precipiterende factoren (zoals bijvoorbeeld Life Events) bepalen welke vorm van psychopathologie ontstaat. Zo hangt het ontstaan van een paniekstoornis mogelijk samen met separatieconflicten (zie hoofdstuk 1), terwijl depressie mogelijk wordt geinduceerd door machteloosheid en demoralisatie.

Ten einde deze hypothese te toetsen is verder prospectief onderzoek noodzakelijk.

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SUMMARY

Chapter 1

In this chapter " Panic disorder, an update", following a historical description on the development of the concept 'panic disorder', an inventory of the characteristic symptomatology of panic attacks and a review of the epidemiological data on panic disorders are presented. There is considerable agreement on the prevalence (0.5-1.5%) of panic disorder from various centers spread all around the world.

It is was also noteworthy that women suffered more frequently from panic disorder than men. The difference between men and women varied in various studies from 50% to 200%.

The genetic aspects of panic disorder are discussed. The conclusion was that panic disorder had a specific genetic entity which was not associated with a broad spectrum of anxiety or other psychiatric disorders with the possible exception of social phobia.

Besides genetic factors, Life Events also played an important role in the development of panic disorder. In particular, the presence of separation problems appeared to be of great importance.

It appeared that for the treatment of panic disorder, both psycho-pharmaceuticals (benzodiazepines, inhibitors of serotonin uptake, tricyclic antidepressants and inhibitors of monoamine oxidase) and psychotherapy (cognitive behavior therapy) were effective. However, the prognosis for patients who suffer from panic disorder is not un-dividedly favorable. In a considerable proportion of the patients, the affliction follows a chronic course. It may be possible to improve the long-term prognosis by continuing medication for a prolonged period and/or by a combination of medication & psychotherapy.

Chapter 2

The results of a survey and critical evaluation of the literature on biologic/psychiatric aspects of panic disorder are presented in this chapter. The following are discussed: serotonergic hypotheses, noradrenergic hypotheses, the GABA hypothesis, the roles of the ß-carboline norharman and cholecystokinin. Subsequently, neuro-anatomical theories concerning panic disorder and the importance of the septo-hippocampal system in particular are briefly presented. A total of ten biological theories explaining the origin of panic disorder are discussed. The conclusion was that none of these biologi-cal theories provide a unifying explanation for the origin of (or one of the?) panic disorder.

It was postulated that a single inter-active model of biopsychosocial causality would qualify as the most important explanation model for the origin of panic disorder.

Chapter 3

A survey of the literature on the co-morbidity between panic disorder and major depression relevant to the set-up of the present study is presented in this chapter. Several factors appeared to be important in the etiology of the co-morbidity between panic disorder and depression: the gender of the patient, the duration of the psychiatric affliction, genetic load and co-morbidity of panic disorder with other psychiatric afflictions such as social phobia and generalized anxiety disorder.

Six theoretical models are discussed in order to explain the simultaneous occurrence of panic disorder and major depression.

1. A model in which the starting point is a common pathogenesis of panic disorder and depression (unitary hypothesis).
2. A model in which it is postulated that two separate and well circumscribed syndromes occur together (by chance?).
3. A predisposition model in which one affliction etiologically, chronologically or psychopathologically leads to another affliction.
4. A model in which the starting point is an artificial overlap between two different afflictions because of the manner in which they are defined.
5. A combined model: 'general neurotic syndrome' in which a combination of anxiety, depression and a dependent personality disorder are assumed.
6. A model in which the simultaneous development of multiple psychopathology whereby the development of panic disorder generally precedes the development of depression is proposed as a hypothesis.

An introduction to our own studies is presented in the second half of this chapter. The importance of psychological defense mechanisms and coping strategy in patients with panic disorder and depression as compared with patients with another psychiatric disorder and in control groups are briefly discussed. In addition, based on the data in the literature, it was investigated if it was possible to establish whether psychological functions, defense and coping were trait or state determined.

The possible meaning of serotonin in the etiology of depression and panic disorder are discussed and presented together with those of amino acids tyrosine & tryptophan and the å-carboline norharman. It was postulated on the basis of previous investigations that plasma norharman probably reflected the intra-psychological processes.

As a central investigational hypothesis, it was established that one could speak of unitary etiology in panic disorder and major depression and that this etiology may lie in a biological substrate whereby psychological characteristics such as defense organization and/or coping strategies determine which psychiatric disorder would develop.

On the basis of this hypothesis, it was expected that it would be possible to distinguish patients with panic disorder or major depression from each other on the basis of symptomatology, defense organization and coping strategies, but not on the grounds of their biochemical profile.

Chapter 4

The set-up of the investigation, inclusion & exclusion criteria for the patients, methods including the treatment of the patients according to protocol and the used questionnaires such as Symptom Check List-90 (SCL-90), Utrechtse Coping List (UCL), Defense Mechanism Inventory (DMI) and Munich Diagnostic Check List (MDCL) are discussed in this chapter.

Chapter 5

In Chapter 5, the population that was investigated, biographic- and psychopathological particulars of the patients and the drop-outs which occurred during the period of investigation are described. The co-morbidity between panic disorder and major depression in our study was lower (15%) than that (25-40%) cited in the literature. The drop-out percentage during the treatment for 6 months was 31%. This percentage was lower than that observed under the same treatment setting in an earlier study in patients with depression and was also lower than the percentage reported in other studies involving comparable groups of patients. It was speculated that this was because of the open nature of the treatment protocol which reduced the uncertainty for the patients and because of the combined treatment with medication & psychotherapy.

Chapter 6

In the studies described in this chapter, the extent to which the groups of patients as a whole differed from a reference group and standardized groups with regards to psychological variables such as complaints, coping strategies and defense organization was evaluated. In addition, it was also investigated whether there were any differences between the groups of patients and the reference group with regards to the biochemical parameters such as the concentration of serotonin in the blood, plasma & thrombocytes, the concentrations of tyrosine & tryptophan and their index in relation to other amino acids and the concentration of ß-carboline norharman.

On the basis of SCL-90 scores, it appeared that in the investigated group of patients, one could speak of a moderately severe to severe symptomatology as compared with other psychiatric out-patients in the Netherlands. The scores of the UCL clearly showed that the group of patients indicated inadequate coping whereby more use was made of palliation, avoidance and depressive reactions as compared with the reference group. The patients also tended to show a lower active problem solving than that in the reference group.

As far as defense organization was concerned, the group of patients tended to make more use of non-adult defense mechanisms such as projection as compared with the reference group. The male patients also tended to use turning aggression against self more as compared with those in the standardized-and reference groups.

On the basis of psychological variables in discriminant analysis, it appeared that a very reliable distinction could be made between the reference group and the group of patients. A correct classification was possible in 94% of the cases.

The SCL-90 sub-scales provided the best distinction followed by the coping strategies avoidance and depressive reactions both of which were used more by the patients than those in the reference group. The defense mechanism turning aggression against self was indicated more in the group of patients than those in the reference group.

A reliable distinction between the group of patients and the reference was also obtained upon discriminant analysis on the basis of biochemical parameters. However, the distinction based on biochemical parameters was evidently less clear-cut than that obtained on the basis of psychological variables.

Of the biochemical parameters, the tyrosine ratio (tyrosine compared with other large neutral amino acids) weighed the heaviest in discriminant analysis. Tyrosine is an amino acid which serves as the precursor for the synthesis noradrenalin and dopamine in the brain. Besides serotonin, these neurotransmitters probably play an important role in the etiology of depression and panic disorder.

Chapter 7

The extent to which the three groups of patients with panic disorder, major depression and panic disorder & major depression respectively could be distinguished from each other on the basis of psychological and biochemical parameters was examined in the studies described in this chapter. It appeared that the three groups could be clearly distinguished from each other at the level of symptoms (SCL-90 scales) among other using the panic score developed by us on the basis of the SCL-90.

However, a reliable distinction between the three groups of patients appeared not to be possible on the basis of psychological defense organization or indicated coping strategies. Biochemically, patients with panic disorder could be distinguished from the other two groups of patients because they had a low concentration of the ß-carboline norharman.

This finding fits in with the possible function of norharman as benzodiazepine agonist. Patients with panic disorder probably have a high level of anxiety because of low concentration of norharman. However, there is no explanation for the normal concentration of norharman in patients with co-morbid panic disorder and depression.

In discriminant analysis, it appeared that 62.1% of the patients could be classified in one of the three groups on the basis of biochemical variables.

Besides norharman, tryptophan and tryptophan ratio, the concentration of serotonin in the blood also contributed the most towards discrimination.

The findings of this investigation provided some evidence for the hypothesis of biological heterogeneity of panic disorder and major depression whereby every psychiatric disorder has its own specific genetic and neurobiological origin. We also found no support for the "unitary" hypothesis of the two disorders because there were no differences in the psychological characteristics such as defense and coping between the patients with panic disorder and/or depression.

Chapter 8

The inter-dependence of the psychological variables prior to treatment are discussed in this chapter.

Within the coping sub-scales of the UCL, in the group of patients, there was a positive correlation between avoidance and depressive reactions; expression of emotions and palliation; depressive reactions and expression of emotions and between seeking support and expression of emotions. Differences in the relationship between coping style as compared with standardized- and reference groups are also presented.

In the defense mechanisms, a positive correlation was observed between turning aggression against others and projection. Negative correlations were observed between turning aggression against others and repression, avoidance and intellectualization.

Projection also correlated negatively with repression, denial, intellectualization and turning aggression against self. In the reference group, the use of defense mechanisms measured using the DMI did not differ from that in the control groups as reported in the literature. The differences in the indicated defense mechanisms between the group of patients and the reference group were only quantitative.

No important significant correlations between coping strategies and defense mechanisms were noted in the reference group. However, in the group of patients, there was a positive correlation between intellectualization and active problem solving and there were negative associations between intellectualization, depressive reactions and expression of emotions. Use of intellectualization as defense mechanism probably offered protection against depressive reactions.

Chapter 9

The changes in the measurements using the SCL-90, UCL, DMI and biochemical parameters six and nine months after the start of the treatment are presented in this chapter. The pattern of complaints by the patients with panic disorder and/or major depression as measured using the SCL-90 scale changed favorably during treatment with a combination of clomipramine and cognitive therapy. The group of patients with co-morbid major depression and panic disorder showed a lower therapeutic response than the other two diagnostic groups.

It appeared from the measurements at the follow-up that in the group of patients in whom clomipramine had been withdrawn after six months of treatment, the observed improvement that had been achieved appeared to have set in three months later.

Changes in the style of coping and indicated defense mechanisms did not depend on the diagnostic group to which the patients belonged. Indicated coping strategy changed during the treatment. However, the changes were unclear except for the scores of the scales avoidance and depressive reactions which decreased during treatment. The defense organization as measured using the DMI changed during the treatment: during the combined treatment with medication and cognitive therapy, the use of the defense mechanisms turning aggression against others increased, whereas turning aggression against self decreased.

Although during treatment changes occurred in the psychological defense and to a lesser extent, in indicated coping strategy, it appeared upon regression analysis that the initial values in the scales used for evaluating defense and coping, the DMI and the UCL were of utmost importance in determining the outcome six and nine months after the start of the treatment.

Chapters 10, 11 and 12

Additional discussions on the patients who were not on any medication at baseline are presented in these three chapters.

In the studies described in ***Chapter 10***, it was examined whether there were differences between the SCL-90, UCL and DMI scores of patients who were on clomipramine and those not on any medication at the beginning of treatment when the blood samples were first taken. It appeared that the scores at this level of psychological functions in the two groups were almost identical. Therefore, the patient population could be regarded as one for the purposes of discussion on the psychological variables.

Clomipramine appeared to have a very strong effect on the concentrations of serotonin in the blood, plasma and in thrombocytes of the patients. The concentration of serotonin in the patients on clomipramine was much lower than that in the patients in the reference group and in the patients who did not use antidepressant at the time blood samples were first taken. The concentration of tryptophan in patients on clomipramine was much lower than that in the group not on any medication.

It can be speculated that the use of clomipramine induced the activation of the enzyme tryptophan pyrrolase in the liver which resulted in an increased degradation of tryptophan. Alternative hypotheses for the low level of tryptophan in the group of patients on clomipramine are also presented for example: a shift from protein-bound to free tryptophan under the influence of the antidepressant or a reduced absorption of tryptophan in the gut.

In ***Chapter 11***, the inter-dependence of psychological and biochemical values is described. The inter-correlations between SCL-90, DMI & UCL and the biochemical parameters, as far as significant, are given for the group of patients and the reference group.

In the group of patients as a whole, negative correlation were observed between the concentration of serotonin in thrombocytes & depression and hostility & turning aggression against others. Serotonin in plasma and tryptophan correlated negatively with hostility. These findings supported the suggested link between aggression and depression with a low functioning serotonergic system. In contrast to previous observations, in the present study, there were no correlations between norharman and intra-psychological mechanisms such as defense organization or coping strategies.

The changes in the group of patients not on any medication at baseline after treatment for six and nine months are described in ***Chapter 12***. As far as the therapeutic effect and the results are concerned, this group did not appear to behave any differently from the patient group as a whole as mentioned in Chapter 8.

After six months of treatment with clomipramine and cognitive therapy, there was a decrease in the intra-punitive mechanism turning aggression against self and an increase in turning aggression against others and reversal.

These changes in the DMI increased further in the period from six to nine months during which the treatment was withdrawn. The biggest change occurred in the compiled scale repression: a decrease of 91% was noted nine months after the start of the treatment.

On the basis of this, it can be postulated that indicated defense mechanisms for an important part depends on the actual psychiatric affliction in the patients.

However, this hypothesis should be viewed with the necessary caution because the repression scale of the DMI is compiled on the basis of different scores (see chapter 4). Relatively small changes in the score of the compiled scales may lead to large changes in the repression scale.

From the coping strategies, depressive reactions and avoidance had changed (negatively) the most. Depressive reactions decreased by 26% and avoidance by 9% nine months after the start of the treatment. It can be remarked that change in the coping strategy depressive reactions is probably state determined and was strongly influenced by the therapeutic effect. The remaining coping strategies appeared to be more trait dependent and changed little (less than 10%) during the combined treatment with antidepressant and cognitive therapy.

The biggest changes in the biochemical variables were noted in the concentrations of serotonin in the blood, plasma and thrombocytes. The concentration of serotonin increased again when clomipramine was withdrawn after 6 months of treatment. It was noteworthy that the concentration of tryptophan, the precursor of serotonin, remained low even after clomipramine had been withdrawn. The cause of this low concentration of tryptophan after six and nine months of treatment remains unknown. One can speculate that the low concentration of tryptophan and to a lesser extent, the low tryptophan ratio which were still observed three months after the withdrawal of clomipramine formed a risk for a recurrence of psychopathology via derangement of the serotonergic system.

The concentration of norharman in the plasma appeared to be highly increased during the treatment with clomipramine. This increase appeared to be linked to the treatment with clomipramine: whereas the therapeutic effect in this group of patients still increased between six and nine months, the concentration of norharman in the plasma decreased again.

Chapters 13 and 14

Concluding remarks in English and Dutch are presented in chapters 13 and 14 respectively. On the basis of defense, coping and limited biochemical investigations, we were unable to find any explanatory model which could clarify as to why one patient develops panic disorder, whereas a second patient develops depression and a third patient develops both disorders. As an explanation hypothesis, we postulate that besides a non-specific vulnerability, precipitating factors such as Life Events determine which form of psychopathology would arise.

SAMENVATTING

Hoofdstuk 1

Dit hoofdstuk " Panic disorder, an update", geeft na een historische beschrijving van de ontwikkeling van het begrip paniekstoornis een inventarisatie van de kenmerkende symptomatologie van paniekaanvallen en een overzicht van de epidemio-logische gegevens van paniekstoornis. Paniekstoornis blijkt in uiteenlopende centra verspreid over de gehele wereld een grote mate van overeenkomst in prevalentie (0.5-1.5 %) te vertonen.

Het valt hierbij op dat vrouwen veel frequenter dan mannen aan een paniekstoornis lijden. Het verschil tussen mannen en vrouwen varieert in uiteenlopende studies van 50 tot 200%.

De genetische aspecten van paniekstoornis worden besproken. Geconcludeerd wordt dat paniekstoornis een specifieke genetische entiteit heeft welke niet geassocieerd is met een breed spectrum van diverse angst-, of andere psychiatrische stoornissen uitgezonderd mogelijk sociale fobie.

Naast genetische factoren spelen ook life events een belangrijke rol in het ontstaan van een paniekstoornis. Met name het bestaan van separatieproblematiek blijkt van groot belang.

Bij de behandeling van paniekstoornis blijkt dat zowel behandeling met psychofarmaca (benzodiazepines, serotonine heropname remmers, tricyclische antidepressiva en monoamine-oxydase remmers) als met psychotherapie (cognitieve gedragstherapie) effectief kan zijn. De prognose voor patiënten die aan een paniekstoornis lijden is echter niet onverdeeld gunstig. Een aanmerkelijk percentage van de patiënten blijkt een chronisch ziektebeloop te vertonen. Mogelijk is de lange termijn prognose te verbeteren door het langer voortzetten van de farmacotherapeutische behandeling en/of een combinatie van farmacotherapie met psychotherapie.

Hoofdstuk 2

In hoofdstuk twee worden de resultaten weergegeven van een kritisch literatuur onderzoek naar de biologisch-psychiatrische aspecten van paniekstoornis. Hierbij worden besproken: serotoninerge hypothesen, noradrenerge hypothesen, de GABA hypothese, de rol van het ß carboline norharman en van cholecystokinine. Vervolgens worden neuroanatomische theorieën betreffende paniekstoornis, met name het belang van het septo-hippocampale systeem kort weergegeven. In het totaal komen tien biologische verklaringstheorieën voor het ontstaan van paniekstoornis ter sprake. Geconcludeerd wordt dat geen van deze biologische theorieën éénduidig een verklaring kan geven voor het ontstaan van de (of een?) paniekstoornis.

Gepostuleerd wordt dat een interactief model van biopsychosociale causaliteit als belangrijkste verklaringsmodel voor het ontstaan van paniekstoornis in aanmerking komt.

Hoofdstuk 3

In hoofdstuk drie wordt een literatuuroverzicht betreffende comorbiditeit tussen paniekstoornis en depressie in engere zin gegeven voor zover relevant in de opzet van de huidige studie. In de etiologie van de comorbiditeit tussen paniekstoornis en depressie blijken een aantal factoren van belang: het geslacht van de patiënt, de tijdsduur gedurende welke de psychiatrische stoornis bestaat, genetische belasting en comorbiditeit van paniekstoornis met andere psychiatrische stoornissen zoals sociale fobie en gegeneraliseerde angststoornis.

Er worden zes theoretische modellen besproken van waaruit het gelijktijdig voorkomen van paniekstoornis en depressie in engere zin kan worden verklaard.

1. Een model waarbij uitgegaan wordt van een gemeenschappelijk pathogenese van paniekstoornis en depressiviteit (unitary hypothese).
2. Een model welke postuleert dat twee separate, goed afgegrensde, syndromen (bij toeval?) samengaan.
3. Een predispositie model, waarbij de ene stoornis etiologisch, chronologisch of psychopathologisch lijdt tot een andere stoornis.
4. Een model dat uitgaat van een artificiële overlap door de wijze van definiëring van twee verschillende aandoeningen.
5. Een gecombineerd model: 'general neurotic syndrome', dat een combinatie van angst, depressie, en een afhankelijke persoonlijkheidsstoornis veronderstelt.
6. Een model dat als hypothese de geleidelijke ontwikkeling van multiple psychopathologie stelt en waarbij het ontstaan van een paniekstoornis in het algemeen voor afgaat aan het ontstaan van een depressie.

Het tweede deel van hoofdstuk drie betreft een inleiding op het eigen onderzoek. Er wordt kort ingegaan op het belang van psychologische afweermechanismen en copingstrategieën bij paniekstoornis en depressie in vergelijking tot patiënten met een andere psychiatrische stoornis en in controlegroepen. Tevens wordt nagegaan of er op basis van de literatuurgegevens een uitspraak kan worden gedaan of deze psychologische functies, afweer en coping, trait of state bepaald zijn.

De mogelijke betekenis van serotonine in de etiologie van depressie en paniekstoornis wordt besproken, evenals die van de aminozuren tyrosine en tryptofaan en het betacarboline norharman. Op basis van eerder onderzoek wordt gepostuleerd dat plasma norharman mogelijk intrapsychische processen weerspiegelt.

Als centrale onderzoekshypothese wordt gesteld dat er sprake is van unitaire etiologie bij paniekstoornis en depressie in engere zin, en dat deze etiologie gelegen kan zijn in een biologisch substraat waarbij psychologische kenmerken in de zin van afweerorganisatie en/of copingstrategieën bepalen welke psychiatrische stoornis ontstaat.

Op basis van deze hypothese wordt verwacht dat patiënten met een paniekstoornis of depressie in engere zin wel op basis van symptomatologie, afweerorganisatie en coping strategieën van elkaar te onderscheiden zijn, maar niet op grond van hun biochemisch profiel.

Hoofdstuk 4

In hoofdstuk vier worden onderzoeksopzet, in-, en exclusie criteria, methoden, waaronder protocollaire behandeling van de patiënten en de gehanteerde vragenlijsten - Symptom Check List -90 (SCL-90), Utrechtse Coping Lijst (UCL), Defense Mechanism Inventory (DMI) en Munich Diagnostic Check List (MDCL)- besproken.

Hoofdstuk 5

Hoofdstuk vijf geeft een beschrijving van de onderzoekspopulatie, biografische en psychopathologische gegevens en beschrijft de drop-outs die gedurende de onderzoeksperiode optreden. Het comorbiditeitspercentage tussen paniekstoornis en depressie in engere zin ligt in onze studie lager (15%) dan in de literatuur wordt aangegeven (25% - 40%). Het drop-out percentage gedurende de totale behandelduur van zes maanden bedroeg 31%. Dit percentage ligt onder dat van een eerder onderzoek bij depressieve patiënten in dezelfde behandelsetting en onder het percentage dat andere onderzoekers in vergelijkbare patiëntengroepen vonden. Er wordt gespeculeerd dat dit komt door het open karakter van de behandeling, hetgeen minder onzekerheid voor de patiënten met zich meebrengt en door de combinatie van medicamenteuze therapie met psychotherapie .

Hoofdstuk 6

In hoofdstuk zes wordt onderzocht in hoeverre de patiëntengroep als geheel verschilt van een referentiegroep en normgroepen op psychologische variabelen: klachten, copingstrategieën en afweerorganisatie. Tevens wordt onderzocht of er verschillen zijn tussen de patiëntengroep en de referentiegroep betreffende een aantal biochemische parameters: Serotonine in bloed, bloedplaatjes en plasma; tyrosine en tryptofaan en hun index ten opzichte van andere aminozuren; het ß carboline norharman.

Bij de onderzoeksgroep bleek op basis van SCL-90-scores sprake van gemiddeld ernstige tot ernstige symptomatologie in vergelijking tot andere poliklinische psychiatrische patiënten in Nederland. De scores op de UCL maken duidelijk dat de patiëntengroep een in vergelijking tot de referentiegroep inadequate coping hanteert waarbij meer gebruik gemaakt wordt van palliatie, vermijden en met een depressief reactiepatroon reageren. Ook neigen de patiënten minder dan in de referentiegroep ertoe problemen actief aan te pakken.

Qua afweerorganisatie maakt de patiëntengroep in vergelijking tot de referentie groep meer gebruik van onvolwassen afweermechanismen als projectie, terwijl de mannelijke patiënten er meer dan in de norm-, en referentiegroep toe neigen agressie op zichzelf te richten.

Bij discriminant analyse op basis van psychologische variabelen blijkt dat er zeer betrouwbaar een onderscheid gemaakt kan worden tussen referentiegroep en patiëntengroep, in 94 % van de gevallen vindt er een correcte classificatie plaats.

Het best discrimineren de SCL-90 subschalen, gevolgd door de coping strategieën vermijden en depressief reageren waarvan de patiënten meer gebruik maken dan de referentiegroep, en het afweermechanisme turning agression against self. Dit afweermechanime wordt in de patiëntengroep meer dan in de referentie-groep gehanteerd.

Ook bij discriminantanalyse op basis van biochemische paramemeters komt het tot een betrouwbaar onderscheid tussen patiënten en referentiegroep, maar in duidelijk mindere mate dan op basis van psychologische variabelen het geval is.

Van de biochemische parameters geeft de ratio van het aminozuur tyrosine ten opzichte van de andere grote neutrale aminozuren het meeste gewicht bij discriminantanalyse. Tyrosine is een aminozuur dat in de hersenen als precursor voor de noradrenaline en dopamine synthese fungeert. Deze neurotransmitters spelen naast serotonine mogelijk een belangrijke rol in de etiologie van depressie en paniekstoornis.

Hoofdstuk 7

In hoofdstuk zeven wordt nagegaan in hoeverre de drie patiëntengroepen met respectievelijk paniekstoornis, depressie in engere zin en paniekstoornis + depressie in engere zin van elkaar te onderscheiden zijn op basis van psychologische en biochemische parameters. Het blijkt dat de drie patiënten groepen zich op symptoomniveau (SCL-90-schalen) goed laten onderscheiden, onder andere middels een door ons op basis van de SCL-90 ontworpen paniekscore.

Betrouwbaar onderscheid tussen de drie patiëntengroepen op basis van psychologische afweerorganisatie of gehanteerde copingstrategieën blijkt echter niet mogelijk.

In biochemisch opzicht onderscheiden patiënten met een paniekstoornis zich ten opzichte van de twee andere patiëntengroepen door een laag gehalte van het ß carboline norharman. Deze bevinding past bij de mogelijke functie van norharman als benzodiazepine-agonist. Patiënten met een paniekstoornis zouden mogelijk een hoog angstniveau kunnen hebben door dit lage norharman gehalte, onverklaard blijft dan echter het normale norharman gehalte bij patiënten met comorbiditeit paniekstoornis en depressie.

Bij discriminantanalyse blijkt op basis van biochemische variabelen in 62.1% van de gevallen een correcte indeling in een van de drie patiëntengroepen mogelijk.

Naast norharman dragen het meest bij aan de discrmininatie: tryptofaan ratio, plasma tryptofaan en serotonine gehalte in het bloed.

De onderzoeksbevindingen geven enige aanwijzingen voor de hypothese van biologische heterogeniteit van paniekstoornis en depressie in engere zin in, waarbij iedere psychiatrische stoornis zijn eigen specifieke genetische en neurobiologische oorsprong heeft. Wij vinden geen steun, mede door het ontbreken van verschil in psychologische kenmerken als afweer en coping tussen patiënten met een paniekstoornis en/ of depressie, voor de "unitary" hypothese van de twee ziekten.

Hoofdstuk 8

In hoofdstuk acht wordt de interdependentie van de psychologische variabelen vóór behandeling besproken.

Binnen de coping subschalen van de UCL blijken er in de patiënten groep positieve correlatie te zijn tussen vermijden en depressief reageren; emoties uiten en palliatie; depressief reageren en emoties uiten en tussen steun zoeken en emoties uiten. Verschillen in verbanden tussen coping stijl ten op-zichte van norm-, en referentie groep worden weergegeven.

Bij de afweermechanismen wordt een positieve correlatie gevonden tussen agressie op anderen richten en projectie; en negatieve correlaties tussen tussen agressie op anderen richten met verdringing, ontkenning en intellectualisatie.

Projectie correleert eveneens negatief met verdringing, ontkenning en intellectualisatie en tevens met agressie op het zelf richten. Het gebruik van afweermechanismen zoals gemeten met de DMI verschilt in de referentie groep niet van de controle groepen zoals gegeven in de literatuur. De verschillen in het hanteren van afweermechanismen tussen patiënten groep en referentie groep zijn slechts kwantitatief.

Tussen de copingstrategieën en afweermechanismen worden geen belangrijke significante correlaties gevonden in de referentie groep. In de patiëntengroep vinden wij echter een positieve correlatie tussen intellectualisatie en actief problemen oplossen en negatieve associaties tussen intellectualisatie met depressief reageren en emoties uiten.

Gebruikmaken van intellectualisatie als afweermechnisme geeft mogelijk bescherming tegen depressieve reactievormen.

Hoofdstuk 9

In hoofdstuk negen worden de veranderingsmetingen op de SCL, UCL, DMI en biochemische parameters zes en negen maanden na aanvang van de behandeling beschreven. Het klachtenpatroon van de patiënten met een paniekstoornis en/of depressie in engere zin, zoals gemeten op de SCL-90-schaal verandert gedurende een gecombineerde behandeling met clomipramine en cognitieve therapie in gunstige zin. De patiëntengroep met comorbiditeit van depressie in engere zin met paniekstoornis heeft een minder goede therapierespons dan de andere twee diagnostische groepen.

De verbetering bereikt na zes maanden behandeling blijkt zich, in de patiëntengroep die op verzoek de clomipramine medicatie stopt na zes maanden behandeling, bij een follow-up meting drie maanden later te hebben voortgezet.

Veranderingen in copingstijl en gehanteerde afweermechanismen zijn niet afhankelijk van de diagnostische groep waartoe patiënten behoren. Gehanteerde copingstrategie verandert tijdens de behandeling, afgezien van de scores op de schalen vermijden en depressief reageren die gedurende de behandeling afnemen, niet duidelijk. De afweerorganisatie zoals gemeten met de DMI verandert gedurende de behandeling: gedurende de gecombineerde medicamenteuse en cognitieve therapie neemt het gebruik van het afweermechanisme agressie naar buiten richten toe en van agressie op het zelf richten af.

Hoewel er in de psychologische afweer en, in mindere mate, in gehanteerde copingstrategie tijdens de behandeling veranderingen optreden, blijkt na regressie analyse de uitgangswaarden op de betreffende DMI- en UCL-schalen, het meest bepalend voor de uitkomsten na zes en negen maanden na aanvang van de behandeling.

Hoofdstuk 10, 11 en 12

Hoofdstuk tien, elf en twaalf geven een nadere beschouwing van die patiëntengroep welke op baseline geen psychofarmaca gebruikte.

In ***hoofdstuk tien*** wordt nagegaan of er verschillen zijn in SCL-90-scores en de UCL en DMI scores tussen patiënten die bij aanvang van het bloedonderzoek reeds clomipramine gebruikt en zij die dit niet deden.

Het blijkt dat de scores op deze maten van psychisch functioneren in de twee groepen vrijwel gelijk zijn, zodat voor een beschouwing van de psychologische variabelen de patiëntengroep als één geheel kan worden beschouwd.

Clomipramine blijkt een zeer sterke invloed te hebben op het serotonine gehalte in bloed, plasma en in trombocyten van de patiënten. Het serotonine gehalte van de clomipramine gebruikende patiënten ligt veel lager dan in de referentie groep en dan bij patiënten die geen anti-depressiva gebruiken ten tijde van de eerste bloedafname. Ook het tryptofaangehalte van de clomipramine gebruikende patiënten blijkt verlaagd ten opzichte van dat in de medicatievrije groep.

Gespeculeerd wordt dat er door clomipraminegebruik enzyminductie in de lever optreedt met activatie van het enzym tryptofaanpyrrolase waardoor de afbraak van tryptofaan toeneemt.

Ook alternatieve verklaringshypothesen voor het lage tryptofaan gehalte in de clomipramine gebruikende patiëntengroep worden gegeven waaronder een verschuiving van eiwit gebonden naar vrij tryptofaan onder invloed van het antidepressivum en verminderde absorptie van tryptofaan uit de darm.

Hoofdstuk elf beschrijft de interdependentie van psychologische en biochemische waarden.

De intercorrelaties tussen SCL-90, DMI en UCL met de biochemische parameters worden, voor zover significant, gegeven voor de patiëntengroep en de referentiegroep.

Er worden negatieve correlaties gevonden in de patiëntengroep als geheel tussen serotonine gehalte in trombocyten met depressiviteit, hostiliteit en agressie op anderen gericht.

Serotonine in plasma en tryptofaan correleren negatief met hostiliteit. Deze bevindingen ondersteunen de gesuggereerde koppeling tussen agressiviteit en depressiviteit met een laag functionerend serotonerg systeem. In tegenstelling tot in eerder onderzoek vinden wij geen correlaties tussen norharman en intrapsychische mechanismen als afweer-organisatie of copingstrategieën.

Hoofdstuk twaalf beschrijft de veranderingen na zes en negen maanden behandeling in de op baseline medicatievrije patiëntengroep. Deze groep blijkt zich qua behandelresultaat en effect niet wezenlijk anders te gedragen dan de patiëntengroep als geheel zoals beschreven in hoofdstuk acht.

Na zes maanden behandeling met clomipramine en cognitieve therapie treedt er een afname op van het intrapunitieve mechanisme turning aggression against self en toename van turning aggression against others en reversal.

Deze veranderingen op de DMI blijken in de periode van zes tot negen maanden, waarin de behandeling gestaakt is, verder toe te nemen. De grootste verandering treedt op in de samengestelde schaal repression: Eén en negentig procent afname negen maanden na aanvang van de behandeling.

Op basis hiervan wordt gepostuleerd dat gehanteerde afweermechanismen voor een belangrijk deel afhankelijk zijn van de actuele psychiatrische stoornis van patiënten.

Voorzichtigheid bij deze hypothese is echter op zijn plaats daar de repression schaal van de DMI een samengestelde schaal is op basis van verschil scores (zie hoofdstuk vier).

Relatief kleine veranderingen qua score in de samenstellende schalen kunnen tot grote veranderingen in de repression schaal leiden. Van de copingstrategieën blijken depressief reageren en vermijden het meest (negatief) aan verandering onderhevig. Depressief reageren neemt met 26% af, negen maanden na start van de behandeling, vermijden met 9%. Opgemerkt wordt dat verandering in de copingstrategie depressief reageren mogelijk state bepaald is en sterk wordt beinvloed door therapie effect. De overige copingstrategieën blijken meer trait afhankelijk en veranderen weinig (minder dan tien procent) gedurende de gecombineerde behandeling met antidepressiva en cognitieve therapie.

In de biochemische variabelen treden de grootste veranderingen op in serotonine in bloed, plasma en trombocyten. Na het staken van de clomipramine na zes maanden behandeling nemen de serotonine concentraties weer toe, opvallend genoeg blijft het tryptofaangehalte, de precursor van serotonine, ook na het staken van de clomipramine laag. De oorzaak van dit lage tryptofaangehalte na zes en negen maanden behandeling is onbekend. Men zou kunnen speculeren dat het lage tryptofaangehalte en in mindere mate ook de lage tryptofaanratio welke nog gevonden wordt drie maanden na het staken van clomipraminemedicatie een risico voor een recidief optreden van psychopathologie vormen door een ontregeling van het serotoninerge systeem. Het plasma norharman blijkt gedurende de behandeling met clomipramine sterk toe te nemen. Deze stijging lijkt in verband te staan met de clomipraminebehandeling. Terwijl het therapie-effect in deze patiëntengroep tussen zes en negen maanden nog toeneemt, daalt het plasma norharmangehalte weer.

Hoofdstuk 13 en 14

Hoofdstuk dertien en veertien geven de concluding remarks in een respectievelijk engelse en nederlandse versie.

Op basis van afweer, coping en beperkte biochemische onderzoeken wordt ons verklaringsmodel waarom de ene patiënt een depressie ontwikkelt, een andere patiënt een paniekstoornis en een derde patiënt beide, niet ondersteund.

Als alternatieve verklaringshypothese postuleren wij dat naast een aspecifieke vulnerabiliteit precipiterende factoren zoals Life Events bepalen welke vorm van psychopathologie ontstaat.

VERANTWOORDING

De in dit proefschrift beschreven studies, werden verricht op de afdeling Psychiatrie van het Drechtstedenziekenhuis, lokatie Refaja te Dordrecht en door de werkgroep Pathofysiologie van Gedrag van de Erasmusuniversiteit Rotterdam (hoofd: Prof. dr. L. Pepplinkhuizen). Op deze plaats wil ik graag die personen bedanken die betrokken waren bij de totstandkoming en uitvoering van het onderzoek.

In de eerste plaats gaat mijn dank uit naar mijn promotoren Lolke Pepplinkhuizen en Jan Passchier die mij gestimuleerd hebben tot het opzetten en uitvoeren van dit onderzoek en die vele constructieve opmerkingen plaatsten bij het vervaardigen van dit proefschrift.

Zonder de medewerkers van het Drechtstedenziekenhuis lokatie Refaja: de psychiaters Arthur Van Gool en Hans Kamp, de medewerkers van het klinisch chemisch laboratorium (hoofd: Dr. R.B. Dinkelaar) en de administratieve ondersteuning van Betty Noorlander en Jolanda Vermeulen, was dit onderzoek niet mogelijk geweest.

De methodologische kant van de verwerking van de onderzoeksresultaten was in handen van Hugo Duivenvoorden (afdeling Medische Psychologie Erasmusuniversiteit Rotterdam) en de statistische bewerking geschiedde door Dick Stronks (Researchbureau Stronks Gouda). Hugo en Dick verrichtten zeer veel werk, waarvan slechts een beperkt deel in dit poefschrift zichtbaar wordt.

De biochemische bepalingen werden uitgevoerd door het laboratorium van de werkgroep Pathofysiologie van Gedrag (hoofd: Durk Fekkes). Het samenwerken met Durk was steeds een genoegen en zal zeker worden voortgezet.

Judica Berkelaar en Ria Keulemans ben ik erkentelijk voor de secretariële ondersteuning bij het totstandkomen van de definitieve versie van dit proefschrift en de vormgeving ervan.

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De engelse vertaling geschiedde door Dr. D. Tank. Tot slot dank ik de patiënten en vrijwilligers die bereid waren in de studies te participeren. Zonder hun gemotiveerde inzet en medewerking was dit onderzoek absoluut onmogelijk.

CURRICULUM VITAE

L. Timmerman werd op 17 april 1954 geboren te Rotterdam. Van 1966 tot 1972 bezocht hij het Libanonlyceum te Rotterdam. In 1974 werd een aanvang gemaakt met de studie geneeskunde aan de Erasmusuniversiteit te Rotterdam. Gedurende deze studie was hij werkzaam als student-assistent bij het instituut Medische Psychologie (hoofd Prof. Dr. F. Verhage) in de periode 1975 en 1976. Na het keuze-onderzoek bij de afdeling Preventieve- en Sociale Psychiatrie betreffende het therapie-effect van drugvrije therapeutische gemeenschappen was hij werkzaam als student-assistent op de afdeling voor Preventieve- en Sociale Psychiatrie (hoofd: Prof. Dr. C.W.J. Trimbos). Maart 1981 werd een aanvang gemaakt met de A-Opleiding tot psychiater in Delta Psychiatrisch Ziekenhuis te Poortugaal (Opleider: Dr. M.H. Cohen Stuart). Na voltooiing van de basisopleiding psychiatrie volgden keuzestages ziekenhuispsychiatrie in het Refajaziekenhuis te Dordrecht (hoofd: Dr. E.W. Heerema), neurochirurgie in Academisch Ziekenhuis Dijkzigt (hoofd: Prof. Dr. R. Braakman) en kinderpsychiatrie in het Sophia Kinderziekenhuis van het Academisch Ziekenhuis te Rotterdam (hoofd: prof. Dr. J.A.R. Sanders-Woudstra).

Na voltooiing van de opleiding tot psychiater en de basiscursus Psychotherapie bij het Instituut voor Multidisciplinaire Psychotherapie te Rotterdam (hoofd: Prof. Dr. J.H. Thiel) volgde hij de technisch-theoretische cursus groepspsychotherapie (Prof. Dr. P.J. Jongerius) en verschillende cursussen op het gebied van de biologische psychiatrie.

Van oktober 1985 tot november 1989 was hij psychiater op de open opname-afdeling en afdeling voor Klinische Psychotherapie 'De Albrandswaard' van Delta Psychiatrisch Ziekenhuis. Gedurende deze periode werkte hij tevens op de polikliniek psychiatrie van het Zuiderziekenhuis te Rotterdam. Van november 1989 tot september 1993 was hij als psychiater verbonden aan het Drechtstedenziekenhuis te Dordrecht en lid van de werkgroep Pathofysiologie van Gedrag (hoofd Prof. dr. L. Pepplinkhuizen) van de Erasmusuniversiteit te Rotterdam. Sinds september 1993 is hij A-Opleider Psychiatrie in Delta Psychiatrisch Ziekenhuis te Poortugaal, hij bekleedt diverse bestuursfuncties binnen de psychiatrie.

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