DEPRESSION AFTER STROKE

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ABSTRACT

DEPRESSION AFTER STROKE

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Both stroke and depression are major health problems in the elderly. In this study, the prevalence of major depression after stroke was investigated in a well-defined sample of acute stroke patients (n=80), followed up at 3 months, 1 year, 2 and 3 years after the stroke event. Links to biological and psychosocial factors were examined. Hypercortisolism was studied by the dexamethasone suppression test and compared with healthy elderly. Living conditions (including demographic characteristics, economic resources, health, functional ability, activity/leisure, social network) and life satisfaction were described before and after stroke in relation to a general elderly population.

Demographic characteristics, economic resources, social network and psychiatric morbidity prestroke did not differ from the general elderly population. Already prior to the stroke, patients reported more health problems and lower functional ability in many aspects of daily life, more passive leisure time and a lower global life satisfaction. After stroke, contacts with children were maintained, whilst contacts outside the family declined and remained lower than in the general elderly population. Stroke involved a marked reduction in global life satisfaction. Poor life satisfaction at 1 year remained poor for the entire three years; these stroke victims had a higher frequency of major depression early after stroke.

The prevalence of major depression was 25% at the acute stage, 31% at 3 months, decreased to 16% at 1 year, was 19% at 2 years and increased to 29% at 3 years. The most important predictors of immediate major depression were left anterior brain lesion, dysphasia, and living alone. Dependence in self-care ability and loss of social contacts outside the family were the most important predictors at 3 months. From 1 year onwards, loss of social contacts contributed most to depression and at 3 years also cerebral atrophy. Sixty percent of patients with early depression (0-3 months) had recovered at 1 year; those not recovered at 1 year had a high risk of chronication.

Hypercortisolism as measured by the dexamethasone suppression test was associated with major depression late (3 years) but not early (0-3 months) after stroke. At 3 years, the dexamethasone suppression test had a sensitivity of 70%, a specificity of 97%, a positive predictive value of 88%, a negative predictive value of 91%, and a diagnostic accuracy of 90%. Nonsuppression of dexamethasone at 3 months was a significant predictor of major depression at 3 years.

Key words: Cerebrovascular disorders, stroke, depression, living conditions, life satisfaction, social network, dysphasia, self-care ability, cerebral atrophy, dexamethasone.
DEPRESSION AFTER STROKE

by

Monica Åström

Umeå 1993
Have Ithaka always in your mind.
Your arrival there is what you are
destined for.
But don't in the least hurry the journey.
Better it last for years,
so that when you reach the island
you are old,
rich with all you have gained on the way,
not expecting Ithaka to give you wealth.

C. P. Cavafy
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ABBREVIATIONS

ADL activities of daily living
CNS central nervous system
CRH corticotropin releasing hormone
CT computed tomography
CVD cerebrovascular disease
DEX dexamethasone
DSM-III diagnostic and statistical manual of mental disorders, 3d edition
DSM-III-R diagnostic and statistical manual of mental disorders, 3d edition (revised)
DST dexamethasone suppression test
HPA axis hypothalamic - pituitary - adrenal axis
LH left hemisphere
LL questionnaire 'questionnaire on living conditions and life satisfaction'
LNU 'level of living survey'
RH right hemisphere
TIA transient ischemic attack
ULF 'survey of living conditions'
ABSTRACT

DEPRESSION AFTER STROKE

Monica Åström, Departments of Psychiatry and Internal Medicine, Umeå University, S-90185 Umeå, Sweden.

Both stroke and depression are major health problems in the elderly. In this study, the prevalence of major depression after stroke was investigated in a well-defined sample of acute stroke patients (n=80), followed up at 3 months, 1 year, 2 and 3 years after the stroke event. Links to biological and psychosocial factors were examined. Hypercortisolism was studied by the dexamethasone suppression test and compared with healthy elderly. Living conditions (including demographic characteristics, economic resources, health, functional ability, activity/leisure, social network) and life satisfaction were described before and after the stroke in relation to a general elderly population.

Demographic characteristics, economic resources, social network and psychiatric morbidity did not differ between the study group before the stroke and the general elderly population. Already prior to the stroke, patients reported more health problems and lower functional ability in many aspects of daily life, more passive leisure time and a lower global life satisfaction. After the stroke, contacts with children were maintained, whilst contacts outside the family declined and remained lower than in the general elderly population. Stroke involved a marked reduction in global life satisfaction. Poor life satisfaction at 1 year remained poor for the entire three years; these stroke victims had a higher frequency of major depression early after the stroke.

The prevalence of major depression was 25% at the acute stage, 31% at 3 months, decreased to 16% at 1 year, was 19% at 2 years and increased to 29% at 3 years. The most important predictors of immediate major depression were left anterior brain lesion, dysphasia, and living alone. Dependence in self-care ability and loss of social contacts outside the family were the most important predictors at 3 months. From 1 year onwards, loss of social contacts contributed most to depression and at 3 years also cerebral atrophy. Sixty percent of patients with early depression (0-3 months) had recovered at 1 year; those not recovered at 1 year had a high risk of a chronic development of depression.

Hypercortisolism as measured by the dexamethasone suppression test was associated with major depression late (3 years) but not early (0-3 months) after the stroke. At 3 years, the dexamethasone suppression test had a sensitivity of 70%, a specificity of 97%, a positive predictive value of 88%, a negative predictive value of 91%, and a diagnostic accuracy of 90%. Nonsuppression of dexamethasone at 3 months was a significant predictor of major depression at 3 years.

Key words: Cerebrovascular disorders, stroke, depression, longitudinal, living conditions, life satisfaction, social network, dysphasia, self-care ability, cerebral atrophy, dexamethasone suppression test, elderly.


INTRODUCTION

HISTORICAL PERSPECTIVES

..'from the brain and from the brain only, arise our pleasures, joys, laughter and jests, as well as our sorrows, pain, grief and tears'...This praise dedicated to the brain comes from the Hippocratic writings\(^1\) (p. 11) attacking magical beliefs of illness as the sign of diabolic possession. Illness was seen as a result of the disturbed equilibrium of the four humours: blood, yellow bile, black bile, and phlegm. An excess of black bile was related to melancholia, a term that literally means 'black bile'. Melancholia was characterized by ..'aversion to food, despondency, sleeplessness, irritability, restlessness'\(^2\) (p. 30). Both Greek and Roman physicians reported that melancholia was common in the elderly.\(^3\)

In the Bible, the Book of Job, classic symptoms of depression are described, including insomnia, poor appetite, recurrent thoughts of death, low self-esteem, and decreased sexual drive. Significant losses in Job's life preceded the onset of depression. The depression remitted when Job's anger with God was interpreted. This can be regarded as an early psychodynamic view of depressive stages.

The writings of Galen from the second century further developed the humoral theory, which then dominated medical thought for more than thousand years. As illness gradually became the responsibility of the early church, mental illness was generally attributed to sin and possession of the devil. Older women with depressive psychoses were frequently accused of witchcraft and were burned on the stake.\(^3\)

By the late middle ages empirical science came back into prominence, and pathological and physiological studies of the brain emerged. Besides the dominating humoral theory, another frame of reference can be found in Burton's 'The Anatomy of Melancholy' (first published 1621), with early psychodynamic concepts of the aetiology of melancholy.\(^4\) From personal experiences he presented classic depressive symptoms which he attributed to a lack of parental affection. He associated loss of status and activity to melancholy in later life. There are similarities to Freud's psychoanalytical interpretation of melancholic symptoms in 'Trauer und Melancholie',\(^5\) further modified and extended by modern psychoanalysis (for review e.g.\(^6\)) and by cognitive theories of depression.\(^7\)\(^8\)

During the nineteenth century physicians claimed that melancholy in the elderly was inseparable from dementia, e.g. the German psychiatrist Griesinger described a 'stadium melancholicum' as an initiatory period of dementia.\(^4\) This debate has continued, and can be found in current research (summarized by Post\(^9,10\)). Even though earlier authors had used the word 'depression' (e.g. in 1761 when Samuel Johnson described himself as 'being under great depression\(^12\)), it was Griesinger who, in 1845,
introduced the term 'depression' instead of the classical 'melancholia'. Devised from the Latin word 'deprimere', it referred to a feeling of being pressed down. The term depression was 1899 accepted and used by Kraepelin, the pioneer of classification of psychiatric disorders. Kraepelin differentiated manic-depressive illness from dementia praecox (i.e. schizophrenia), and emphasized differences in their longitudinal course. He regarded depression with and without mania as the same illness. This unitary conception has later been a matter of controversy and subsequent investigations. Over the past fifty years several systems for classification of depression have been suggested, most of them dichotomous and based on etiological assumptions. These controversial classifications have recently been summarized by Åsberg, who points out that their use is declining after the acceptance of the American DSM-III system.

In the United States, psychiatry during the first half of this century was greatly influenced by Meyer who taught that individuals, not diseases, were the objects of study. He described depression as a type of reaction (i.e. adaptation) to the total life situation of the individual.

The ancient thought that mental disorders may reflect physiological disturbances (i.e. changes in the composition of body fluids), can be traced to current research in the biochemistry of depression. Over the last decades this research (for review, see e.g.) together with other advances in neuroscience, molecular genetics, and an increasingly systematic psychotherapy research, have gradually narrowed the Cartesian separation between the mind and the brain, thus improving our ability to link mental processes to brain processes. Freedman in a lecture from 1992 to The American Psychiatric Association entitled: 'The Search: Body, Mind, and Human Purpose', emphasized the importance for psychiatry not to lose neither its mind nor its brain - nor its essential function to search in any realm yielding to probing inquiry.

Stroke patients constitute the realm of inquiry of this thesis. Like melancholy, stroke is known since medicine began. Stroke or apoplexy (from a Greek term meaning 'to strike down') was related to the flow of black bile into the head because of the heating of the blood vessels. In the Hippocratic aphorisms on apoplexy many aspects of the apoplectic attacks are described, and in the Epidemics the first written account of aphasia as connected with right-sided paralysis can be found. The association between apoplexy and cerebrovascular disease was uncertain until the epoch-making contributions by Wepfer (1620-1695) who demonstrated that one cause of stroke was intracranial haemorrhage which he distinguished from occlusion, the other main cause of stroke. He stated that individuals with hypertension or heart disease were most liable to apoplexy.

Shakespeare mentioned apoplexy in his play 'Henry IV' from 1592, where Falstaff had heard that: 'his highness is fallen into this same whoreson apoplexy'. In 1761 Morgagni confirmed the earlier observations (at least from Aretaios,
50 or 150 A.D.) of contralateral innervation. Van Swieten (1754) added cerebral embolism to the causes of stroke and also described a pure anomic aphasia. In Sweden, Olof Dahlin (1745) called attention to another distinctive clinical picture, i.e. complete loss of expressive speech though the ability to sing was retained. By the end of the eighteenth century several descriptions of specific symptoms, mostly aphasic symptomatology, had appeared (for review). Although it was still not possible to identify the pathological basis for these and other specific defects, these observations carried implications for localization theory. After Broca’s revolutionary association of non-fluent aphasia with left frontal lobe disease, an era of clinico-pathological studies resulted in modern descriptions of the structure of the cerebral hemispheres. Histological studies of nerve fibres and their function led to the concept of neural transmission (for review). Detailed knowledge of the cerebral vasculature was achieved, and clinicians found typical symptomatic manifestations of specific vascular abnormalities. Since 1970 the development of techniques for brain imaging has revolutionized the studies of the pathophysiology of vascular disease. Among others, Damasio et al. have emphasized that overlapping in the distribution of the vascular supply, as well as individual variations, often complicate diagnostic inference. Nevertheless, stroke has always played a significant role in the clinical study of brain-behavior associations.

ON STROKE

Aspects of diagnosis and epidemiology.

Stroke is defined by the World Health Organisation (WHO) as ‘rapidly developing signs of focal (or global) disturbance of cerebral function, with symptoms lasting 24 hours or longer or leading to death, with no apparent cause other than of vascular origin’. Common neurological disturbances in the initial stage are according to a review by Wade et al., decreased level of consciousness in 30% of patients, confusion 45% (of non-comatose patients) paralysis (hemiplegia) or weakness (hemiparesis) of one side in between 50% and 80% of cases, sensory abnormalities of the limbs 25%, dysphasia and slurred speech, each occuring in about 30% of patients.

The syndrome of stroke results from different pathological processes (haemorrhage, thrombosis, embolus). In a Swedish population-based sample of stroke patients, 11% had intracerebral haemorrhage, 13% transient ischemic attack (TIA), 51% non-embolic and 25% embolic brain infarction.

In a Swedish region (Söderhamn) the incidence of stroke was 3.9/1000. Variations in incidence between regions have mainly been attributed to different age distributions of the populations, since stroke incidence rates rise exponentially with increasing age. In Sweden, the age-standardised incidence rate has been constant during the last years. Prevalence of stroke varies between 5.0 and 8.0 per 1000 population
in most of the Western countries. In Sweden, prevalence rate have been estimated from known incidence and survival data to 9.0/1000.

Stroke is the third major cause of death in the Western world. In Sweden about 10,000 people per year die due to stroke or TIA. The mortality from stroke has continually decreased in many countries, including Sweden, partly due to more effective treatment of hypertension.

Aspects of treatment and prognosis.

No other physical disease demands as many in-hospital days in Sweden, i.e. more than 3 millions annually. Stroke is a medical emergency necessitating hospitalization for diagnostic purposes. Hospitalization is the best way to optimize patient care and to identify preventable causes and complications (e.g. pneumonia, pulmonary emboli, cardiac complications etc.). At present, no general accepted medical treatment has proved to be beneficial to the neuronal damage. However, it has been demonstrated that non-intensive stroke units with team care and early rehabilitation can reduce functional disability and the need for long-term hospitalization.

Death during the first days after stroke usually is a direct consequence of the brain lesion, whilst later, systemic causes dominate. In a study from Umeå the survival rate after one month was 84%, after one year 69%, and after three years 52%. In the longer term, initial survivors run an 8-10 per cent annual risk of having a further stroke, but are more likely to die from cardiac events than from recurrence of stroke.

In Umeå, 20% of patients admitted for acute stroke were living in an institutional setting at 3 months, and 13% at 12 months. The main part of long-term care lies on family and community services. Jongbloed has reviewed studies on functional status after stroke, and pointed out methodological problems (e.g. patient selection, varying inclusion time, classification and rating scales etc.) Between 50% to 75% of stroke patients surviving the initial event return to functional independence. Most of the recovery occurs within three months after the initial event. Spontaneous recovery of aphasia is also fastest in the first few months, but will occur at least up to 6 months after a stroke.

PSYCHOSOCIAL FUNCTION AND LIFE SATISFACTION AFTER STROKE

Both psychosocial function and life satisfaction are unprecise but widely used concepts. Psychosocial function comprises a number of variables of great complexity and importance in stroke survivors. When Gresham made use of this term in the Framingham study, he included indices of social integration but also cognitive impairment and psychiatric symptoms. Wade has pointed out that the term mixes social and mental parameters, each of which should be assessed separately. Since the patient's
mental state may have a profound influence upon his social function, and vice versa, it is an important research strategy to disentangle the two as far as possible.

Epidemiological data about psychosocial effects of stroke can be found in the Framingham survey. Decreased vocational function was present significantly more often in stroke patients than in matched controls. In Sweden, Fugl-Meyer has shown that the majority of stroke patients in their vocationally active years never returned to work. Decrease in leisure activities and socializing have been documented. In a study from Umeå, 90% of younger stroke survivors did not fully resume their previous leisure activities. Labi et al. showed that a decrease in socializing was evident also despite complete physical restoration. Friedland examined the effect of social support as a mediator between stressful life events and psychosocial outcome. She reported that 27% of patients suffered from psychosocial dysfunction, however, social support explained only a small part of total variance.

The concepts of quality of life and life satisfaction have been widely applied in the behavioral sciences and health care during the last decades (for reviews, see ). Relatively few studies on stroke have used these important outcome variables. Some of the well-grounded scepticism concerning these variables is related to their loose definitions. Furthermore, different theoretical models have been used. In the Scandinavian countries, Allardt has influenced quality of life research in behavioral sciences emphasizing both objective and subjective indicators. In the United States the terms life satisfaction, well-being, and quality of life often have been used interchangeably and were based on the individual's subjective reporting. As a result, some studies have described high levels of life satisfaction in clearly underprivileged groups, for example in poor and ill people. Thus, for interpretation of data both a description of level of living and an assessment of life satisfaction are needed. In a good deal of the research there is agreement that domains to be covered are a person's health, material resources, interpersonal relations within and outside the family, work, recreation and leisure time.

Viitanen et al. found a decreased life satisfaction in 61% of stroke survivors. Among functionally restored patients nearly 30% had decreased life satisfaction five years after stroke. Sjögren has shown that in a younger group of stroke survivors, about 80% reported decrease in satisfaction regarding leisure, and about 50% in sexual life. Ahlsio et al. reported decreased life satisfaction in 77% of patients two years after a stroke. Niemi et al. found that although the survivors four years after a stroke had recovered in terms of ADL and return to work, most (83%) reported deterioration in the quality of life.
PSYCHIATRIC DISORDERS AFTER STROKE

An overview

Many early investigators have reported on mood disorders associated with brain injury. Meyer\textsuperscript{71} in 1904 noted a relationship between the ‘traumatic insanities’ and specific locations of brain damage. Kraepelin\textsuperscript{72} recognized that cerebral infarcts may ‘engender a state of depression’. In 1922, Babinski\textsuperscript{73} observed that patients with right hemispheric lesions often showed euphoria, indifference, and anosognosia (i.e. denial of illness). Bleuler\textsuperscript{74} found that severe and long-lasting depressions were often associated with brain injury. In his studies of brain injuries in war, Goldstein\textsuperscript{75} described the ‘catastrophic reaction’ as an explosive emotional response in brain damaged patients when they were urged to perform a task, and faced with failure (exemplified by dysphasic patients failing to make themselves understood). Thirty years later, Gainotti\textsuperscript{76} confirmed that the ‘catastrophic reaction’ was significantly more frequent among left hemisphere damaged patients, especially those with dysphasia. On the other side, he found ‘indifference reactions’ significantly more often in right hemisphere damaged patients; implying indifference towards failures and disabilities, socially inappropriate jocularity, and loss of interest in other people.

During the last decades, a great variety of psychiatric syndromes after stroke have been described. Confusion is common in the immediate poststroke period.\textsuperscript{25,77,78} Some studies have reported higher frequency in connection with right,\textsuperscript{77,79} and others with left\textsuperscript{78} hemispheric lesions. Distinctions between confusion and dementia have not always been regarded. In a study from Umeå,\textsuperscript{78} acute confusional state (DSM-III\textsuperscript{14}) was diagnosed in 48% of patients within one week after admission, and within two weeks, more than half of the patients had improved.

Often confusion, dysphasia, and constructional difficulties complicate assessment of intellectual impairments. Adams et al.\textsuperscript{80} coined the phrase ‘the mental barriers to recovery’ and was among the first to use cognitive functions in predicting outcome of stroke. Its utility in prognostic studies have been confirmed by others.\textsuperscript{81-83} It has been shown that visual perceptual/spatial disturbances, and among those visual neglect, have profound effects on a patient’s activities of daily living and rehabilitation outcome.\textsuperscript{48,49,76,84,85} Memory deficits after stroke are less well documented, although over half of surviving patients in a survey,\textsuperscript{86} complained of a poor memory. Most studies have focused on localizing memory function (for review, e.g.\textsuperscript{87}) and only a few on the impact of memory on recovery of functional abilities.\textsuperscript{50,88} Wade et al.\textsuperscript{88} showed that about one third of stroke survivors had poor immediate memory three months after a stroke, whereas recovery was significant six months later.

Few studies have attempted to determine the prevalence of dementia produced by stroke. A consensus has not even been reached regarding appropriate terms for the
vascular dementia syndromes. Cummings et al., in a comprehensive review, conclude that about 25-50% of stroke patients eventually develop ‘cerebrovascular dementia’. Cognitive impairment is associated with depression (i.e. pseudo-dementia or dementia of depression) which must be regarded in studies of dementia after stroke. In summary, it has been documented that cognitive impairments after a stroke are serious sequelae delaying and compromising rehabilitation.

Among other psychiatric disorders, agitation is common after stroke, often part of the confusional syndrome. Poststroke mania is a rare consequence of stroke, reported in the literature mainly in patients with right hemispheric lesions. A hypomanic syndrome has been described by Robinson et al. in right brain damaged patients. House challenged the description of this euphoria or jocularity as hypomanic, since it shares no other features of the hypomanic syndrome.

Delusions and hallucinations following stroke are uncommon, but have been reported after right hemispheric infarctions. Peroutka claimed that delusions depended more on premorbid brain atrophy than on infarct parameters. Price et al. described five patients with acute psychotic disturbances (paranoid delusions, hallucinations, agitation) in conjunction with right hemisphere infarct. As the neurological signs were subtle, the authors suggested that in patients presenting an acute psychotic episode, focal brain disease must be considered. Concerning potential anatomical substrates of these conditions, the authors proposed that lesions (right prefrontal, and posterior parietal regions) may disrupt interactions between high-order association cortex and limbic structures leading to behavioral disturbances including psychotic episodes.

Obsessive-compulsive disorders, changes in sexual behavior, rage syndromes, anxiety syndromes and agoraphobia are also reported. House et al. have pointed at other less clearly delineated types of adjustment reactions including irritability, social withdrawal, worrying about recurrence, fatiguability, and a range of ‘non-specific’ physical symptoms. These symptoms are often referred to as personality changes which is unfortunate because this term implies an assumption of irreversibility. Personality changes in relation to specific lesion locations have been described for many years (for review), but have not been systematically studied in stroke patients. House et al. found pathological emotionalism (also known as emotional lability) in 15% of acute stroke patients, often associated with depression.
Depressive disorders after stroke

Aspects of diagnosis and epidemiology. Depression often follows a stroke. A review of the literature from the past fifteen years (Table 1), reveals prevalences ranging from 15% or less\(^{47,106,109,110}\) to more than 60%\(^{58,111,112}\). Differences are mainly depending on methodological issues (patient sample, time since stroke, different rating scales and/or criteria applied; illustrated in Table 1).

TABLE 1. Frequency of depression in studies of stroke patients.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Year</th>
<th>Patient Sample</th>
<th>n</th>
<th>Time since stroke</th>
<th>Depression Measure/Criteria</th>
<th>Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Folstein et al.(^{113})</td>
<td>1977</td>
<td>Rehab unit</td>
<td>20</td>
<td>1 m</td>
<td>PSE</td>
<td>45</td>
</tr>
<tr>
<td>Robinson et al.(^{111})</td>
<td>1981</td>
<td>Inpatients*</td>
<td>8</td>
<td>&lt;2 w</td>
<td>Zung/VAMS/HRSD</td>
<td>61</td>
</tr>
<tr>
<td>Feibel et al.(^{56})</td>
<td>1982</td>
<td>Former inpatients</td>
<td>91</td>
<td>&lt;6 m</td>
<td>Nurses' observation</td>
<td>26</td>
</tr>
<tr>
<td>Finklestein et al.(^{114})</td>
<td>1982</td>
<td>Rehab unit</td>
<td>25</td>
<td>11 - 111 d</td>
<td>HRSD</td>
<td>48</td>
</tr>
<tr>
<td>Robinson et al.(^{115})</td>
<td>1982</td>
<td>Rehab unit</td>
<td>23</td>
<td>7 - 12 m</td>
<td>Self-report</td>
<td>65</td>
</tr>
<tr>
<td>Bauer et al.(^{109})</td>
<td>1983</td>
<td>Inpatients</td>
<td>20</td>
<td>16 - 74 d</td>
<td>HRSD</td>
<td>15</td>
</tr>
<tr>
<td>Lim et al.(^{116})</td>
<td>1983</td>
<td>Inpatients</td>
<td>61</td>
<td>First weeks</td>
<td>Not stated</td>
<td>30</td>
</tr>
<tr>
<td>Robinson et al.(^{117})</td>
<td>1983</td>
<td>Inpatients</td>
<td>103</td>
<td>First weeks</td>
<td>DSM III (major depr)</td>
<td>27</td>
</tr>
<tr>
<td>Ahlsö et al.(^{47})</td>
<td>1984</td>
<td>Inpatients</td>
<td>96</td>
<td>2 yr</td>
<td>Self-report</td>
<td>14</td>
</tr>
<tr>
<td>Reding et al.(^{118})</td>
<td>1985</td>
<td>Inpatients</td>
<td>61</td>
<td>Mean 7 w</td>
<td>HRSD</td>
<td>62</td>
</tr>
<tr>
<td>Sinyor et al.(^{119})</td>
<td>1986</td>
<td>Rehab unit</td>
<td>64</td>
<td>First weeks</td>
<td>Zung/BHS/HSCL</td>
<td>47</td>
</tr>
<tr>
<td>Ebrahim et al.(^{120})</td>
<td>1987</td>
<td>Former inpatients</td>
<td>149</td>
<td>6 m</td>
<td>GHQ</td>
<td>23</td>
</tr>
<tr>
<td>Wade et al.(^{121})</td>
<td>1987</td>
<td>Community sample</td>
<td>976</td>
<td>3 w</td>
<td>Wakefield</td>
<td>22</td>
</tr>
<tr>
<td>Viiitanen et al.(^{41})</td>
<td>1987</td>
<td>Former inpatients</td>
<td>62</td>
<td>4 - 6 yr</td>
<td>MADRS</td>
<td>16</td>
</tr>
<tr>
<td>Dam et al.(^{122})</td>
<td>1989</td>
<td>In- and outpatients</td>
<td>92</td>
<td>&gt;1 w - 3.5 yr</td>
<td>RDC (modified)</td>
<td>30</td>
</tr>
<tr>
<td>Eastwood et al.(^{123})</td>
<td>1989</td>
<td>Rehab unit</td>
<td>87</td>
<td>Mean 97 d</td>
<td>RDC</td>
<td>50</td>
</tr>
<tr>
<td>Morris et al.(^{110})</td>
<td>1990</td>
<td>Inpatients</td>
<td>99</td>
<td>2 - 5 m</td>
<td>DSM III (major depr)</td>
<td>14</td>
</tr>
<tr>
<td>Santus et al.(^{124})</td>
<td>1990</td>
<td>Inpatients</td>
<td>76</td>
<td>1 yr</td>
<td>HRSD</td>
<td>36</td>
</tr>
<tr>
<td>Sharpe et al.(^{125})</td>
<td>1990</td>
<td>Community sample</td>
<td>60</td>
<td>3 - 5 yr</td>
<td>DSM III (major depr)</td>
<td>18</td>
</tr>
<tr>
<td>House et al.(^{106})</td>
<td>1991</td>
<td>Community sample</td>
<td>128</td>
<td>1 m</td>
<td>DSM III (major depr)</td>
<td>11</td>
</tr>
</tbody>
</table>

* only left hemisphere lesions

BDI = Beck Depression Inventory\(^{126}\)
BHS = Beck Hopelessness Scale\(^{127}\)
DSM III = Diagnostic and Statistical Manual of Mental Disorders\(^{14}\)
GHQ = General Health Questionnaire\(^{128}\)
HRSD = Hamilton Rating Scale for Depression\(^{129}\)
HSCL = Hopkins Symptom Checklist\(^{130}\)
MADRS = Montgomery-Asberg Depression Rating Scale\(^{131}\)
PSE = Present State Examination\(^{132}\)
RDC = Research Diagnostic Criteria\(^{133}\)
Wakefield = Wakefield Self-Assessment Depression Inventory\(^{134}\)
VAMS = Visual Analogue Mood Scale\(^{135}\)
Zerssen = Die Befindlichkeitsskala\(^{136}\)
Zung = Zung Depression Scale\(^{137}\)
The ambiguity of the term 'depression' has led to its use as a catch-all term for all varieties of emotional problems after stroke. 'Depression' has been used for describing an affect, a symptom, a syndrome, and an illness entity. The prevalence will vary depending on which of these levels of 'depression' the investigator has chosen. Different screening tools and/or criteria used for case definition further complicate comparisons between studies.

Aspects of aetiology. Numerous studies, recently summarized,99,138-140 have given conflicting information not only on prevalence and definition but also on aetiology, phenomenology and course of depressive disorders after stroke.

From a neurobiological view, depression has been regarded as an illness provoked by biological consequences of the brain damage. Consequently, the importance of the brain lesion itself (i.e. particularly lesion location) has been emphasized (see Table 2). From a psychological frame of reference, the disorder has been explained as an understandable emotional response of patients to their losses; physical and psychological (e.g. loss of independence, loss of self-esteem), as well as cognitive and psychosocial losses; including role changes in family, decrease in sexuality, stigmatization, loss of friends, activities, employment.48,143-146

The research group at Johns Hopkins (i.e. Robinson et al.) has almost consistently found a higher frequency of depression in patients with left hemisphere lesion (for a recent summary of these studies, see Lipsey et al.147), confirmed by Lim116 and de Bonis.136 The majority of other studies (Table 2), did not find any interhemispheric difference in rate of depression. The table shows two studies reporting a higher depression rate in right hemispheric stroke.113,122

The Robinson group148 has also claimed that intrahemispheric lesion location is critical in the aetiology of poststroke disorder - major depression being most frequent after anterior lesions in the left hemisphere. Also depression severity was associated with proximity to left frontal pole. For right hemisphere lesions, depression severity increased with increasing lesion proximity to the occipital lobe, although patients with right hemisphere injury, had less severe depressions overall (mostly 'minor depression'; this category - from RDC terminology - was diagnosed according to DSM III criteria of dysthymic disorder without regard to its 2-year time criterion). When controlling for aphasia, these associations remained.
TABLE 2. Depression rate in studies of stroke patients with left (LH) vs right (RH) hemispheric lesion.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Year</th>
<th>Patient Sample</th>
<th>n</th>
<th>Time since stroke</th>
<th>Depression Measure/Criteria</th>
<th>Depression rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Folstein et al.113</td>
<td>1977</td>
<td>Rehab unit</td>
<td>20</td>
<td>1 m</td>
<td>PSE</td>
<td>RH&gt;LH</td>
</tr>
<tr>
<td>Feibel et al.56</td>
<td>1982</td>
<td>Former inpatients</td>
<td>91</td>
<td>&lt;6 m</td>
<td>Nurses' observation</td>
<td>LH=RH</td>
</tr>
<tr>
<td>Finklestein et al.114</td>
<td>1982</td>
<td>Rehab unit</td>
<td>25</td>
<td>11 - 111 d</td>
<td>HRSD</td>
<td>LH=RH</td>
</tr>
<tr>
<td>Robinson et al.111</td>
<td>1982</td>
<td>Rehab unit</td>
<td>103</td>
<td>6 m - &lt;10 yr</td>
<td>GHQ</td>
<td>LH&gt;RH</td>
</tr>
<tr>
<td>Lim et al.116</td>
<td>1983</td>
<td>Inpatients</td>
<td>61</td>
<td>First weeks</td>
<td>Not stated</td>
<td>LH&gt;RH</td>
</tr>
<tr>
<td>Robinson et al.117</td>
<td>1983</td>
<td>Inpatients</td>
<td>103</td>
<td>First weeks</td>
<td>DSM III (major depr)</td>
<td>LH&gt;RH</td>
</tr>
<tr>
<td>de Bonis et al.136</td>
<td>1985</td>
<td>Inpatients</td>
<td>17</td>
<td>First week</td>
<td>Zerssen</td>
<td>LH&gt;RH</td>
</tr>
<tr>
<td>Reding et al.118</td>
<td>1985</td>
<td>Inpatients</td>
<td>61</td>
<td>Mean 7 w</td>
<td>HRSD</td>
<td>LH=RH</td>
</tr>
<tr>
<td>Sinyor et al.141</td>
<td>1986</td>
<td>Rehab unit</td>
<td>35</td>
<td>First weeks</td>
<td>Zung/BHS/HSCL</td>
<td>LH=RH</td>
</tr>
<tr>
<td>Ebrahim et al.120</td>
<td>1987</td>
<td>Former inpatients</td>
<td>149</td>
<td>6 m</td>
<td>GHQ</td>
<td>LH=RH</td>
</tr>
<tr>
<td>Dam et al.122</td>
<td>1989</td>
<td>In- and outpatients</td>
<td>92</td>
<td>&gt;1 w - 3.5 yr</td>
<td>HRSD/BDI</td>
<td>RH&gt;LH</td>
</tr>
<tr>
<td>House et al.142</td>
<td>1990</td>
<td>Community sample</td>
<td>73</td>
<td>1 m</td>
<td>DSM III (major depr)</td>
<td>LH=RH</td>
</tr>
<tr>
<td>Morris et al.110</td>
<td>1990</td>
<td>Inpatients</td>
<td>99</td>
<td>2 - 5 m</td>
<td>DSM III (major depr)</td>
<td>LH=RH</td>
</tr>
<tr>
<td>Sharpe et al.125</td>
<td>1990</td>
<td>Community sample</td>
<td>60</td>
<td>3 - 5 yr</td>
<td>DSM III (major depr)</td>
<td>LH=RH</td>
</tr>
</tbody>
</table>

For abbreviations of rating scales/criteria, see under Table 1.

At the biochemical level, and based on experimental studies in rats, Robinson et al. have hypothesized that stroke-induced damage to catecholaminergic pathways may be an important aetiologic factor in the development of poststroke depression.149,150 In line with this hypothesis, Lipsey et al.151 designed a double-blind placebo-controlled trial of tricyclic antidepressant in patients with poststroke depression, and found it as effective as in ‘functional’ depression. They concluded that successful treatment resulted from modulation of neurotransmitter system which may be disrupted by focal brain injury.

Another line of evidence concerning lateralization of affect, links lesion in the right hemisphere with disturbed processing of emotionally important material.152,153 Ross and Rush154 have suggested that ‘aprosodiasis’ (i.e. disorder of affective
language), may prevent patients with right hemisphere lesions from recognizing symptoms of depression. Thus, the case for depression after a stroke being associated with left hemisphere lesion is far from proved, and different theories of underlying intra- and interhemispheric mechanisms have been proposed to explain the diverging results.154-156

It has been shown that elderly who have chronic health problems or have recently been ill have higher rates of depression than the general elderly population.157 Thus, a question of importance is if stroke is associated with a higher rate of depression than are other medical illnesses in the elderly. Three studies113,114,158 used ‘equally disabled’ (orthopedic) patients as controls, and two113,114 found a significantly higher rate of depression in stroke patients, whilst one study158 did not. The last study, however, was a cross-sectional analysis of chronically institutionalized patients (up to 5 years post-stroke). A further study showed depression to be more common among stroke patients than among patients with myocardial infarctions.159

The contribution of physical and cognitive impairments as well as psychosocial factors to depression after stroke is less well known and probably changes over time.160,161 As most studies do not have the time factor under control (see Table 1), these conditions have not been clarified. There is evidence that depression after stroke seriously delays functional recovery,162,163 and adversely affects resumption of social activities.56

Aspects of treatment and course. Few systematic treatment evaluations have been performed. The double-blind placebo-controlled trial by Lipsey et al.151 (see above, p.10) has shown that depression after stroke can be successfully treated with the antidepressant nortriptyline in those completing the trial. It has to be pointed out that one third of the patients dropped out of the study because of adverse side-effects of the drug, emphasizing the need for cautious treatment with antidepressants in elderly stroke patients, who often present numerous medical problems.164 However, in those who completed the trial, nortriptyline improved all measures of depression.165 Reding et al.166 showed that treatment with trazodone gave significant improvement in ADL, but only those with pathological dexamethasone suppression test improved. The authors emphasized that antidepressants may enhance the rehabilitation outcome.

Electroconvulsive therapy has been reported as both safe and effective in treatment of poststroke depression.167,168 Other studies have highlighted the need for counselling and psychosocial interventions,60,169,170 Cognitive psychotherapy has been modified for treatment of patients with poststroke depression.171 However, there is need of a systematic evaluation of treatment studies. In general, there is evidence that post-stroke depression does not receive ample recognition and treatment.

In the two-year follow-up study by Robinson et al.,172 all patients with major depression in hospital had recovered by two years, whereas those with ‘minor de-
pression' (cf p. 17) remained depressed. From a follow-up of a community sample, House et al.\textsuperscript{106} reported that one year after a stroke most of the psychiatric morbidity had been resolved. Two further studies\textsuperscript{110,121} have presented data on course and prognosis of depressive disorder after stroke, but the results are conflicting.

**THE CORTISOL AXIS IN RELATION TO STROKE AND DEPRESSION**

**An overview**

More than half a century ago, Cannon\textsuperscript{173} published his now classic work 'Wisdom of the Body', in which the adrenal glands were found to be involved in the organism's response to stress. During the following decades, the sensitivity of the hypothalamic-pituitary-adrenal (HPA) axis to a variety of physical as well as psychological stress was documented. Among others, Sachar et al.\textsuperscript{174} presented dysregulation of plasma cortisol and ACTH in depressive illness. The most utilized measure of HPA abnormality is the dexamethasone suppression test (DST); since the 1950's used as a diagnostic tool for Cushing's syndrome. In 1981, Carroll et al.\textsuperscript{175} presented data on DST as a specific test for the diagnosis of melancholia, which caused a great amount of research in this area. Several reviews of this extensive literature have been published (e.g.\textsuperscript{176-179}).

Nonsuppression of cortisol levels after dexamethasone (DEX) administration is an example of failure of the hypothalamus to inhibit the corticotrophic releasing factor (CRF) secretion and the pituitary to shut down ACTH release in response to rising corticoid levels, i.e. normal negative feedback control.\textsuperscript{180} The mechanisms of the hypercortisolemia and resistance to dexamethasone suppression found in depressive disorder are still poorly understood.\textsuperscript{178}

For evaluation of the depressed patient, DST was standardized by Carroll et al.\textsuperscript{175} According to their review of over 5100 cases with major depression, Arana et al.\textsuperscript{176} reported that 44% of patients with major depression failed to suppress plasma cortisol levels the next day after intake of 1mg of dexamethasone the prior evening. More severe depressive symptomatology, as judged by melancholic and psychotic symptoms, increased the sensitivity to 50% and 67%, respectively. As regards the specificity, cortisol 'escape' from dexamethasone-induced suppression has been shown to occur also in dementia, schizoaffective disorder, alcoholism and many other psychiatric disorders, as well as in Cushing's disease, many acute medical illnesses and recent hospitalization, drug withdrawal, weight loss etc.\textsuperscript{176} (for general accepted medical and pharmacological exclusion criteria, see \textsuperscript{176}). In a more recent review, Arana et al.\textsuperscript{181} concludes that the DST is not specific enough as to be of diagnostic value in psychiatry but eventually may help to confirm the existence of potentially treatable depression in other conditions, such as in stroke patients.
The cortisol axis and depression after stroke

Stroke patients are exposed to a severe stress situation. Previous studies in stroke patients have documented increased activity of the HPA axis,\textsuperscript{78,186,187} associated with an increased mortality\textsuperscript{186} and also with cognitive disturbances.\textsuperscript{78,182,188}

**TABLE 3. Studies of dexamethasone suppression test (DST) in stroke patients.**

<table>
<thead>
<tr>
<th>Authors</th>
<th>Year</th>
<th>Patient Sample</th>
<th>n</th>
<th>Time since stroke</th>
<th>Depression measure/ criteria</th>
<th>DST</th>
</tr>
</thead>
<tbody>
<tr>
<td>Finklestein et al.\textsuperscript{114}</td>
<td>1982</td>
<td>Rehab unit</td>
<td>25</td>
<td>11 - 111 d</td>
<td>HRSD (modified)</td>
<td>52</td>
</tr>
<tr>
<td>Bauer et al.\textsuperscript{109}</td>
<td>1983</td>
<td>Inpatients</td>
<td>20</td>
<td>16 - 74 d</td>
<td>HRSD/Zung</td>
<td>15</td>
</tr>
<tr>
<td>Lipsey et al.\textsuperscript{182}</td>
<td>1985</td>
<td>In- and outpatients</td>
<td>48</td>
<td>&lt;1 yr</td>
<td>HRSD/Zung/PSE/DSM III</td>
<td>42</td>
</tr>
<tr>
<td>Reding et al.\textsuperscript{112}</td>
<td>1985</td>
<td>Inpatients</td>
<td>78</td>
<td>Mean 7 w (range ?)</td>
<td>HRSD/Zung/DSM III</td>
<td>49</td>
</tr>
<tr>
<td>Agarwal et al.\textsuperscript{188}</td>
<td>1987</td>
<td>Inpatients</td>
<td>31</td>
<td>&gt;3 w - ?</td>
<td>4-point scale\textsuperscript{†}</td>
<td>26</td>
</tr>
<tr>
<td>Malec et al.\textsuperscript{183}</td>
<td>1990</td>
<td>Rehab unit</td>
<td>20</td>
<td>8 - 30 d</td>
<td>HRSD/RDC</td>
<td>100</td>
</tr>
<tr>
<td>Dam et al.\textsuperscript{184}</td>
<td>1991</td>
<td>In- and outpatients</td>
<td>65</td>
<td>&gt;1 w - 3.5 yr</td>
<td>RDC</td>
<td>5</td>
</tr>
<tr>
<td>Grober et al.\textsuperscript{185}</td>
<td>1991</td>
<td>Outpatients</td>
<td>29</td>
<td>Mean 2 yr (range ?)</td>
<td>HRSD/DSM III</td>
<td>21</td>
</tr>
</tbody>
</table>

* Nonsuppr = Nonsuppressors (proportion of total number of patients included in the study). Criterion for nonsuppression: serum cortisol >138 nmol/l at 8 AM or 4 PM after 1 mg dexamethasone given at 11 PM the night before.  
\textsuperscript{†} Based on a clinical interview; the scale not established.  
DSM III = Diagnostic and Statistical Manual of Mental Disorders\textsuperscript{14}  
HRSD = Hamilton Rating Scale for Depression\textsuperscript{129}  
PSE = Present State Examination\textsuperscript{132}  
RDC = Research Diagnostic Criteria\textsuperscript{133}  
Zung = Zung Depression Scale\textsuperscript{137}
Consistent evidence regarding the association of pathological DST (nonsuppression) with level of impairment, lesion volume and lesion location has not been found. In one study\textsuperscript{188} the frequency of nonsuppression was higher in patients with left hemisphere lesion, whilst one study\textsuperscript{184} reported a higher rate in right hemispheric stroke. The majority of studies did not find any interhemispheric difference in rate of nonsuppression. No extended longitudinal studies have been reported.

Common sequelae of stroke, such as confusion and aphasia, complicate the diagnosis of depression. Most studies of DST have excluded these patient groups, for whom a 'biological marker' of depression would have been of great value.

Some\textsuperscript{112,114,182,188} but not all\textsuperscript{183-185} research groups have reported an association between nonsuppression to dexamethasone and poststroke depression. As illustrated in Table 3, the specificity and the sensitivity of the dexamethasone test for diagnosing depression in stroke patients have been reported as highly variable.\textsuperscript{112,114,182,188} One reason is the problem of varying case definitions as regards depression, i.e. Dam et al.\textsuperscript{184} included both major and minor depression (RDC) in their category of depression, and Grober et al.\textsuperscript{185} combined major depression and dysthymia in their analysis.

Furthermore, the dexamethasone test obviously has been performed at different time-points after the stroke event. The inclusion time has varied from one week to more than three years within the same study.\textsuperscript{184} In other studies the inclusion time has been stated as 'more than three weeks after onset'\textsuperscript{188} without giving the range, or 'less than one year after onset'.\textsuperscript{182} This may have influenced the test results, as the HPA axis may theoretically be influenced by a number of different factors - both internal and external - which may vary depending on the time elapsed since stroke.

**CONCLUDING INTRODUCTORY REMARKS**

This review of the literature has demonstrated the need for a longitudinal study of depressive disorder in a well-defined sample of acute stroke patients carefully followed up regarding associations with factors from both biological and psychosocial levels. Comparisons with a general elderly population and with conditions prior to the stroke are required to make meaningful interpretations.
AIMS OF THE STUDY

1. To describe, in a well-defined sample of stroke patients, living conditions (including demographic characteristics, economic resources, health, functional ability, activity/leisure, social network) and life satisfaction before and early after a stroke in relation to a general elderly population.

2. To examine in a prospective study of long-term survivors of stroke
   (a) changes over time as regards living conditions and life satisfaction
   (b) identify factors associated with poor life satisfaction late after a stroke.

3. To (a) determine the prevalence of major depression during the immediate poststroke period, and after 3 months, 1 year, 2 and 3 years, respectively
   (b) identify neurobiological, functional and psychosocial factors related to major depression at the various time-points, and examine their relative importance over time, and
   (c) examine the longitudinal course of major depression after a stroke.

4. To investigate the suppressibility of the cortisol axis early after a stroke in relation to the brain lesion itself, major depression, cognitive and functional impairment.

5. To (a) investigate the suppressibility of the cortisol axis and its clinical determinants at various time-points after a stroke
   (b) evaluate the utility of the dexamethsone suppression test in the diagnosis of major depression in stroke patients early and late after a stroke.
SUBJECTS

Description of the stroke unit at the Department of Medicine, Umeå University Hospital

Admission criteria to the stroke unit were: patients from the catchment area of Umeå University Hospital, regardless of age, who without preceding trauma to the head, presented with focal neurological deficits of a duration not exceeding one week or patients with TIA during the last week. Patients with symptoms of cerebral dysfunction without focal neurological signs were not admitted to the unit, nor were patients with subarachnoid haemorrhage (referred to the department of Neurosurgery).

The patients were admitted directly from the emergency room to the stroke unit, which was a 6-bed, non-intensive care and research unit for patients who met the admission criteria. It has been described in detail in previous publications. At the time of the study (January 1984-January 1987), Umeå University Hospital had a catchment population of 116,000 and was the only hospital in the district which treated patients with acute stroke. The mode of patient allocation has been shown to provide a representative sample of all patients admitted for acute stroke in the hospital catchment area.

FIGURE 1. A map of Sweden showing Umeå and the catchment area of the University Hospital.
The patient group

During one year 98 patients were admitted to the stroke unit, 16 died shortly after admission. The majority of those who died had impaired consciousness upon admission. One patient was excluded due to congenital mental handicap and one refused to participate. The remaining 80 patients are the subject of this study. Mean age was 73 years (range 44-100); 49 were males (mean age 72 years) and 31 females (mean age 75 years). The majority (80%) suffered from their first stroke.

The criteria for subtypes of stroke used in the stroke unit were as follows: (1) intracerebral haemorrhage = signs of intracerebral hematoma on CT scan, or haemorrhagic pattern in spinal fluid analysis, (2) cerebral infarction = neurological deficits persisting more than 24 hours or until death with no signs of bleeding on CT scan, or haemorrhagic pattern in spinal fluid analysis, (3) transient ischemic attack (TIA) = focal neurological deficit of presumed ischemic origin and of less than 24-h duration. The stroke diagnoses were: cerebral infarction 79%, intracerebral haemorrhage 5% and TIA 16%. CT-scan of the brain was performed in all patients; in 51 patients (64%) recent lesions were visualized. Based on clinical and CT-evaluation 32 patients (40%) were judged to have a right hemisphere lesion, 38 (48%) a left hemisphere lesion and 10 (12%) a brainstem/cerebellum or undefined lesion.

After three months, 3 patients had died. One patient refused to participate; all others were seen (n=76). After one year, another 3 patients had died. Two patients were excluded due to recurrent stroke. One patient refused to participate; all others were seen (n=70). After two years, 11 more patients had died. All survivors were seen except 1 patient who had moved out of the region (n=58). At the 3-year follow-up, another 4 patients had died. Two patients had a recurrent stroke and were excluded. Two patients refused to participate, one partly refused (excluded in paper III). All other survivors were seen (n=50).

Paper I - III

The original study group of 80 patients included at the acute stage after stroke are subject of paper I and III. In paper I they are followed up at 3 months (n=76); in paper III also at 1 year (n=70), at 2 years (n=58), and at 3 years (n=49).

Paper II is restricted to the 50 long-term survivors at 3 years after the stroke, who are prospectively followed up. The cohort included in the study did not differ significantly from the original consecutive sample of 98 stroke patients, except in having less severe symptoms at onset of stroke.

The general population data are based on two national sample surveys in Sweden; ULF189 (‘the Survey of Living Conditions’. Subjects from the four northern-most counties of Sweden were selected; n=294) and LNU190 (‘the Level of Living Survey’).
This survey is smaller and data from the entire national sample of elderly people was used; n=828).

The mean age for the ULF sample was 73 years (range 65-84), and for the LNU sample 70 years (range 65-76). As there were more men than women in the stroke group and the national samples had equal numbers of both sexes, the reference group data have been weighted (male: female = 1.6:1). Thus, the national samples are comparable with the stroke patients concerning both age and sex.

**Paper IV**

From the original 80 patients (I and III) and from patients admitted to the stroke unit during the following two months, those with supratentorial ischemic stroke localized to the carotid territory, were considered for study. Exclusion criteria were: pronounced decrease in consciousness, i.e. more than drowsiness, high fever (>38.5 C), renal failure (plasma creatinine level >200 \( \mu \text{mol/l} \)), known extensive weight loss and/or malnutrition, hypo-/hyperthyroidism, pituitary insufficiency, uncontrolled diabetes mellitus, obvious abstinence reactions from alcohol and/or other central nervous stimulants, epilepsy and certain medications (glucocorticoids, estrogens, anticonvulsants, high-dose benzodiazepines, ephedrine). Included were 62 patients (37 men and 25 women), with a mean±SD age of 74.6±9.4 years.

The first control group consisted of 25 patients (13 women and 12 men; mean±SD age 76.8±8.4 years) acutely admitted to the hospital because of various acute medical disorders. None had known central nervous disease including previous stroke or epilepsy. The same exclusion criteria as for the stroke patients were applied regarding renal function, medications, etc.

The second control group was selected from the official population census register of the Umeå city population. Thirty-three randomly selected 80-year-old people were included.\(^{191}\) Twenty were men and 13 women. The same exclusion criteria (except for hospitalization) as for the first control group were used.

**Paper V**

The same patients as in paper I and III (n=80) were considered for study. In 8 patients the dexamethasone test was not made or laboratory data were incomplete. Exclusion criteria were the same as in paper IV. One patient was excluded due to a plasma creatinine level >200 \( \mu \text{mol/l} \) and one due to obesity (body mass index >30). Thus, 70 patients were included in this study. There were 44 men and 26 women with a mean±SD age of 73±11 years. Of these patients, 57 had an ischemic stroke, 3 had a cerebral hemorrhage and 10 had a transitory ischemic attack.
Controls were healthy volunteers who underwent a physical as well as a neuropsychiatric examination (including CT scan). All were hospitalized during the investigations. There were 8 men and 9 women with a mean±SD age of 68±5 years.

**METHODS**

**Clinical investigations at the stroke unit**

All patients admitted to the stroke unit were followed by a standardized clinical investigation; including repeated physical/neurological examinations, laboratory tests, CT scan of the brain, and spinal fluid analysis.

The extent of paresis (i.e. the extremity most afflicted) was quantified using a four-point scale. Activity of daily living (ADL) in the patient group was recorded according to Katz et al. The paresis scale correlated strongly with scores on Katz's scale of ADL-dependence (r=0.70, p<0.001). A three-point scale for disorientation was used.

**Computed tomography (CT) scan of the brain**

The CT scans were analyzed by the same neuroradiologist who was blind to the clinical assessments. The following structural brain measurements were made: brain volume was expressed as the volume of brain substance on three consecutive slices beginning with the first slice passing through the lateral ventricles. Lesion volume was measured by a computerized calculation procedure, summing the lesion volumes in each slice where the lesion was visible. The lesion volume was divided by the overall brain volume giving a relative lesion volume. The distance of the lesion from the frontal pole was determined by measuring the minimum distance of the anterior border of the lesion to the frontal pole. By dividing this distance by the overall anterior-posterior length of the cerebral hemisphere in the same slice, the relative lesion distance was determined. According to criteria described by Starkstein et al. lesions were classified as 'anterior' if their A-P position was less than 40%, otherwise they were classified as 'posterior' (Paper III). The lesions were classified as cortical and/or deep. The cortical lesions were further classified with regard to the lobes involved. The amount of oedema surrounding the lesion was quantified using a four-point scale. Anterior horn index was defined as the maximum distance between the tips of the anterior horns divided by the maximum transverse inner diameter of the skull. Cortical brain atrophy was estimated by using a three-point scale according to principles previously used at our x-ray department, in Paper III cortical brain atrophy was dichotomized as evident or not. Old lesions visible were dichotomized into yes/no for each patient.
Assessment of living conditions and life satisfaction

A structured interview form was constructed on living conditions and life satisfaction with questions to the patients selected from ULF\textsuperscript{189} and LNU\textsuperscript{190} (cf p.25). ULF contains objective aspects of the living conditions whereas LNU also contains a few subjective aspects, in order to give knowledge of how life is perceived by the individual. By using a sample of indicators (questions) from these surveys we could compare our stroke patients with the national samples. Domains considered were: housing conditions, economic resources, health (experience of both physical and mental health), functional ability (both primary and secondary ADL), activity/leisure, social network, and global life satisfaction. Where appropriate, informants' accounts were used to supplement patient interviews regarding living conditions.

Psychiatric examination

The psychiatric interviews were conducted by the same psychiatrist without knowledge of the radiological/neurological assessments. The diagnosis of a major depression was made on the basis of DSM-III symptom criteria\textsuperscript{14} with the physical disorder (i.e. stroke) on axis III. Patients were interviewed 4-5 days after admission, at 10 days and at discharge, as a control for stability of symptoms (to respect DSM-III time criterion). Thus, a major depressive syndrome was diagnosed according to criteria A and B in DSM-III.\textsuperscript{14} (For further elucidation of diagnostic problems, see Paper III and the Discussion section below). Where appropriate, informants' accounts and information from the staff were used to supplement patient interviews. Cognitive ability at three years was screened by the Mini-Mental State Examination.\textsuperscript{196}

Dexamethasone suppression test (DST)

The patients were investigated on the fourth day after admission (in all cases between the third and seventh day). Blood was drawn at 7 a.m. after an over-night fast for the analysis of plasma cortisol. They were given 1 mg of dexamethasone (DEX) orally (Decadron\textsuperscript{®}, Merck Sharp \& Dohme International, Rahway, N.J., USA) at 11 p.m. the same day. Blood was drawn on the following day at 7 a.m., 4 p.m. and 11 p.m. for serum cortisol analyses. A postDEX cortisol level $\geq 138$ nmol/l at 4 p.m. was considered to indicate nonsuppression.\textsuperscript{175} The same procedure was undertaken for the control group of patients with acute medical disorders and for the hospitalized group of healthy elderly volunteers. In subjects who were not hospitalized, 1 mg of dexamethasone was taken 10-11 p.m. and blood was drawn for serum cortisol analyses at 3-4 p.m. the following day (Paper V).

Cortisol was analysed with a radioimmunoassay kit from Farmos Diagnostica, Turku, Finland. The interassay coefficient of variation for the analysis was below 10%.
Time-points for assessments

In Figure 2, the time-points for the different assessments are shown. Interviews on living conditions, life satisfaction and ADL before the stroke were performed 4-10 days after admission. As shown, psychiatric examinations (i.e. diagnosis of major depression) were undertaken three times in hospital, and were - together with assessments of living conditions/life satisfaction and ADL - repeated after three months, one year, two years, and three years. CT scan of the brain was performed on admission and after three years. DST was performed in-hospital, after three months, and after three years.

<table>
<thead>
<tr>
<th>Day 1</th>
<th>4</th>
<th>10</th>
<th>Discharge</th>
<th>90</th>
<th>Year 1</th>
<th>2</th>
<th>3</th>
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<td>Physical/neurological examination</td>
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<td>CT scan of the brain</td>
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<tr>
<td>Activities of daily living (ADL)</td>
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<td>Dexamethasone suppression test</td>
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<tr>
<td>Psychiatric interview (DSM-III; major depression)</td>
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<td>Assessment of living conditions/life satisfaction</td>
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<td>(prestroke)</td>
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<tr>
<td>Mini Mental State Examination</td>
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FIGURE 2. Time-points for the different assessments during the 3-year follow-up period.

Statistics

All analyses were made in a computerized statistical program, SYSTAT®. For comparisons between the national samples and the study group, 95%-confidence intervals were calculated. Significant differences between the national sample and the study group are reported as p<0.05, and NS denotes p>0.05. For categorical data, chi-square were used as follows. For two-way square tables, in which data represent paired comparisons, McNemar's symmetry chi-square test was used; otherwise Pearson chi-square or, when appropriate, Fisher's exact test was used. In the case of continuous measures, comparisons between groups were made by means of the Student's t-test. All tests were two-tailed.
Cortisol level distributions in paper IV have been described by the median levels (m) and 10th and 90th percentiles. A post-hoc contrast analysis was utilized to test mean differences between the stroke patients and control groups.

In paper V, statistical calculations of mean differences between the stroke patients and the control group, adjusted by age and gender, were performed as a multi-way analysis of variance (MANOVA) and by analysis of covariance. Odds ratios with their 95% confidence intervals were calculated as described by Miettinen.198

Pearson correlation coefficients were used for the calculation of correlations; in paper I Bonferroni adjustment of p-values was used. The factor analyses in papers III and IV, were performed using the principle component analysis model in SYSTAT® with varimax rotation of the factors, which then were used in the multiple regression analyses and discriminant function analyses. Analyses were performed with the use of dummy variables (0/1 corresponding to no/yes) when necessary. Two-tailed t-tests were used for test of the regression coefficients of each independent variable against the dependent variable. A p-value of <0.05 was chosen as the level of statistical significance.

RESULTS

Paper I. Living conditions and life satisfaction before and early after a stroke in relation to a general elderly population.

Demographic characteristics and economic resources did not differ between the study group before the stroke and the general elderly population. Thus, 51% of the stroke patients were married, 13% single/divorced, and 36% widowed. The majority lived at home (91%) while 9% lived in homes for the aged. Among health problems, stroke patients already prior to their stroke had a significantly higher frequency of heart complaints, hypertension and diabetes (p<0.05), whereas the frequency of psychiatric symptoms (sleeping problems, general tiredness, nervousness/anxiety, sadness) did not differ from the general elderly population. In primary ADL (self-care) - such as dressing and personal hygiene - independence prestroke was the same as in the national sample. By the criteria of Katz et al.,192 88% of the patients were ADL independent before stroke. In secondary (instrumental) ADL - such as shopping, cooking, cleaning, etc - stroke patients already had a significantly lower ability prior to the stroke (p<0.05).

The social network before a stroke, did not differ significantly from that of the national sample. Global life satisfaction was already significantly reduced before the stroke (Table 4). Poor life satisfaction prior to the stroke was associated with ADL dependence (p<0.01).
TABLE 4. Global life satisfaction (percentages).

<table>
<thead>
<tr>
<th>National sample</th>
<th>Study group</th>
<th>3m after stroke</th>
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<tbody>
<tr>
<td>LNU (n=828)</td>
<td>Before stroke (n=77)*</td>
<td>(n=73)</td>
</tr>
<tr>
<td></td>
<td>23</td>
<td>6</td>
</tr>
<tr>
<td>Good</td>
<td>93</td>
<td>71a</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>23a</td>
</tr>
<tr>
<td>Fair</td>
<td>5</td>
<td>23a</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Bad</td>
<td>2</td>
<td>6</td>
</tr>
</tbody>
</table>

We have asked you many questions about various aspects of your living conditions; seen globally, do you think life is Good 93 71a 25b, c Fair 5 23a 3 lb, c Bad 2 6 44b, c

Looking back on the last 5-6 years, do you think your living conditions have changed for the Better 23 1a 1b Unchanged 58 50 13b, c Worse 19 49a 86b, c

Seen globally, do you think life after stroke have changed for the Better - - 0 Unchanged - - 23 Worse - - 77

* Three patients were not assessable due to severe comprehension deficits.

a p<0.05; significant difference national sample vs prestroke group
b p<0.05; significant difference national sample vs poststroke group
c p<0.05; significant difference pre- vs poststroke group

At the 3 month follow-up, the frequency of psychiatric symptoms was conspicuous. General tiredness, sleeping problems, nervousness/anxiety and sadness were significantly more frequent than in the national sample and prestroke (p<0.001). Major depression was present in 32% of the patients (analyzed in paper III). Activity/leisure and functional ability had declined further at 3 months, and differed significantly on almost all indicators compared with both the national sample and prestroke conditions. Also, the social networks had deteriorated; patients early after stroke met their children with the same frequency, but they met other relatives and friends significantly less (p<0.05). Almost half of the patients reported low life satisfaction, compared to only two percent in the national sample (Table 4). ADL dependence and major depression were associated with low life satisfaction at 3 months of follow-up.

**Paper II. Living conditions and life satisfaction in long-term stroke survivors; factors associated with changes over time.**

Prestroke psychiatric symptoms in the long-term survivors (sleeping problems, general tiredness, nervousness/anxiety, sadness) were in accordance with the cross-
sectional study (paper I) and did not differ from the general elderly population. After the stroke there was a significant increase (p<0.05) in the proportion who reported these symptoms. Three years after the stroke, the frequency of anxiety/nervousness and sadness were still significantly higher than before the stroke and also significantly higher than in the general elderly population (p<0.05).

A major depressive syndrome was found in 25% of the patients at discharge from the stroke unit but decreased significantly (p=0.01) up to one year (12%), thereafter occurring more often, so that at three years after the stroke 25% of the long-term survivors were depressed (Figure 3).

![Figure 3](image-url)

**FIGURE 3. Prevalence (per cent) of major depression, ADL dependence, and disorientation in long-term survivors of stroke (n=50).** P, prestroke; D, at discharge; A, at 3 months; 1, 2, and 3, at 1, 2, and 3 years of follow-up.

Figure 3 illustrates primary ADL. Also secondary ADL showed the corresponding development over time; a significant decreased ability after a stroke with only little change (NS) occurring over the rest of the 3-year follow-up period. Activity/leisure and social contacts likewise decreased significantly after a stroke, but were partly resumed up to one year later. The proportion of patients who had contacts with friends and relatives other than their spouse or children was significantly reduced at 3 months (p<0.05), whereas the ties with children seemed to remain quantitatively unchanged. At the one year follow-up stage, social contacts with friends were partly improved (NS)
with essentially no further change over time, so that three years after the stroke fewer patients still had contact with people other than their children (p<0.05).

Stroke involved a very marked reduction in global life satisfaction, being lowest at three months after the stroke, when only 33% reported their life as being 'good' (Figure 4). This proportion increased significantly to 53% at one year (p=0.01), thereafter it was essentially unchanged and significantly lower than in the general elderly population. Poor life satisfaction at one year remained poor for the entire three years. Stroke victims with permanently reduced life satisfaction were older, felt more tired and anxious, were dependent on others in secondary ADL, spent a passive leisure-time, had fewer social contacts, and early after their stroke, had a higher frequency of major depression.

![Stroke patients and gen. pop. life satisfaction graph](image)

**FIGURE 4** Global life satisfaction in a national sample of elderly (Gen. pop., n=828) and in long-term survivors of stroke (n=50). P, pre-stroke; A, at 3 months; 1, 2, and 3; at 1, 2 and 3 years of follow-up.

**Paper III. Prevalence of major depression; its neurobiological, functional and psychosocial predictors at different time-points after the stroke, and its longitudinal course.**

For description of the patients, see paper I. The prevalence of major depression was 25% at the acute stage, approximately the same at three months (31%), decreased significantly to 16% at one year (p<0.01), was 19% at 2 years and increased to 29% at 3 years (Figure 5).
FIGURE 5. Prevalence (percent) of major depression in stroke patients at different follow-up periods.

FIGURE 6. Prevalence (percent) of major depression in patients with left hemispheric (LH) and right hemispheric (RH) lesions at different follow-up periods after stroke.
Figure 5 illustrates that significantly more patients with left-sided (LH) than right-sided (RH) hemispheric lesions were depressed at the acute stage after stroke (p<0.001). This difference between right and left hemisphere diminished at 3 months and was not significant later in the course. Patients with anterior LH lesions were significantly more often depressed at the acute stage than patients with posterior LH lesions (p<0.05). In the right hemisphere no intrahemispheric association was found. At the acute stage, also patients with dysphasia and patients who lived alone prior to their stroke had a significantly higher rate of major depression (p<0.001 and p<0.05, respectively). In Table 5, associated variables at different follow-up periods after a stroke are shown.

TABLE 5. Cross-sectional analyses of variables significantly differing between depressed and nondepressed patients at different follow-up periods after a stroke.*

<table>
<thead>
<tr>
<th></th>
<th>Acute (n=76)</th>
<th>3 months (n=73)</th>
<th>1 year (n=68)</th>
<th>2 years (n=57)</th>
<th>3 years (n=49)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left hemispheric lesion</td>
<td>Few social contacts</td>
<td>Few social contacts</td>
<td>Few social contacts</td>
<td>Few social contacts</td>
<td></td>
</tr>
<tr>
<td>'Anterior lesion'</td>
<td>Dependence in activities of daily living</td>
<td></td>
<td></td>
<td>Cortical atrophy†</td>
<td></td>
</tr>
<tr>
<td>Dysphasia</td>
<td>Dysphasia</td>
<td></td>
<td></td>
<td>Subcortical atrophy†</td>
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<tr>
<td>'Living alone'</td>
<td></td>
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</tbody>
</table>

* Fisher exact test (df=1) except for subcortical atrophy (t-test); p<0.05
† The CT scan was performed 3 years after the index stroke

Discriminant function analyses confirmed the cross-sectional results above - namely - that the most important predictors of immediate major depression were left anterior brain lesion, dysphasia, and living alone. Dependence in activities of daily living (ADL) was the most important predictor at 3 months. From 12 months onwards, 'few social contacts outside the immediate family' contributed most to depression, whilst at 3 years cerebral atrophy contributed as well.

At one year, 60% of the patients with early depression (0-3 months) had recovered. Those not recovered at this follow-up stage had a high risk of a chronic development of depression (only one more patient recovered between 1 and 3 years).
Paper IV. *The suppressibility of the cortisol axis early after a stroke in relation to the brain lesion itself, major depression, disorientation and disability.*

Stroke patients had significantly higher morning cortisol levels after dexamethasone (DEX) than the healthy elderly controls (p<0.001) and also higher than the control patients (other acute medical disorders), but this difference was not significant (p=0.08).

In a multiple regression analysis, disorientation and right-sided lesion location were significantly associated with high cortisol levels after DEX (p<0.05 and p<0.01, respectively) whilst lowered consciousness, limb paresis and major depression were not. Also when the nonsuppression criteria were used, major depression was not associated with nonsuppression early after a stroke.

The CT variables for the stroke patients with visible fresh brain lesions were analyzed in the same way. High cortisol levels after DEX were associated with proximity of the lesion to the frontal pole of the brain and also to lower brain volumes (p<0.01 and p<0.05, respectively). No association with side of lesion could be verified. A corresponding analysis based on involvement of the various brain regions showed that frontal lobe involvement was associated with higher postDEX cortisol levels (p=0.05), whereas involvement of deep structures and the occipital lobe tended to show associations with lower levels (p=0.05 and 0.09, respectively).

Paper V. *The suppressibility of the cortisol axis and its clinical determinants over time; the utility of the dexamethasone suppression test in the diagnosis of major depression in stroke patients early and late after a stroke.*

Early after a stroke, 24% of the patients were nonsuppressors with about the same proportion at 3 months (22%) and 3 years (21%). None of the controls (17 healthy elderly volunteers) was a nonsuppressor. The number of patients with major depression being nonsuppressors at different time-points is shown in Table 6.

<table>
<thead>
<tr>
<th>Acute (n=66)</th>
<th>3 months (n=60)</th>
<th>3 years (n=42)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Nonsuppr</td>
<td>Suppr</td>
</tr>
<tr>
<td>Depressed</td>
<td>5 (26)</td>
<td>14 (74)</td>
</tr>
<tr>
<td>Nondepressed</td>
<td>9 (19)</td>
<td>38 (81)</td>
</tr>
</tbody>
</table>

Values in parentheses are percent. Criterion for non-suppression = serum cortisol >138 nmol/l at 4 pm after 1 mg of dexamethasone at 11 pm the evening before. n, Number of patients.
The postDEX cortisol levels for patients with and without major depression at 3 years are shown in Figure 7.

![Figure 7](image)

**FIGURE 7.** Scatter plot of serum cortisol concentrations at 4 pm after 1 mg of dexamethasone at 11 pm the evening before in depressed (n=10) and non-depressed (n=32) patients 3 years after stroke. Broken line indicates serum cortisol level of 138 nmol/l.

High cortisol levels at the acute stage after stroke were significantly associated with functional impairment and disorientation (p<0.05). Three months later, these associations were not significant, whilst at three years poststroke, high postdexamethasone cortisol levels were significantly associated with major depression (r=0.57; p<0.001). At three years, using the conventional cut-off criterion of 138 nmol/l, the DST had a sensitivity of 70%, a specificity 97%, a positive predictive value of a positive test of 88%, a negative predictive value of 91%, and a diagnostic accuracy of 90%.

Restricting the analyses to long-term survivors, nonsuppression at three months was a statistically significant predictor of major depression at three years with an odds ratio of 14 (95% confidence interval 2.7-76.5).

In multiple regression analyses neither disorientation, functional ability nor major depression were significant predictors of postDEX levels early after a stroke (0-3 months). Three years after a stroke, major depression was a significant predictor of postDEX cortisol values (p<0.001). When the nonsuppression criterion was used, a discriminant function analysis gave the same results, i.e. major depression was the main predictor for nonsuppression at three years.
DISCUSSION

In this thesis, a consecutive sample of stroke patients was followed up at regular time-points after a stroke. The method for patient selection ascertained a representative sample of patients admitted to hospital for stroke. The problem of spurious associations in studies of hospital in-patients may be less in the Scandinavian countries than elsewhere, as more than 90% of stroke patients (excluding TIA) are admitted to hospital. We have avoided sampling bias by studying a consecutive series of patients during one year. This population-based cohort was almost completely followed up at the different time intervals up to three years. Thus, our study group should permit the results to be generalized to other stroke patients.

The sample of stroke patients was described as regards living conditions (including demographic characteristics, economic resources, health, functional ability, activity/leisure, social network) and global life satisfaction before and early after a stroke in relation to general elderly population data which were based on two national sample surveys in Sweden; ULF and LNU (cf p. 25 and p. 28). After weighting for different sex ratios, the national samples could be regarded as comparable with the sample of stroke patients concerning both age and gender. The ULF-sample was large enough to permit a local reference group of elderly people from northern Sweden; the purpose was to minimize the bias from metropolitan areas concerning aspects of living conditions, opportunities for leisure activities etc.

Demographic characteristics, economic resources, primary ADL ability and social network before the stroke, did not differ significantly from that of the national sample (paper I). In secondary ADL, stroke patients had significantly lower ability prior to the stroke, and approximately half needed weekly help at home; a rate which is more than twice as high as that in the general elderly population. Patients reported that health problems (mainly heart disease) had restricted many of their activities even before experiencing a stroke. Thus, not all impairments and disabilities present after a stroke can be linked to the stroke itself. Important for our interpretation of later psychiatric symptomatology, was the finding that psychiatric morbidity prior to the stroke did not differ from that of the general population. Satisfaction with life as a whole was already reduced prestroke. When asked to look back over the past 5-6 years, half of the patients reported that life before stroke had already changed significantly for the worse. This cannot be explained by increasing age, as only one fifth in the national sample reported that life had changed for the worse during these five years. The association between age and life satisfaction has been studied with diverging results, e.g. Bradburn found higher life satisfaction in younger individuals, others reported no age differences or higher satisfaction in the elderly due to narrowed discrepancies between life aspirations and achievements. Viitanen et al. found stable life satisfaction throughout a 20-year
period in healthy elderly subjects. In our control group of healthy elderly volunteers (paper V), all rated life satisfaction as good. In the general population in Sweden (LNU) the vast majority of elderly (93%) had a high global life satisfaction. Our results showed that low life satisfaction before stroke was associated with dependence in self-care. This is in line with other findings that elderly people rate health factors as important contributors to life satisfaction. Maladaptive coping (coping is defined by Lazarus as adaptation under existential threat/stress) and difficulties in finding new and realizable goals are well-known after a stroke. Our results indicate that for many stroke patients this coping process must have started long before their stroke. This has implications for the rehabilitation process and the intervention strategies.

In many studies, comparisons with conditions prior to the stroke are lacking. If there is a comparison, it is often based on a retrospective evaluation of conditions many years ago. The results may be biased by loss of memory and a tendency to glorify pre-stroke life. A further difficulty is that many other factors can serve to change life circumstances over such a long period of time. To minimize these biases in our study, the evaluation of prestroke conditions was completed close to the admission to hospital (mostly within 4-5 days after the stroke).

Our selection of welfare components and indicators from the surveys is based on theoretical considerations as well as more pragmatic approaches in order to cover the most important aspects for this age group. By necessity, these surveys are limited to conditions measurable with sufficient accuracy by means of standardized interviews. The survey questions are not formulated in strict medical terms and therefore the same terms have been used in our patient interviews. However, there is good agreement between the self-assessed data and the medical files, e.g. high blood pressure was reported by 40% of the patients prestroke vs 41% from the medical files, and diabetes in 21% and 19%, respectively. It seems that this information was valid. In fact, the health indicators that differed significantly between the national sample and the study group (hypertension, diabetes, heart disease) are all considered risk factors for stroke.

Life satisfaction was further reduced 3 months after a stroke. Reduced life satisfaction was associated with independence in self-care and with major depression assessed in hospital as well as at the 3 months follow-up stage. Three months after a stroke 2 out of 3 patients were independent in activities of daily life. In this group, 1 in 3 was still dissatisfied with life, independent of concurrent depression, but associated with in-hospital depression. Thus, ADL-independent patients who were depressed at discharge, often had a low life satisfaction after 3 months. This indicates that the immediate poststroke depression had an important interactive influence on both ADL ability and life satisfaction.

One confounding factor could be distortion of perception due to depressed mood; i.e. patients who are depressed may perceive life more negatively, resulting in
associations between depression and disabilities, reduced social contacts etc. However, ADL ability according to Katz et al.\textsuperscript{192} is based on observations of ability completed by information from staff and relatives, and thus is not influenced. Our questions about living conditions have a neutral and concrete formulation of the type: ‘How often have you’...with fixed alternatives; thus they are less likely to be influenced by distortion of perception.

Since missing cases (i.e. deceased) may contribute to changes between groups over time, further analysis of time-dependent changes of living conditions and life satisfaction are restricted to the group of long-term survivors followed over the 3-year period (paper II).

The long-term outcome in patients surviving a stroke is usually described in terms of neurological deficits and functional dependency. The patient's own experienced life satisfaction can be seen as the most important outcome variable - however, rarely used in studies of stroke survivors. Its associates and development over time, have not previously been investigated in a prospective extended follow-up study. In paper II, we have shown that stroke involved a very marked reduction in global life satisfaction, being lowest at three months after the stroke, when only 33\% reported their life as being 'good', increased significantly to 52\% at one year, thereafter it was essentially unchanged and significantly lower than in the general elderly population. Between three and twelve months poststroke, the prevalence of major depression decreased, leisure-time activities and social contacts were partly resumed and also life satisfaction improved. Once good life satisfaction was restored, it was maintained. Poor life satisfaction at one year remained poor for the entire three years. Stroke victims with permanently reduced life satisfaction were older, felt more tired and anxious, were dependent on others in secondary ADL, had a passive leisure-time, fewer social contacts and early after stroke had a higher frequency of major depression. Thus, major depression early after stroke has to be regarded as an important determinant of long-term outcome in stroke patients.

The special problems in connection with diagnosis of depressive disorder in this patient group, have been discussed among others by House\textsuperscript{99} and Robinson.\textsuperscript{206} It has been argued that the DSM-III diagnostic criteria for major depression may be invalid in stroke patients, because the structural brain lesion may cause somatic dysfunction - difficult to separate from depressive symptoms - and consequently to an overdiagnosis of depression. Other investigators have claimed that patients with major depression may be underdiagnosed because they do not have ability to recognize and express symptoms.\textsuperscript{154,207} In a study of this issue, Fedoroff et al.\textsuperscript{208} found the rate of misdiagnoses based on DSM-III criteria small, ranging from an underdiagnosis of 5\% to overdiagnosis of 2\%. Thus, depressive symptoms reflecting nonspecific effects of an acute medical
illness are not rampant in patients who have suffered an acute stroke. DSM-III criteria for major depression are as useful as among patients without known neuropathology. In our study, a careful clinical interview conducted by the same psychiatrist at all seven time-points was considered the best tool for assessing - with minimal exclusions - also patients with dysphasia, denial of affective symptoms, intellectual impairment, pathological emotionalism (cf p. 15) and general fragility. As evident from the Method section (cf p. 28), we exclusively applied the DSM-III criteria of major depression with the physical disorder (i.e. stroke) on axis III. Patients were interviewed 4-5 days after admission, at 10 days and at discharge, as a control for stability of symptoms (to respect DSM-III time criterion). Thus, a major depressive syndrome was diagnosed according to criteria A and B in DSM-III (DSM-III-R had not been published in Swedish, when this study was started). We did not use the category of dysthymia because of its 2-year time-criterion, nor the modified construction of ‘minor depression’. Price has pointed out that irrespective of an eventual aetiological organic factor (criterion E in DSM-III), patients can be described as fulfilling the symptom criteria for major depression. This opinion was later confirmed through the definition of ‘a major depressive syndrome’ in DSM-III-R. In accordance with others, all psychiatric symptoms were evaluated without assumptions of their cause, so as not to prejudge this issue. For that reason, we did not apply the DSM-III categories of ‘organic mood disorder’ or ‘adjustment disorder with depression’. The lack of criteria in DSM-III to define these clinical syndromes and also the organic factors linked to depression in organic mood disorder, limits the utility of these diagnoses; both syndromic clusters are too vaguely defined for research purposes. Furthermore, there is no evidence that depression following organic illness is phenomenologically different from ‘functional depression’, another reason for keeping strictly to the criteria of major depression.

Study III confirms the high prevalence of depression in the acute stage after stroke. In a recent community-based study of mood disorders in the year after the first stroke, House et al. found major depression in 11% of the patients one month poststroke as compared to 25% in our study. As the 95% confidence intervals (15%-35% vs 4%-18%) are overlapping, the prevalences of major depression can not be said to differ significantly. Neither social characteristics, mean age or independence in activities of daily living before and after stroke differed between the studies. In another community-based study, Wade et al. reported 22% ‘definitely depressed’ at three weeks after a stroke, according to a self report inventory. Robinson et al. assessed their patients within two weeks after the stroke, and reported a prevalence of major depression of about the same magnitude (27%), although this research group was studying younger patients (mean age 59 yrs) from mainly lower socioeconomic groups.

At one year, we found a significant decrease in prevalence of depression (from 31% at three months to 16%) which differs from Robinson et al. who in a subsample
of their original group, found a stable prevalence of major depression up to two years. Our result conforms to House et al.\textsuperscript{106} and Morris et al.\textsuperscript{110} who reported that the prevalence of major depression was approximately halved at twelve and seventeen months poststroke, respectively. Our study is the only prospective longitudinal study extended to three years poststroke. At this later stage, there was an increased prevalence of major depression, so that three years after a stroke, the prevalence was as high as at the acute stage (29%).

As we have a very low rate of missing cases, our longitudinal data allow individuals to be followed through the three years. At one year, 60% of the patients with early depression after stroke (0-3 months) had recovered. House et al.\textsuperscript{106} reported a better prognosis; depression persisted throughout the year in only two of the ten patients with early major depression (80% one-year outcome). In the follow-up by Robinson et al.\textsuperscript{172} it could be calculated that 80% of patients with major depression had recovered after one year. The corresponding proportion in a study by Morris et al.\textsuperscript{110} was 71% and by Wade et al.\textsuperscript{121} 50%. Robinson and colleagues\textsuperscript{172} reported that all patients with major depression in-hospital had recovered by two years; but their results are uncertain due to the high attrition rate. In our study, patients who recovered did so within one year, and only one more patient recovered between one and three years. We therefore conclude that if the patient with early depression has not recovered after one year, there is a high risk of a chronic development and of a long-lasting depressive suffering.

In the acute poststroke period, the single most important determinant of major depression was the location of lesion in the left anterior hemisphere; thus confirming results from Robinson et al.\textsuperscript{148} In our study, when the lesion was located in the left frontal hemisphere, the rate of major depression was three times higher than with a left posterior lesion and as much as ten times higher than with a lesion in the right hemisphere. It should be noted, however, that our results showed a time-dependency not clearly demonstrated previously. Patients with RH lesions developed depression later in the course than patients with LH lesions. After three months and throughout the follow-up period, the immediate intra- and interhemispheric differences were no longer significant. This change over time, can explain much of the contradictory results from other investigations in this field (Table 2, p. 18).\textsuperscript{113,115,121,122,142,215,216} Other lesion parameters as volume and subcortical or cortical location were not associated with depression, a result in accordance with other reports.\textsuperscript{95,148}

Thus, our results indicate that major depression evolving early after a stroke was influenced by acute neuropathological changes (i.e. location of lesion in the left anterior hemisphere). In line with this finding - but still in the realm of tentative speculations - are reports from animal experiments but also studies using PET in humans that interruption of ascending transmitter pathways, asymmetrical distribution of transmitters...
to the hemispheres and altered compensatory biochemical response to brain injury may be important underlying biochemical and neurophysiological mechanisms.\textsuperscript{140,217-219}

Multivariate statistics showed that dysphasia had an independent effect on the development of depression. It goes without saying that dysphasia is a frustrating condition with considerable psychological and psychosocial consequences which - according to our results - contribute to depression. One study\textsuperscript{215} has reported a high depression rate in patients with dysphasia but often dysphatic patients have been excluded from studies and this association has accordingly been concealed.

Together with lesion location and dysphasia, the social support parameter 'living alone' was a determinant of immediate depression. Hence, under the stressful condition of an acute stroke, being without the social support from a family to live with, seems to have a provoking effect on depression. To conclude, we recognized contributions from both biological and psychosocial factors interacting in the development of depression in the immediate poststroke period.

Impairment in activities of daily living was not associated with immediate depression, but after three months this factor was the most important determinant of depression. Our results indicate that functional impairment does not determine the onset of immediate depression, but interacts with depression resulting in a poorer long-term functional recovery; other causal conclusions are not possible to draw in this type of study. These results from our population-based cohort of stroke patients confirm a few previous reports on more selected samples.\textsuperscript{160,163}

The social network before the stroke did not differ from the general elderly population (paper I). After the stroke, contacts outside the immediate family declined and remained lower than in the general elderly population. In paper III we have shown that after the stroke and throughout the following three years, the depressed patients had fewer social contacts than the nondepressed patients who actually had an intact social network. At one year and onwards, 'few social contacts' was the most important predictor of depression. Reduced social contacts can be a cause as well as a result of depression; dependent and independent variables in this system of continuous interaction can hardly be isolated. More important is the clinical implication: this vicious circle has to be broken by early and more active treatment at all levels: drug therapy\textsuperscript{151,166} or electroconvulsive treatment (ECT)\textsuperscript{168} psychotherapy and family work\textsuperscript{169,171} education and psychosocial interventions.\textsuperscript{60} Otherwise, there is a risk that these elderly patients, also when recovered, can not re-establish social ties.

There is evidence that degenerative changes in the brain are associated with depression in old age.\textsuperscript{220,221} In one investigation of stroke patients, subcortical atrophy was associated with depression.\textsuperscript{222} We have shown that early after a stroke, depression had other determinants. However, at three years poststroke, cortical as well as subcortical atrophy contributed to depression. It should be observed that the total group of de-
pressed patients at the 3-years follow-up stage consisted partly of patients with depression occurring late after stroke (1-3 years) and partly of early depressed patients with a chronic course. Cerebral atrophy was equally frequent in both subgroups, suggesting influence on both maintenance and onset of depression late after stroke. This linkage between depression after stroke and cerebral atrophy raises important questions about common underlying neurobiological changes.

Elevated activity in the HPA axis after stroke has been documented in paper IV and V. No association between major depression and cortisol levels was found at the acute stage after stroke. Previous studies reporting such an association (Table 3, p. 21) have examined stroke patients at variable lengths of time after the stroke event; a condition which we confirmed as a major confounding factor in paper V. When the study was restricted to acute ischemic supratentorial stroke (paper IV) an association between disorientation and decreased suppressibility to dexamethasone was found. Although we studied only one aspect of cognition, i.e. disorientation, our result are in accordance with other studies reporting association between high cortisol levels and cognitive impairment after stroke.\textsuperscript{182,188,223} Many CNS information-processing capabilities are supposed to be glucocorticoid-dependent\textsuperscript{224} and - based on animal studies - glucocorticoids may exert a modulatory influence on behavior,\textsuperscript{225} and also interfere with neuron function and cause neuronal death.\textsuperscript{226,227} Sapolsky et al.,\textsuperscript{226} on the basis of a series of experiments, has suggested that sustained hypercortisolism might damage the human hippocampus. Thus, theoretically, hypercortisolism thereby could contribute to cognitive disturbances after stroke.

Smaller brain volumes were associated with a decreased suppressibility to dexamethasone. It has been suggested that degenerative changes in the brain (e.g. Alzheimer’s disease) and especially in the hippocampus,\textsuperscript{228} can contribute to a higher activity in the HPA axis through a decreased inhibitory influence on the HPA axis.\textsuperscript{229} We observed a negative correlation between activity in the HPA axis and relative distance of the brain lesion from the frontal pole. No hemispheric difference in cortisol levels was verified when CT parameters were analyzed. The cortisol axis is substantially influenced by the CNS through the release of corticotropin releasing hormone (CRH) from the hypothalamus. Norepinephrine (NE) influences CRH release in animal experiments.\textsuperscript{230} In rats, large areas of the cortex can be deprived of noradrenergic innervation by a relatively small lesion in the frontal cortex.\textsuperscript{217} Theoretically, anteriorly located lesions could therefore profoundly affect the balance between the biogenic amines and the cortisol system.

Patients at the acute stage after stroke, are subject to repeated stress situations, e.g. emotional reactions as fear and anxiety, hospitalization per se, sudden inability in self-care and communicating, medical complications as heart failure, etc. Repeated stresses may increase adrenal sensitivity to ACTH and therefore prolong the hypercorti-
solism which in turn can potentially induce a cascade of negative consequences, e.g. on myocardium, immune system, etc. It has also been hypothesized that steroids themselves may be important in causing and perpetuating depression. In paper V, we have documented a significant association between hypercortisolism and major depression late (3 years) but not early (0-3 months) after stroke. Chronic stress has been suggested to influence the later development of depression in vulnerable patients. Our data on the predictive value of high postdexamethasone cortisol levels at 3 months after stroke on the later development of major depression support this theory. Stroke can thus be the key event predisposing to later stress activation of the hypothalamic-pituitary-adrenal axis which in itself may contribute to the development of depression. This can be mediated through changes in the levels of CRH in the central nervous system or an alteration of cortisol metabolites. Interestingly, treatment with steroid suppressive drugs has recently been reported to induce a prompt remission in some depressive patients with a profound activity of the cortisol axis resistant to antidepressant therapy.

The dexamethasone suppression test had a high specificity (97%) with a lower sensitivity (70%) in detecting major depression late after stroke. Since other studies have diverging case definitions and deficient control of inclusion times, further comparison of results are deceptive. One important conclusion is that hypercortisolism 3 months after the stroke seemed to predict major depression later in the course. Thus, this subgroup of patients warrants careful follow-up from a psychiatric point of view.

Our prospective longitudinal design has given evidence of a differentiation of factors likely to be implicated in major depression in relation to the period of time since the stroke event. Close to the stroke event, the influence of the location of structural CNS damage seems prevailing. The exact nature of how this structural brain damage leads to depression remains unclear. The strategic lesion (left anterior hemisphere) can be seen as a precipitant of depression. A severe physical illness (i.e. stroke) - as other major negative life events - also exerts its impact through the losses it causes to the individual. Immediately after the stroke, dysphasia was such a provoking agent and also the social support parameter ‘living alone’. Later in the course (3 months), loss of independence in self-care and loss of social contacts outside the immediate family were more important. From the organic level, hypercortisolism (as measured by the DST) at 3 months can be seen as a vulnerability enhancing factor for later development of depression. In addition, late after stroke (3 years) degenerative brain changes enhanced vulnerability for depression.

It has been suggested that depression after CNS damage has a lower loading of constitutional predisposition than depression following psychological stress or certain drugs. There is evidence that a family history of depression is less frequent in

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depression with onset in old age.\textsuperscript{238} This is in line with our findings. The frequency of past personal history of psychiatric disorder was not associated with depression development after stroke nor did it differ from the national sample. We could not get reliable information concerning family history of depression.

Recent research in the broader psychiatric literature on life events, vulnerability factors and social support (e.g.\textsuperscript{7,8,239,240}) describes vulnerability for depression at different levels within a complex interacting system, where also personal features (e.g. low self-esteem, negative self-evaluation) are included; factors not assessed in our study or in other stroke research to this point. However, we can hypothesize from our description of prestroke conditions (paper I) that poor health, reduced ability in many sectors of daily life, and low satisfaction with life as a whole may generate negative self-evaluation in many individuals and increased individual vulnerability for depression already prior to the stroke. In his work on depression from an interactionistic integrating perspective carried out at our department, Perris\textsuperscript{240} has pointed out that interacting factors might have been operating long before onset of the depressive breakdown. Except for the social support parameter ‘living alone’, our data did not show any association between prestroke conditions and development of depression after a stroke. Small sample size in the subgroups can partly explain this. However, personal vulnerability was not directly assessed. This represents an important field for future research with implications for psychotherapy and intervention studies in stroke patients.

We have shown that stroke survivors maintained contacts with their children but lost contacts outside the family. For the purpose of reliable measures - minimally distorted by negative thoughts and depression - our assessments focus on the availability and frequency of social contacts. This also made possible comparison with the general elderly population. We concluded (paper II) that the patient's social network was apparently as good as in the general elderly population before the stroke, but this important resource for well-being deteriorates after the stroke. This may leave the spouse and/or the children with an excessive supportive burden. Clinical experience and research data suggest a high degree of emotional distress in primary support persons, with more than half of caregivers having medical and psychiatric disturbances.\textsuperscript{241–244} Wade et al.\textsuperscript{242} has reported that depression in the stroke patient was associated with depression in the carer. Evans et al.\textsuperscript{243} has shown positive effects of family intervention and education in the recovery of stroke patients. In the light of our findings, we can hypothesize that there are critical periods of caregiving when interventions might be most helpful. Prospective longitudinal studies are required for evaluation of different intervention strategies and also for a better identification of cause-and-effect relationships still unanswered in our study.

As pointed out more than a decade ago by Feibi et al.\textsuperscript{245} concerning ‘the unmet needs of stroke survivors’, any kind of treatment of depression has rarely been offered
to this patient population. In their initial study of 103 stroke outpatients, Robinson et al.\textsuperscript{115} reported that none of the 30 depressed patients received any type of psychiatric treatment. At the start of our study, controlled clinical trials of antidepressant drugs in these patients were not yet documented. Only three patients in our study group received antidepressants for a longer period. As summarized above (cf p. 18 and p. 19), there is evidence\textsuperscript{164,166} for the usefulness of antidepressants in the treatment of major depression after stroke. Adequate antidepressant treatment trials ought to be performed as it is lege artis in other patients with major depression ("functional depressions").\textsuperscript{246} Drug side-effects complicate treatment in these medically ill elderly patients, and often may make effective pharmacotherapy impossible. Promising results of cognitive psychotherapy, singly and in combination with pharmacotherapy (e.g.\textsuperscript{247}), ought to be further evaluated in this context.\textsuperscript{171} In the light of our findings of long-lasting depressive suffering in stroke patients and the deleterious influence of depression on later life satisfaction, functional recovery and social life, early and more active treatment at all levels (drug therapy\textsuperscript{151,166} or ECT,\textsuperscript{168} psychotherapy and family work,\textsuperscript{169,171} education programs and psychosocial interventions\textsuperscript{60}) is clearly needed to deal with the complexity of depression in stroke patients. However, the main barrier toward the treatment of depression after a stroke, and in other physically ill elderly as well, is probably that the existence and consequences of depression are not recognized. Health care professionals involved in stroke care, have to increase their level of awareness of major depression in the stroke patient. In psychiatry, models for consultation-liaison has to be improved.
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