CENTRAL NERVOUS SYSTEM (CNS) dysfunction has occasionally cast a shadow over the results of cardiac surgery. The development of surgical and anesthesiological equipment has notably improved cerebral safety, and the occurrence of severe complications has become rare. The well-being of the CNS, however, has not become self-evident and secure because several potentially harmful factors always remain in such complicated procedures as open-heart operations. It must also be emphasized that when only clinical criteria have been used to evaluate the CNS outcome, the appraisal of the results seems to have been too optimistic. Clinical measures have been shown to provide only a narrow view over the actual CNS events, for the involvement of the subclinical levels has been revealed in electroencephalographical (EEG), and radiological studies.

Previous studies investigating the long-term outcome of open-heart operations have concentrated their attention on cardiological and surgical aspects. By contrast, the outcome of the higher cerebral functions has been given little attention, the earlier investigations having focused on describing the prevalence, nature and determinants of immediate postoperative disturbances using follow-up times limited to a few weeks or months. Frank et al performed a 6 months' study after operation and reported improvement in all the measured areas of intellectual performance. Preoperative anxiety seemed to worsen the improvement, probably by rendering the patients less apt to recall the test items. The intellectual changes were independent of cardiac functional measures. It was concluded that the observed improvement was only due to practice effects and that improved cerebral perfusion did not measurably enhance intellectual functioning. In another study with one year's follow-up, Heller et al stated that although over 90% of the patients showed improvement in their physical condition compared with preoperative evaluation, general psychological adjustment declined. Other studies with shorter follow-up times have revealed disturbances in memory, attention span, perceptualmotor coordination and psychomotor speed. Contrary to the above mentioned studies in adult patients, investigations in children have failed to verify psychomotor or intellectual disturbances after cardiac operations.

In a previous report, we presented the results of our study on clinical, neuropsychological and EEG outcome in 49 valvular replacement patients up to one year after operation. The present study was designed as a continuation of the follow-up to 5 years, aiming to elucidate the later course of the same patients. The unaltered investigatory setting and the multidimensional approach were thought to provide appropriate qualifications for reconsidering the cerebral outcome and its determinants in the long-term course.

Patients and Methods

Of the 49 valvular replacement patients examined pre- and post-operatively, 44 were available for investigations 5 years after operation. Of the remaining 5 patients, one had died of cardiac causes, 4 further patients had moved too far away and therefore did not wish to participate in the study. The follow-up time ranged from 4 years 6 months to 5 years 9 months (mean 5.2 ± 0.3 years). There were 28 men and 16 women, whose age range was 21–71 (mean 46 ± 10 years). Aortic valve replacement had been performed in 32 patients, mitral in 9 and both aortic and mitral in 3 patients. The Björk-Shiley tilting disc valve prosthesis had been used in all the patients. All the operations had been carried out with the aid of a bubble oxygenator (Rygg-Kyvsgard) using non-pulsatile flows, moderate hypothermia (oesophageal temperature 31.5–32°C). Moderate hemodilution technique had been used in all the cases and the oxygenator had been
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primed with a mixture of blood, gelatine and Ringer’s solution. The methods of premedication, anaesthesia, postoperative care and controls had been uniform with no essential alterations during the operative period under survey.

All the patients had been under regular cardiological surveillance and their medication had been adjusted optimally. All had anticoagulant (warfarin) treatment.

Clinical neurological examination including consideration of cognitive functions was always carried out by the same neurologist (K.A.S.). The neuropsychologist administering and scoring the tests was all the time unaware of the patients’ clinical outcome. Similar practice was pursued in the analysis of the patients’ EEG examinations which were performed using both conventional and computerized quantitative EEG (QEEG) with the methods and parameters described earlier.8,32

Psychometric Test

The neuropsychological examination was carried out using the same unaltered battery of the following 7 tests: 1) Color Naming (a test for normal flexibility, ability to shift perceptual set, color vision and reading fluency).33-35 A modification of the Stroop Color Test36 was used. In this version, the subject reads as quickly as possible 12 rows, with 7 color names on each, typed in black on each row, and then is given another set of the same color names printed in a different color to the color named. The subject is asked to name the color used and not to read the text. Variables include the time used (in seconds) (Color Text Time) and the number of errors made (Color Text Errors).

2) Learning (a pure verbal test).36 A series of 12 words is learned by rote. The variable is the number of words learned.

3) Triangles (a test of psychomotor speed).36, 37 Small triangles printed on paper are connected with a line; the subject is asked to mark as many triangles as possible in 60 seconds. The variable is the number of triangles marked.

4) Maze Time (a measure of planning ability and frontal lobe functions).35, 38 The used test is a version of the Porteus Maze Test.39 The variable is the performance time in seconds.

5) Symmetric Drawing.36, 37, 40 The subject is asked to draw a symmetric mirror image of a model of a half of an oak leaf. The variable is the general form level, score 1-10.

6) Recognition.39 The subject is shown 11 abstract designs for 5 seconds each. Thereafter, he is shown 11 series of designs, 5 alternatives on each, one of the 5 being one of the test designs which should be recognized. The variable is the number of correct recognitions. (Both Symmetric Drawing and Recognition have strong visual components and thus measure mainly the functions of the nondominant hemisphere).

7) Digits Backwards (a test of attention and audio-verbal memory). The digit series used was adopted from Wechsler Adult Intelligence (WAIS) Scale (Finnish version).41 The variable is the number of digits remembered correctly in the longest series.

The test scores ranged from 0 to 10.17 The overall neuropsychological (NP) performance was measured using both the subtests and the sum score of the 7 subtests which are called the NP-Index.

Patient Grouping

The patients were grouped according to their postoperative neurological outcome and NP-Index course.

Neurological Outcome Group

Ten days after the operation, 23 patients showed completely normal neurological finding (NON-COMPLIC group), while 21 displayed some kind of dysfunction which had not been present in preoperative investigations (COMPLIC group). Motor or sensorimotor abnormalities (mostly slight unilateral hyperreflexia with or without corresponding hemisensory dysfunction) were found in 17 patients, the remaining 4 cases displaying cerebellar or brain-stem signs. Most commonly, the signs were mild and rapidly reversible, but residual signs could be found in 4 patients one year after the operation (hemispherical and brain stem signs in 2 patients each).

NP-Index Course Group

As for the postoperative NP-Index course, 32 patients experienced NP-Index improvement (NP-Improv group), and 12 patients had impairment (NP-Impair) in the first NP examination (2 months) after operation when compared with the preoperative performance.

Chi square test and Student’s t-test for independent means were used in comparing the patient groups with each other and t-test for correlated means for comparing the score changes within a given group.

Results

General Aspects

Except for 2 cases, (a patient with cardiac failure unrelated to the prosthesis and another one who suffered from a declining clinical condition due to advanced gynaecological malignancy), all patients reported an overall beneficial outcome. They described notable improvement in their general condition of health, in durability in both physical and mental stress and, what they regarded as most important, enhancement in their ability to participate in social and leisure activities. At the time of the operation, 28 patients were able to work, 14 had sick-leave and 2 had retired for old age. Five years later, the numbers were 23, 18, and 3, respectively. The main reason for an inability to work was neurological in one case (residual hemiparesis after stroke) out of 14 at the time of the operation, while the respective number at 5 years was 3 cases out of 18.

Ten patients reported some degree of memory decline, which however, was considered unimportant in daily activities. Of these 10 patients, 7 belonged to both COMPLIC and NP-Impair groups.
Clinical Aspects

Five years after surgery 3 patients still displayed residual motor hemisyndrome attributable to operative complications. Two further patients showed renewed signs (slight unilateral hyperreflexia) similar to those which appeared in the operation but which had recovered in a few weeks.

Three patients had suffered from transient ischaemia attacks (TIA) which consisted of bilateral amaurosis fugax in 2 and motor symptoms of the left hemisphere in 1. No more severe cerebrovascular accidents than TIA had occurred.

Cardiological evaluation, also performed 5 years postoperatively, showed highly satisfactory or optimal results in all except one mentioned above who had developed intractable cardiac failure.

The Subtests and the N-Index

Table 1 shows the comparison of the subtest and NP-Index score values before and 5 years after the operation. The NON-COMPLIC and COMPLIC groups had no other preoperative difference than the Color Text Errors, in which the COMPLIC group had low values. This test was also the only one with predictive importance: 10 out of the 12 patients who showed score values of 5 or less in 0–10 scale developed signs of hemispheral involvement in operation. By 5 years the above difference disappeared, while the COMPLIC group achieved statistically significant lower scores in Maze Time, Symmetric Drawing, Learning and Recognition. Accordingly, the COMPLIC group also developed a significantly lower NP-Index than the NON-COMPLIC group.

The score changes in each subtest through the follow-up time are visualized in figure 1. The NON-COMPLIC group gained greater score improvement than the COMPLIC group through the entire 5-year period. The COMPLIC group displayed a fall in Learning and Symmetric Drawing and a marked rise in Color Text Errors, while the NON-COMPLIC group either continued in improvement or kept its level.

The postoperative NP-Index (the performance sum score) course is presented in figure 2. The NON-COMPLIC and COMPLIC groups were equal before operation (table 1) but after the first postoperative investigation (2 months after surgery) the COMPLIC group showed lower scores than the NON-COMPLIC group and had a notable rise only at 1 year; thereafter, however, it could not keep its level. In contrast, the NON-COMPLIC group experienced a constant rise in score. The absolute score values of two groups reached statistical significance first at 5 years (table 1, fig. 2).

Table 2 presents the mode of the NP-Index score change in the NON-COMPLIC and COMPLIC groups through the follow-up time. The immediate postoperative clinical and neuropsychological outcomes were closely interrelated. Thereafter, a great majority in both of the clinical groups experienced an NP-Index rise up to first year. During the subsequent 4 years, the

<table>
<thead>
<tr>
<th>Test</th>
<th>Clinical group</th>
<th>Score values</th>
<th>5 Years after operation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Triangles</td>
<td>NON-COMPLIC</td>
<td>5.1 ± 2.3</td>
<td>5.7 ± 1.8</td>
</tr>
<tr>
<td></td>
<td>COMPLIC</td>
<td>5.4 ± 2.7</td>
<td>5.3 ± 3.0</td>
</tr>
<tr>
<td>Maze time</td>
<td>NON-COMPLIC</td>
<td>6.1 ± 2.8</td>
<td>8.8 ± 1.4</td>
</tr>
<tr>
<td></td>
<td>COMPLIC</td>
<td>6.0 ± 3.7</td>
<td>7.5 ± 2.6</td>
</tr>
<tr>
<td>Color text time</td>
<td>NON-COMPLIC</td>
<td>6.0 ± 3.4</td>
<td>8.0 ± 3.2</td>
</tr>
<tr>
<td></td>
<td>COMPLIC</td>
<td>4.8 ± 3.6</td>
<td>6.7 ± 3.3</td>
</tr>
<tr>
<td>Color text errors</td>
<td>NON-COMPLIC</td>
<td>9.1 ± 1.4</td>
<td>9.7 ± 0.4</td>
</tr>
<tr>
<td></td>
<td>COMPLIC</td>
<td>6.9 ± 3.1</td>
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</tr>
<tr>
<td>Symmetric drawing</td>
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</tr>
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<td>COMPLIC</td>
<td>7.0 ± 3.3</td>
<td>5.3 ± 3.1</td>
</tr>
<tr>
<td>Recognition</td>
<td>NON-COMPLIC</td>
<td>5.5 ± 1.8</td>
<td>8.0 ± 2.0</td>
</tr>
<tr>
<td></td>
<td>COMPLIC</td>
<td>4.9 ± 2.2</td>
<td>6.2 ± 3.0</td>
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<tr>
<td>Learning</td>
<td>NON-COMPLIC</td>
<td>6.2 ± 1.8</td>
<td>8.6 ± 1.7</td>
</tr>
<tr>
<td></td>
<td>COMPLIC</td>
<td>5.8 ± 2.7</td>
<td>6.7 ± 3.5</td>
</tr>
<tr>
<td>Digits backwards</td>
<td>NON-COMPLIC</td>
<td>5.8 ± 1.1</td>
<td>5.8 ± 1.0</td>
</tr>
<tr>
<td></td>
<td>COMPLIC</td>
<td>5.5 ± 1.1</td>
<td>5.4 ± 1.3</td>
</tr>
<tr>
<td>NP-Index</td>
<td>NON-COMPLIC</td>
<td>40.6 ± 10.7</td>
<td>52.5 ± 10.0</td>
</tr>
<tr>
<td></td>
<td>COMPLIC</td>
<td>39.1 ± 13.5</td>
<td>43.1 ± 15.4</td>
</tr>
</tbody>
</table>

NS: not significant
*: p < .05
†: p < .01
‡: p < .001
COMPLIC group displayed a renewed decline, the magnitude of the fall being comparable to that observed immediately after operation.

Age, sex and presence of atrial fibrillation or arterial hypertension did not affect the long-term NP-Index course. The aortic and mitral patients showed some differences; the aortic patients' scores reached a constant level within the first year, while the mitral and both aortic and mitral patients showed a much slower score rise which provided essential improvement first by 5 years. The performance decline seen after the first year in some patients (table 2) was found to be unrelated to the cardiological grouping and to the measures mentioned above. The occurrence of TIA had no effect on the outcome.

NP-Improv and NP-Impair Groups

Figure 3 presents the follow-up of the NP-Improv and NP-Impair groups. The latter group never gained any notable NP-Index benefit while the former group had a statistically significant score rise through the follow-up time. The first postoperative (2 mo) result seemed to predict the later outcome.

Perfusion Time and Neuropsychological Performance

The effect of intraoperative perfusion time on the NP-Index was investigated by dividing the patients into two groups according to whether they had had a short (<2 h, N 22) or a long (≥ 2 hr, N 22) perfusion time in the operation. The short perfusion time group showed (fig. 4) a significant score rise through all the follow-up period in contrast to a less beneficial course in the other group. The difference in the absolute NP-Index values of the two groups reached statistical significance (p < 0.05) first at 5 years. The NP-Index score rise after a short perfusion was two times greater than the rise after a long perfusion, and significantly, this difference was seen not only in the COMPLIC patients but also in the NON-COMPLIC patients.

<table>
<thead>
<tr>
<th>Follow-up period considered</th>
<th>Group</th>
<th>NP-Index change</th>
<th>Significance of the difference between the NON-COMPLIC and COMPLIC groups (p value)</th>
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</thead>
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<tr>
<td>Preoper.→2 months</td>
<td>NON-COMPLIC</td>
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<td>Unchanges: 10</td>
<td>Rise: 10</td>
</tr>
<tr>
<td>2 months→1 year</td>
<td>NON-COMPLIC</td>
<td>Fall: 1</td>
<td>Rise: 20</td>
</tr>
<tr>
<td></td>
<td>COMPLIC</td>
<td>Unchanges: 17</td>
<td>Rise: 17</td>
</tr>
<tr>
<td>1 year→5 years</td>
<td>NON-COMPLIC</td>
<td>Fall: 9</td>
<td>Rise: 12</td>
</tr>
<tr>
<td></td>
<td>COMPLIC</td>
<td>Unchanges: 5</td>
<td>Rise: 5</td>
</tr>
<tr>
<td>Preoper.→1 year</td>
<td>NON-COMPLIC</td>
<td>Fall: 3</td>
<td>Rise: 20</td>
</tr>
<tr>
<td></td>
<td>COMPLIC</td>
<td>Unchanges: 15</td>
<td>Rise: 15</td>
</tr>
<tr>
<td>Preoper.→5 years</td>
<td>NON-COMPLIC</td>
<td>Fall: 6</td>
<td>Rise: 23</td>
</tr>
<tr>
<td></td>
<td>COMPLIC</td>
<td>Unchanges: 9</td>
<td>Rise: 9</td>
</tr>
</tbody>
</table>
NP-IMPROV. • NP-IMPAIR.
5YEARS NVESTIGATKDN TWE

Figure 3. Postoperative NP-Index change scores in the patients showing NP-Index improvement (NP-Improv, N 32) and impairment (NP-Impair, N 12) in the first postoperative investigation (2 months after operation). (**p < .001)

EEG and NP Outcome

Episodic theta range abnormalities appearing predominantly in the temporal regions were the most common EEG disturbances both before and after operation. In the great majority, the abnormalities recovered in the long-term, rendering an overall EEG improvement. There were no EEG measures corresponding to the NP performance except for two particular findings: The NP-Improv group experienced a more beneficial EEG outcome than the NP-Impair group, the prevalence values of abnormal EEG before and 5 years after operation being 47% and 19% in the NP-Improv group and 42% and 33% in the NP-Impair group, respectively. The QEEG analysis revealed that both the increase in the slow (delta) activity in the latter group, and its respective decrease in alpha activity between one year and 5 years after the operation were both two times greater than in the former group.

Discussion

In agreement with our short-term results, there was also a clear-cut correspondence between the immediate postoperative clinical outcome and long-term neuropsychological (NP) performance (fig. 2, table 2). Although most of the clinical consequences recovered within months after operation, the NP differences between those who had been clinically non-affected (NON-COMPLIC) and affected (COMPLIC) after operation increased with time. Significantly, the performance score difference between the NON-COMPLIC and COMPLIC groups reached statistical significance first and only at 5 years. The final outcome would have appeared completely different from the present results if the clinical grouping mentioned above had not been considered: a statistically highly significant improvement in all the scores except Digits backwards would have been achieved. This would agree well with some previous results reporting overall postoperative improvement but would fail to reveal the essential interrelationship between NP disorders and even slight clinical involvement which was evident in this study. In this context, it is important to recall that the observed clinical signs of CNS dysfunction were very mild in the majority of cases and that their detection would not have been probable without thorough and repeated clinical investigation. It is also worth remembering that our previously presented EEG and QEEG findings confirmed the existence of CNS level involvement. Our study differs from previous investigations not only because of its long postoperative follow-up time but also because of its multidimensional character which allows simultaneous consideration of clinical, NP and EEG aspects. According to the present observations, it seems evident that there are strong reasons for not overlooking even the slightest degree of clinical disturbance related to operation, because it may indicate the presence of other disorders which otherwise remain unrecognized but may even entail later consequences.

Besides the clinical criteria, the duration of perfusion (extra-corporeal circulation) in the operation was one of the main determinants of long-term outcome (fig. 4). This would seem to be due to the positive correlation between perfusion time and clinical complications established in a number of previous investigations and also in the present series. Prolongation of perfusion is often due to intraoperative technical or surgical difficulties, the effect of which may be reflected in the appearance of clinical disturbances after operation. Significantly, it was observed that a long duration of perfusion impaired NP performance independent of the clinical outcome; for example, also in those patients who showed no abnormalities after operation. In this context, one should recall that at the time when the above mentioned previous studies were carried out, the practice of measuring blood pressure at operation was to register the pressure at 5 minute intervals instead of continuous monitoring. Therefore, some of the possible hypotensive episodes may have escaped detection but, on the other hand, even in those cases in which moderate hypotensive episodes...
were registered, no clinical or NP consequences could be ascertained. It is noteworthy that the difference in NP performance scores between the short and long perfusion time groups was accentuated during the follow-up time and this phenomenon could not be correlated to any neurological or cardiological cause. Thus, intraoperative conditions, of which perfusion time is perhaps only one, may entail consequences which are not necessarily apparent until long after the procedure. Therefore the present observations still underline the necessity of guarding the interoperative safety measures and conduction a short perfusion time policy.

The clinical groups (NON-COMPLIC and COMPLIC) were preoperatively equal in essential aspects (e.g. age, sex, education, type and duration of cardiac disease, and history of neurological diseases). No one had a history of diabetes, alcoholism or intoxications. In the COMPLIC group, one patient had been treated for depression and two in the NON-COMPLIC group for arterial hypertension; otherwise the medications used uniformly when necessary, were digitalis, diuretics, antiarrhythmic agents and warfarin. The use of other drugs, such as analgetics, sleeping pills or tranquilizers, was particularly occasional. The only notable difference was the poor Color Text Errors score in the COMPLIC group (table 1) which would seem to be considered incidental unless this very test proved to have predictive clinical value and showed particular changes in later course. Interestingly, the Color Text Errors performance improved in the COMPLIC group (table 1) but first at 5 years (table 1) and this did not occur at the cost of the performance time in the test. Both of the hemispheres are involved in performance in the Color Naming test and the integration of several functions is required: visual functions, speech and color discrimination. Due to these multifactorial requirements, this test may be more sensitive to dysfunction than the less complicated tests used.

In the long-term course, Learning (verbal functions), Symmetric Drawing and Recognition (mainly visual functions) were the tests which differentiated the NON-COMPLIC and COMPLIC groups from each other. This appears logical because they represent integrative functions which are obviously more vulnerable than, for instance, simple functions which are reflected in reaction times (e.g. Maze Time, Triangles) (fig. 1). The decline in the above mentioned tests in the COMPLIC GROUP, and the opposite course in the Color Naming, show that the psychometric performance responses vary depending not only on the characteristics of the test used but also on the functional conditions created by the different phases of the underlying disease and its treatment. Some tests seem to be able to reflect mainly the possible actual dysfunction (complications) related to the operative procedures, while other tests, such as Color Naming, may be thought of as giving evidence of the beneficial effects of the treatment.

Previous studies have denied the possibility of real enhancement of psychometric performance attributable to treatment and the role of the practice effect has been emphasized as the main determinant of rising test scores. Although test-specific long-term learning effect curves are not available for healthy persons nor for cerebral dysfunction patients so that one could conclude much from the course of the performance scores, some evidence suggesting that the possibility of real improvement of performance should perhaps not be completely abandoned. Firstly, the changes in the Color Naming test took place long after the first year period during which the tests were most frequently repeated (2, 5, 8 and 12 months after operation), and indeed after an interval of 4 years (fig. 1). Secondly, the mitral patients and both aortic and mitral patients differed from the aortic patients showing performance score rise continuing after the first year. The difference between the aortic and mitral patients could be based on the characteristics of the course of these diseases. It is well known that the aortic patients come to operation several years earlier than the mitral patients whose disease advances less dramatically. The mitral patients are predisposed to circulatory disturbances for several years longer than the aortic patients, and therefore, one might also expect differences in recovery. Furthermore, because the mitral and nonaortic and mitral patients' score improvement occurred in the late phase, the practice effect is not likely to be the only cause. Thirdly, the EEG and QEEG findings of this series provided evidence of stable and improved CNS functional conditions, reflecting the beneficial effect achieved by correcting the major circulatory disturbance. The EEG changes, of course, cannot be interpreted as confirming the enhancement of cognitive functions but they verify that the metabolic prerequisites of the CNS functions improved after treatment.

In conclusion, our results show that the clinical and neuropsychological outcomes are closely interrelated and, not only immediately after operation, but also in the long-term course. This interrelationship seems to remain independent of the nature and duration of the clinical signs of CNS disorders sometimes induced in operation. This, together with our EEG findings, suggests that diffuse CNS dysfunction rather than focal damage is the most common cause of occasional cerebral disturbances related to operative procedures in modern open-heart surgery. Although the occurrence of severe CNS complications has diminished strikingly owing to all surgical and technical development, our observations point out that the influence of harmful intraoperative factors may only be reflected at the subclinical level and in the long-term course. This obliges us to continuously consider all the potential harmful factors of open-heart surgery, despite a successful immediate clinical outcome. Since there seems to be evidence that the duration of cardiac disease itself may affect the outcome of the higher cerebral functions, more emphasis should be paid to obtaining an understanding of the correct timing of operative treatment and to taking account of the CNS functions and not only the cardiac condition. This would be particularly important if evidence of real enhancement of cerebral
functions due to treatment can be ascertained. The higher cerebral functions determine the quality of life of the years achieved with successful treatment and, therefore, much higher priority, than in the practice today, should be given to the evaluation of the CNS in severe cardiac disease and its treatment.

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