Chemonucleolysis versus discectomy: a randomized multicenter trial

H. August M. van Alphen, M.D., Ph.D., Reinder Braakman, M.D., Ph.D., P. Dick Bezemer, Ph.D., Gijs Broere, M.D., Ph.D., and M. Willem Berfel, M.D.

Department of Neurosurgery, Free University Hospital, Amsterdam; Department of Neurosurgery, Erasmus University Hospital, Rotterdam; Department of Neurosurgery, De Wever Hospital, Heerlen; and Department of Theory of Medicine, Epidemiology and Biostatistics, Free University, Amsterdam, The Netherlands

A randomized clinical trial was carried out to compare the results of open discectomy with those of chemonucleolysis in 151 patients suffering from a disc herniation at L4-5 or L5-S1. All patients fulfilled strict entry criteria; 78 patients underwent open discectomy and 73 were subjected to chemonucleolysis.

An increase in radicular pain immediately after treatment was encountered in 16 patients (22%) in the chemonucleolysis group, as compared to none in the discectomy group. The efficacy of discectomy appeared to be definitely superior to that of chemonucleolysis. Within a follow-up period of 1 year, 18 patients (25%) required open discectomy following failed chemonucleolysis; two patients (3%) in the discectomy group needed a second operation. Open discectomy following previous chemonucleolysis was successful in only 44% of cases. Comparison of the final results of the two modes of treatment 12 months after the last intervention (including second treatment) did not reveal any significant differences.

The duration of the preoperative symptoms, the level of disc herniation, and the leakage of contrast medium out of the disc appeared to be of no relevance to the final outcome. The complication rates in both treatment groups were low.

Key Words: discectomy, chemonucleolysis, herniated nucleus pulposus, lumbar spine, multicenter trial

Chemonucleolysis using chymopapain was introduced in 1964 as an alternative treatment for lumbar herniated discs. The method was abandoned in the United States in 1975, after a first double-blind study had shown no statistically significant difference in efficacy between chymopapain and a placebo. During the same period, the effect of chymopapain was compared with intradiscal injection of hydrocortisone; again, no difference was found. The method received a new impetus when more recent double-blind studies disclosed evidence that the effect of chymopapain on disc herniation was better than that of a placebo.

In recent years, the results of chemonucleolysis and surgical discectomy in patients with lumbar herniated disc have been compared on a larger scale by means of retrospective studies. Leavitt, et al., compared open discectomy and chemonucleolysis in a prospective study of 77 patients. They found no difference between the effects of the two methods of treatment; however, the follow-up period in this study was only 14 weeks — too short a time to assess the final result of treatment.

Until now, only two small randomized trials comparing discectomy and chemonucleolysis have been carried out. In both studies the therapeutic effect of chemonucleolysis was significantly lower than that of surgical treatment. In one of these studies the results of surgery following failed chemonucleolysis were poor, whereas the other study showed no difference between surgery alone and chemonucleolysis with or without subsequent surgery after a follow-up period of 1 year.

The conflicting results of the different studies reported in the literature prompted a randomized clinical trial conducted in three neurosurgical centers in the Netherlands, with the aim of establishing whether chemonucleolysis is a good alternative to operative treatment of lumbar disc herniation.

Clinical Material and Methods

Patient Population

All patients were between 18 and 45 years of age, suffering from a unilateral or bilateral radicular syndrome due to a lumbar disc herniation at the L4-5 or
L5–S1 vertebral level. All were referred to the neurosurgical centers of the Free University Hospital (Amsterdam), Erasmus University Hospital (Rotterdam), or De Wever Hospital (Heerlen), between March, 1984, and April, 1986. The disc herniation must have been proven indisputably by myelography, sometimes supplemented by computerized tomography. Further inclusion criteria were that conservative treatment, consisting of at least 2 weeks of bed rest followed by physiotherapy, had not given satisfactory results and that consent to participate in the trial, after receiving extensive verbal and written information, was given by the patient. The study was approved by the ethics committees of the participating hospitals.

Excluded were patients with severe neurological deficits who were considered to be candidates for emergency surgery, those who had previously been operated on or subjected to chemonucleolysis for a lumbar disc herniation, those in whom bone compression was thought to be the most likely cause of the radicular syndrome, and women who were pregnant. Suspicion of a sequestered or extruded disc was no reason for exclusion from the study.

Two subgroups of patients were distinguished: in one subgroup, patients had suffered radicular complaints for 6 months or less and, in the other, symptoms had been present for longer than 6 months. With the three participating centers, this resulted in six strata. In each stratum, patients were randomized into two approximately equal groups. Of every four consecutive patients, two underwent open discectomy and two chemonucleolysis.

Neurosurgical Management

Chemonucleolysis was performed under general anesthesia and radiographic control with the patient in the lateral position. Discography was carried out, using 1 to 2 ml water-soluble contrast medium, for verification of the proper position of the needle in the disc and to check whether the annulus fibrosus was ruptured. After an interval of at least 15 minutes, 2 ml (4000 U) of chymopapain (Chymodiactin) was injected. The patients were discharged 4 to 7 days after chemonucleolysis.

Discectomy was performed under general anesthesia using an interlaminar approach. The herniated or sequestered disc was removed and the intervertebral disc space involved was emptied. Subsequently, the root was checked to ascertain whether it had a free course in the spinal canal and, as far as visible, in the intervertebral foramen. The procedure was not performed under the operating microscope. The patients were discharged 7 to 10 days after surgery. After both procedures the patients were treated with physiotherapy.

Evaluation Criteria

The patients were examined immediately before treatment and evaluated 2, 6, and 12 months after treatment according to a protocol drawn up previously to assess: 1) the result of the initial treatment after 12 months (failure of this treatment was considered as an endpoint); and 2) the final outcome of treatment 12 months after the last intervention, including the second treatment in the case of failure. These results were assessed based on the posttreatment clinical course, the physician's opinion, and the patient's judgment.

The posttreatment clinical course was assessed on the basis of an increase or decrease in radicular pain and radicular symptoms and the occurrence of complications. Failures of treatment included: failure to puncture or inject the disc; persistence of or increase in the radicular signs and symptoms for more than 2 months after treatment; and recurrence of radicular signs and symptoms within 12 months after treatment. In the case of treatment failure, the patient was subjected to a second treatment. In all cases, this was open surgery.

The physicians' opinion was scored in four categories (see Table 3); the first two categories were considered to be satisfactory and the last two unsatisfactory. The second treatment was evaluated separately by the same criteria. In patients who needed surgery following failed chemonucleolysis, the findings at discography and at surgery were compared. The patients' opinion was asked by means of a questionnaire approximately 12 months after the last intervention. In response to the question "Are you satisfied with the result of the treatment?", four possible answers could be given (see Table 4). If the answer was "yes" or "largely," the treatment was considered to be successful. In the other two categories the result of treatment was classified as unsuccessful. In addition, the duration of complaints before treatment and the level of disc herniation were compared with clinical outcome, patient's satisfaction, and work resumption in both treatment groups.

Statistical Methods

Because no clear indications for heterogeneity were found among the three participating neurosurgical centers, comparisons between the two groups of patients (chemonucleolysis vs. open surgery) were made after pooling these three strata. In most comparisons, the patients with pretreatment complaints lasting 6 months or less and more than 6 months could be pooled. Percentages were compared with Fisher's test, and mean scores with Yates' test. A result was considered to be significant when the p value was 0.05 or less. The most relevant percentages are accompanied by their 95% confidence interval.

Results

The study group included 151 patients: 99 (66%) males and 52 (34%) females. Of these, 78 patients underwent discectomy by open surgery, and 73 were subjected to chemonucleolysis (Table 1). During the same period, 96 other patients in the three participating centers fulfilled the criteria for inclusion but refused participation in the trial. Of these, 35 preferred open surgery, 41 preferred chemonucleolysis, and 20 patients...
Chemonucleolysis versus discectomy

### TABLE 1

Numbers of patients randomized according to type and location of treatment and duration of symptoms

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Amsterdam</th>
<th>Rotterdam</th>
<th>Heeren</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≤ 6 Mos</td>
<td>≤ 6 Mos</td>
<td>≤ 6 Mos</td>
</tr>
<tr>
<td>open surgery</td>
<td>17</td>
<td>14</td>
<td>16</td>
</tr>
<tr>
<td>chemonucleolysis</td>
<td>16</td>
<td>12</td>
<td>11</td>
</tr>
<tr>
<td>total cases</td>
<td>33</td>
<td>26</td>
<td>24</td>
</tr>
</tbody>
</table>

**Abbreviations:** Surg = surgery; Chemo = chemonucleolysis.

Refused for other reasons. Some characteristics of all 247 patients eligible for the trial are presented in Table 2. There was a slightly higher percentage of patients with radicular complaints present for longer than 6 months in the group of patients who refused consent, compared to the participants in the trial (54% vs. 45%); however, the difference is not statistically significant. In other respects the two groups were comparable.

In the chemonucleolysis group, 16 patients (22%) experienced a marked increase in radicular pain within 30 days after treatment. In seven of these patients the complaints were still present in the same intensity 2 months after chemonucleolysis, which was considered to be a failure of treatment and an indication for surgery. Of the other nine patients, four improved markedly and five made a full recovery within 12 months posttreatment. In the surgery group there was no increase in radicular pain during the postoperative period.

Table 3 shows the physicians' assessment of the results of the initial treatment after 12 months, graded into four categories. The most striking difference between the two groups is the number of patients requiring a second treatment (which was open surgery in all cases) because of a failure of the first treatment within the follow-up period of 1 year. In the surgery group this number was two (3%; 95% confidence interval 0.3% to 9%), and in the chemonucleolysis group 18 (25%; 95% confidence interval 15% to 36%). This difference is statistically significant (p < 0.0001). In the chemonucleolysis group this failure was due to: a failure to puncture the disc in two patients; a persistence of or increase in radicular pain more than 2 months after chemonucleolysis (seven patients); or a recurrence of radicular signs within 12 months (nine patients). In the physicians' opinion, the result of open surgery was satisfactory in 85% of cases (95% confidence interval 75% to 92%) and the result of chemonucleolysis was satisfactory in 63% (95% confidence interval 51% to 74%). This difference is also significant (p < 0.01). The patients' judgment of the results of the initial treatment was almost identical to the physicians' assessment. The result of open surgery was found to be satisfactory by 78% of the patients, compared with 60% for chemonucleolysis. One should note that the categories for the physicians' and the patients' assessments are not absolutely identical.

In Table 4 the final result 12 months after the last treatment is presented for those patients who needed a second treatment in the follow-up period because of failure of the initial treatment. In 16 patients (10 males and six females), open surgery was performed after failure of chemonucleolysis. The mean age in this group was 38 years compared with 34 years in the total group. The final outcome was successful in seven patients confidence interval 15% to 36%).

### TABLE 2

Characteristics of patients entering the trial compared with those who refused consent

<table>
<thead>
<tr>
<th>Feature</th>
<th>Patients in Trial</th>
<th>Consent Refused</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Surg Chemo</td>
<td>Surg Chemo</td>
</tr>
<tr>
<td>total cases</td>
<td>44/39</td>
<td>34/34</td>
</tr>
<tr>
<td>male/female</td>
<td>30/14</td>
<td>20/14</td>
</tr>
<tr>
<td>mean age (yrs)</td>
<td>33/34</td>
<td>34/34</td>
</tr>
<tr>
<td>occupation†</td>
<td>4/35</td>
<td>6/27</td>
</tr>
</tbody>
</table>

- Of 247 eligible patients, 151 (61%) gave their informed consent. Surg = surgery; Chemo = chemonucleolysis.
- Data are given as independent/paid employment. Not all patients could be classified as "occupation."

### TABLE 3

Physicians' opinion 12 months after initial treatment

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Physicians' Opinion</th>
<th>Total Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1 2 3 4</td>
<td></td>
</tr>
<tr>
<td>open surgery</td>
<td>32 34 10 2</td>
<td>78</td>
</tr>
<tr>
<td>chemonucleolysis</td>
<td>26 20 9 18</td>
<td>73</td>
</tr>
<tr>
<td>total cases</td>
<td>58 54 19 20</td>
<td>151</td>
</tr>
</tbody>
</table>

**Note:** Definition of score: 1 = pain disappeared and neurological function normal or normalized; 2 = pain lessened and neurological function normalized; 3 = pain not lessened or pain not disappeared and neurological function not normalized; 4 = second treatment (surgery) before completion of 1-year follow-up period. Scores of 1 or 2 were considered satisfactory, scores of 3 or 4 unsatisfactory.

### TABLE 4

Assessment of results 12 months after treatment by patients who underwent second treatment

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Patients' Opinion</th>
<th>Total Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>open surgery failed</td>
<td>1 1 1 2</td>
<td></td>
</tr>
<tr>
<td>disc puncture failed</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>chemonucleolysis</td>
<td>3 4 2 7</td>
<td>16</td>
</tr>
<tr>
<td>total cases</td>
<td>5 5 2 8</td>
<td>20</td>
</tr>
</tbody>
</table>

**Note:** Answer to the question "Are you satisfied with the final result of treatment?" scored: 1 = yes; 2 = largely; 3 = barely; and 4 = no. Scores of 1 or 2 were considered successful, scores of 3 or 4 unsuccessful.
Table 5 presents the patients' assessment of the final result of treatment (including second treatment) 12 months after the last intervention for the total group. The result was successful in the surgery group in 61 cases (79%; 95% confidence interval 68% to 88%), and in the chemonucleolysis group in 53 cases (73%; 95% confidence interval 61% to 82%). The mean scores for the two groups are also compared in greater detail according to the four categories of scores 1 to 4. The difference between the two modes of treatment seems to be more pronounced (1.71 vs. 1.95), but is again not significant (p = 0.20). The duration of the preoperative complaints was irrelevant to the outcome.

With regard to pain, the overall results 6 and 12 months after the last intervention were similar for either form of treatment. However, in both groups there were some individual shifts between 6 and 12 months after treatment: 17 patients showed a further improvement and 17 patients deteriorated in the same period. In

Table 6 the progress of pain 12 months after treatment is compared to the preoperative symptoms for the surgery group and the chemonucleolysis group. The groups are split according to duration of preoperative complaints (< 6 months and > 6 months). There is no statistically significant difference in progress between the two methods of treatment or between the two patient groups.

Considering the two levels of disc herniation, L4–5 and L5–S1, no difference with respect to pain relief was found between the two methods of treatment. Both methods appeared to produce slightly better results at the L5–S1 level (Table 7, see categories “pain disappeared” and “pain improved”). When differentiating according to the location of pain, leg pain symptoms generally showed greater improvement after 12 months than low-back pain. Also, in patients who had suffered symptoms for 6 or less months, there was an indication that open surgery was more effective in relieving leg pain than chemonucleolysis (90% vs. 74% successful, 0.05 < p < 0.10).

Table 8 presents the number of patients resuming work 12 months after final treatment. There was little difference between the two treatment groups. The duration of the preoperative complaints appeared to be of no relevance. Of the patients who had returned to work either full-time or for a large proportion of the time after 12 months, five indicated that they could not manage their work, although their preoperative pain had disappeared; 13 patients mentioned the same al-
Chemonucleolysis versus discectomy

though their pain had diminished. Obviously, work satisfaction in these patients depends on more than their radicular complaints. Finally, of 66 patients who were free of pain according to the physicians' assessment after 12 months, six indicated on their questionnaire that they were still suffering some pain.

In both treatment groups there were only a few complications. One patient showed an increase of neurological symptoms after surgical discectomy due to a partial lesion of the nerve root involved. In one case a small dural defect occurred during surgery with subsequent leakage of cerebrospinal fluid, which caused no further consequences. One patient suffered a urinary tract infection postoperatively. One patient showed a slight allergic erythema after chemonucleolysis. No other allergic reactions were seen. Of the two patients in whom puncture of the disc for chemonucleolysis failed, one underwent surgical discectomy during the same session under general anesthesia. Following this procedure, the patient woke up with a partial cauda equina lesion, which lasted for some weeks. It is not clear whether this lesion was caused by the repeated puncturing or by the subsequent surgical intervention.

In all patients a discography was performed preparatory to the chemonucleolysis, using 1 to 2 ml of watersoluble contrast medium. In 19 patients, contrast medium was seen to leak out of the disc. Only three of these patients required a second treatment, in each case an open discectomy. In two of these a free disc fragment was found in the spinal canal. No free fragment was found in the third patient.

Discussion

The most common forms of treatment for lumbar disc herniation with radicular signs and symptoms are bed rest, physiotherapy, open surgery, and chemonucleolysis. In the long term, conservative therapy (such as bed rest and physiotherapy) or even no specific therapy at all almost always results in an improvement or cure of the radicular syndrome. Comparing the results of conservative and surgical therapy, Weber found that these results converge in the long term and do not differ remarkably after a follow-up period of 5 to 10 years. No randomized or nonrandomized studies have been performed comparing the efficacy of chemonucleolysis with prolonged bed rest, physiotherapy, or no specific treatment; however, it is most likely that the long-term outcome would be the same as found by Weber for open surgery. The only reason for applying anything other than conservative therapy is to reach a better therapeutic effect in the short term. If the intensity of pain, the neurological (in particular motor) deficit, or the degree and duration of handicap is disabling the patient in his daily life, active intervention must be considered and a choice made between chemonucleolysis and discectomy. Which of the two methods of treatment gives the better and quicker therapeutic effect in cases of severe or disabling radicular symptoms has yet to be established.

Since the first description of surgical disc removal by Mixter and Barr some 50 years ago, the beneficial effects of open surgery on radicular signs and symptoms has been proved in many retrospective and prospective studies. More recently, it has become well known that patients suffering from sciatica due to a herniated disc may also benefit from chemonucleolysis. The efficacy of chymopapain has been shown in nonrandomized and randomized studies, in which it was compared with placebo. Chemonucleolysis has been associated with success percentages between 44% and 98%, with half of the studies reporting a success rate between 70% and 81% (mean 73%). This variation of success rates in different studies is not primarily the result of a difference in efficacy, but is most probably due to a difference in selection of patients and in criteria for the judgment of outcome. With regard to the selection of patients it is essential to realize that chymopapain is only effective on soft disc tissue. Therefore, patients suffering from sciatica due to bone compression secondary to spondylosis must be excluded from receiving chemonucleolysis. This selection is sometimes very difficult and is probably not made in the same way in different studies.

The criteria for the effect of treatment in most studies are the subjective satisfaction of the patient, relief of pain, improvement of neurological signs, and resumption of work. Howe and Frymoyer have shown that many differences in outcome between different studies can be explained by the choice of questions in the questionnaire used to assess outcome. Best results are commonly obtained when subjective satisfaction of the patient is considered, and worst results when attempts are made to measure changes objectively. For these reasons, it is essential that a study to compare the therapeutic effects of chemonucleolysis and open surgery is randomized. It should also be borne in mind that such a comparison is only valid for those patients who are suffering from sciatica due to soft-disc herniation. It is probable that open surgery will be the only choice of treatment in a much higher percentage of patients, in whom the radicular syndrome is caused by bone compression.

In the current randomized study, the study group was selected in such a way as to exclude as many patients as possible with radicular compression not caused by a soft-disc herniation. The age limits were 18 and 45 years. With increasing age, spondylotic changes of the spine are more responsible for radicular signs. If those patients had been entered into the study, even randomly, the comparison of the two methods of treatment might have been influenced negatively for chemonucleolysis without saying anything about the efficacy of chemonucleolysis for the treatment of lumbar disc herniation per se. These restricted age limits diminished the number of patients in our study.

It is difficult to properly quantify on an absolute scale individual results at different times following treatment, especially the neurological signs. Therefore, we used...
relative measurements and did not analyze these different neurological signs explicitly; we only presented an overall judgment of the relative changes in relation to the preoperative state.

According to the physicians, the results 1 year after open surgery as initial treatment appeared to be satisfactory in 85% of cases compared with 63% for chemonucleolysis. According to the patients, the incidence of a favorable outcome was 78% for surgical cases and 60% for chemonucleolysis cases. In 25% (95% confidence interval 15% to 36%) of the patients undergoing chemonucleolysis, the effect on the radicular signs was so poor that they had to be operated on within 1 year in an attempt to obtain a better result. In the surgery group only 3% (95% confidence interval 0.3% to 9%) of the patients had to be subjected to a second operation. In addition, 22% of the patients subjected to chemonucleolysis definitely had more radicular complaints in the period immediately postoperatively than before the procedure in contrast to none of the patients subjected to open surgery. The conclusion is that the success rate of open surgery is superior to that of chemonucleolysis. The success rate of chemonucleolysis (about 60%) is definitely lower than in many non-randomized studies but is in accordance with the findings in the small randomized studies of Crawshaw, et al., and Ejeskär, et al.

The decision that the initial treatment had failed was made immediately in two cases in whom disc puncture had failed. In seven patients an increase in radicular pain occurred following chemonucleolysis and did not subside within 2 months after treatment. This period of time is arbitrary but, considering that the goal of aggressive treatment is improvement after failed conservative therapy in the short term, this period of time must be considered sufficient.

The results of open surgery following failed chemonucleolysis are worse than in patients who underwent surgery primarily. The success rate in this group was 44% (95% confidence interval 20% to 70%). Crawshaw, et al., found that the response to surgery following chemonucleolysis was satisfactory only in patients who relapsed after an initial good response to chymopapain. The reason for this might be that an immediate failure is due to a free disc fragment. In our series, however, a free fragment was found in only two patients undergoing surgery following chemonucleolysis.

Twelve months after final treatment, no statistically significant difference in results between the two procedures (chemonucleolysis or open surgery, including subsequent surgery in the case of failure) could be demonstrated. This is in accordance with the findings of Ejeskär, et al. A difference may still be present but is too small to be detected in this study. It also might be an argument for the statement by Weber that, in the long term, there is no difference in outcome whichever method of treatment has been chosen.

The disc herniations at the L5–S1 level fared slightly better than those at the L4–5 level, probably because the smaller diameter of the spinal canal at the L4–5 level plays a more important role in the genesis of a radicular syndrome than at the L5–S1 level.

There was no less favorable result of chemonucleolysis in those patients where discography showed a leak of the contrast medium out of the disc space in comparison to those without leakage. In our opinion, therefore, leakage of contrast material from the disc space does not constitute a contraindication for the procedure.

The complication rate in our study was low, both after chemonucleolysis and after open surgery. The low rate of complications in chemonucleolysis is in agreement with findings in the literature, which indicate a mortality rate of approximately 0.05% and an anaphylactic reaction of 0.5%.

The conclusion of a recent nonrandomized Italian study carried out on 156 patients with a radicular syndrome treated by chemonucleolysis is that, in the case of a small herniation, chemonucleolysis is preferable. In disc herniations of medium size, chemonucleolysis offers an alternative to surgery, but recovery after surgery is quicker. In the case of a large herniation and also in patients with neurological deficit, chemonucleolysis (according to that study) is not indicated because recovery after operation is quicker and better. Other investigations are required to provide more definite answers. Our study does not allow conclusions in this regard.

In conclusion, a patient who has a radicular syndrome caused by a lumbar disc herniation can benefit from chemonucleolysis, and it may be that radicular signs and symptoms disappear rapidly; however, pain may also persist or recur, requiring open surgery in 25% of cases. The clinical course is, therefore, more complicated when chemonucleolysis rather than open surgery is chosen as the primary treatment.

Acknowledgments

The authors express their gratitude to Mr. F. C. van Ginkel of the Department of Theory of Medicine, Epidemiology and Biostatistics, Free University, Amsterdam, for his advice and assistance in the computation. Miss Ann Ramcharan of the Department of Neurosurgery, Free University, assisted expertly in the preparation of the manuscript.

References

Chemonucleolysis versus discectomy


Manuscript received August 12, 1988.
This material was presented in part before the Eighth European Congress of Neurosurgery, Barcelona, Spain, in September, 1987.
Address for Dr. Braakman: Department of Neurosurgery, Erasmus University Hospital, Rotterdam, The Netherlands.
Address for Dr. Berfelo: Department of Neurosurgery, De Wever Hospital, Heerlen, The Netherlands.
Address for Dr. Bezemer: Department of Theory of Medicine, Epidemiology and Biostatistics, Free University, Amsterdam, The Netherlands.
Address reprint requests to: H. August M. van Alphen, M.D., Ph.D., Department of Neurosurgery, Free University Hospital, P.O. Box 7057, 1007 MB Amsterdam, The Netherlands.