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Published in:

Journal of the European Academy of Dermatology and Venereology

DOI:

[10.1111/j.1468-3083.2004.00724.x](https://doi.org/10.1111/j.1468-3083.2004.00724.x)

2004

[Link to publication](#)

Citation for published version (APA):

Nilsson, H.-J., Psouni, E., Carstam, R., & Schouenborg, J. (2004). Profound inhibition of chronic itch induced by stimulation of thin cutaneous nerve fibres. *Journal of the European Academy of Dermatology and Venereology*, 18(1), 37-43. <https://doi.org/10.1111/j.1468-3083.2004.00724.x>

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4

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Profound inhibition of chronic itch induced by stimulation of thin cutaneous nerve fibres

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ABSTRACT

Background Despite the fact that severe itch is common in many dermatological diseases, the therapeutic arsenal against itching is limited. From neurophysiological experiments, using a new technique termed cutaneous field stimulation, it is known that acute itch can be effectively relieved by stimulation of cutaneous nociceptors.

Methods We tested the effects of cutaneous field stimulation (25 min, 16 electrodes, 4 Hz per electrode, up to 0.8 mA) on chronic itch due to atopic dermatitis. Transcutaneous electrical nerve stimulation (100 Hz, up to 26 mA) was used for comparison. In 27 patients, itch was measured just prior to, during and at regular intervals up to 12 h after either type of treatment.

Results Both treatments augmented the itch sensation during ongoing stimulation, presumably reflecting an altered sensory processing in the somatosensory pathways of chronic itch patients. However, after cessation of cutaneous field stimulation, but not transcutaneous electrical nerve stimulation, the itch sensation was significantly depressed for up to 7 h. The peak inhibitory effect (about 25% of control) was reached between 1 and 5 h poststimulation. Neither treatment had any significant effect on allodynia, as measured before and 10 min after stimulation.

Conclusion It is concluded that cutaneous field stimulation strongly depresses chronic itch, and is a potentially useful symptomatic treatment of itch.

Key words: dermatitis, itchy skin, pruritus, somatosensory, TENS

Received: 28 March 2002, accepted 2 September 2002

Introduction

Itch is among the cardinal symptoms of several dermatological diseases such as lichen simplex, lichen planus and atopic dermatitis.^{1–4} Pruritus is often the most crippling feature of the disease, causing the patient severe discomfort. However, the therapeutic arsenal to reduce the symptom of itch is rather limited and the effect of the various treatments to date highly variable.^{2,5,6}

Itch is often defined as a sensation that induces the urge to scratch. Scratching, in turn, gives instant relief from itch, presumably through activation of mechano-nociceptors in the skin.^{3,5,7} It is known that painful stimuli inhibit the sensation of itch.⁵ Unfortunately, scratching will in the long run exacerbate the underlying skin condition by inducing additional lesions in the skin. The itch may in fact sustain the underlying disease by

inducing a vicious itch–scratch cycle.³ A treatment method that mimics the beneficial effects of scratching without hurting the skin would therefore be valuable.

A technique has recently been developed in our laboratory that permits controlled electrical stimulation preferentially of thin nerve fibres, including nociceptors, in the dermo-epidermal junction.^{8–10} This technique, termed cutaneous field stimulation (CFS), has in experimental studies proved to induce very robust and long-lasting inhibition of acute histamine-evoked itch in healthy subjects.^{9,10} Here, we have studied the effects of CFS on patients suffering from chronic itch. Because of its high prevalence, chronic atopic dermatitis was selected as the target condition.

The primary aim was to examine whether CFS induced any acute effects on itch intensity over a 12-h period following

treatment. For comparison, conventional transcutaneous electrical nerve stimulation (TENS) was used. In view of the prevalence of alloknesis (i.e. itch caused by stimuli such as touch that does not normally produce itch^{11–13}) often experienced by patients with atopic dermatitis, the secondary aim of this study was to investigate any potential effects of CFS on alloknesis.

Materials and methods

Thirty-five patients, 24 females and 11 males (age 20–65 years, median 32 years), suffering from atopic dermatitis, responded to our inquiry to participate in a study designed to evaluate the effects of two harmless cutaneous electrical techniques (CFS and TENS) to treat itch. All patients had a history of atopic dermatitis as diagnosed by the UK working party's diagnostic criteria.^{14–16} In order to be included, the patient had to exhibit an on-going eczema. Among areas of active eczematous skin, one was selected where the patient indicated that he/she had experienced itch in the last few days. The area chosen also exhibited erythema, lichenification, scratch marks and sometimes oozing. Among alternative lesions the one most suitable for applying the electrode plate (see below) was chosen.

The study was performed in accordance with the World Medical Association Declaration of Helsinki¹⁷ and was approved in advance by a regional ethical committee. Patients were initially contacted by a letter that informed them about technical and practical aspects of the study, without revealing any information as to the theoretical background or possible outcomes of the treatments. Each subject gave written informed consent.

To avoid possible bias, none of the authors was involved in the actual testing sessions, which were led by an employee at the dermatological clinic and a university employee otherwise unconnected to the study and without knowledge as to the nature of the project. Furthermore, during data analysis the authors were blinded regarding what treatment each patient had been subjected to.

Itch and alloknesis intensities were measured via a 100-mm long visual analogue scale (VAS), presented horizontally and marked with 'no itch' on the left end and 'maximal imaginable itch' at the other end.^{18–21} A control measurement for each patient was calculated by averaging VAS indications over a period of 3 days prior to treatment. A baseline measurement was taken just prior to commencing CFS/TENS treatment. For comparison, mean VAS values were normalized with respect to baseline.

Certain criteria had to be met in order for patient treatment protocols to be included in the final analysis. Patients were excluded if (1) the code to the type of treatment a particular patient had tried was inadvertently broken before the analysis was completed ($n = 1$); (2) the current of the apparatus had not been turned on, i.e. no actual electrical stimulation

had taken place ($n = 1$); (3) no itch was reported in the baseline measurement ($n = 6$); (4) the control measurement indicated an itch intensity below 2 mm on the VAS. In total, data from eight patients were excluded from the analysis.

Experimental protocol

The intensities of itch sensation and alloknesis were tested prior to, during and after CFS/TENS treatment in all patients ($n = 27$). Starting 3 days prior to the day of treatment, patients had to record their itch intensity twice daily (morning and evening) in an 'itch book' consisting of several pages, a separate VAS presented on each. The objective was to train patients in rating their perceived itch intensity on the VAS and to obtain the control measure to be used as a patient inclusion criterion. On the day of treatment each patient was placed in a separate examination room, with no possibility to communicate with other patients. An experienced dermatologist examined the patients and clinically evaluated the severity of their eczema according to SCORAD²² and indicated which part of the body should be stimulated (fig. 1). The patients were then transferred to another room and randomly assigned to either CFS or TENS treatment. A baseline measurement was taken just prior to commencing CFS/TENS treatment. During treatment, the CFS electrode plate (cathode) or TENS cathode was applied directly on the itchy skin area indicated by the dermatologist.

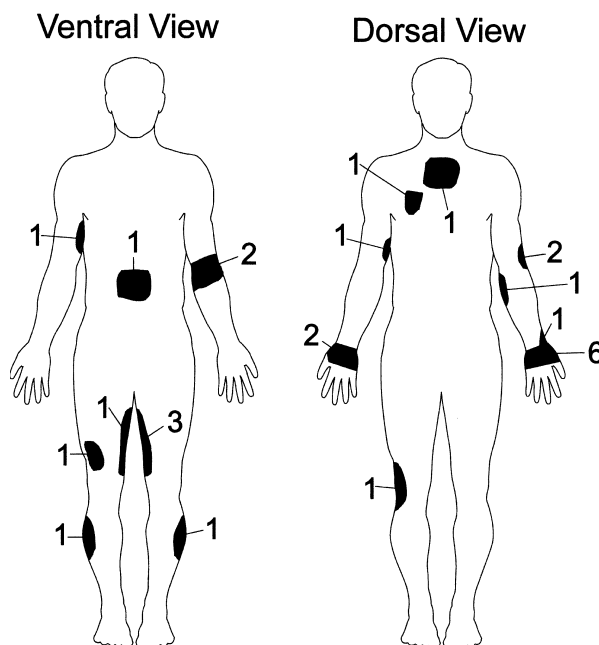


fig. 1 Body schematic of the sites stimulated with CFS or TENS. The number of patients is indicated for each site. In total, 27 patients were included (CFS, $n = 15$; TENS, $n = 12$).

Conditioning stimulation

CFS was used for localized stimulation of thin myelinated and unmyelinated fibres in the superficial skin. CFS uses a flexible rubber plate with 16 needle-like electrodes regularly fixed at 2-cm intervals (4×4 matrix). Each electrode is surrounded by a 'stop device' 2.0 mm in diameter that protrudes 2.0 mm from the plate. The electrode tip protrudes 0.3 mm from the stop device. When gently pressing the electrode plate against the skin, the electrode tips are introduced adjacent to the receptors in the epidermis and the superficial part of dermis. Since the electrodes traverse the electrically isolating horny layer of the epidermis and the current density is high near the sharp electrode tips, the voltage and current necessary to stimulate cutaneous nerve fibres are small, typically less than 10 V and up to 0.8 mA, respectively. As the current density decreases rapidly with distance, localized stimulation is achieved. In the present study, the electrodes were stimulated consecutively with a constant current stimulator (64 pulses/s), each electrode with a frequency of 4 Hz (pulse duration 1.0 ms). A self-adhesive surface electrode (Uni-patch, Re-Ply) served as anode and was placed about 5 cm away from the needle electrode plate.

Conventional TENS (0.2 ms, 10–26 mA, 100 Hz)^{23–25} was used for comparison. Self-adhesive surface electrodes were used for TENS (see above).

Identical procedures were employed for CFS and TENS. The cathode was always placed directly overlying the itchy skin, with the anode placed approximately 5 cm from it. Patients were instructed to increase the intensity of the conditioning stimulation to the perception threshold (T), thereafter slowly to increase up to $2T$ over a 10-min period and subsequently to maintain this intensity for the rest of the stimulation period. The total conditioning stimulation time was 25 min.

Measurement of itch

Itch intensity was measured just prior to commencing CFS/TENS treatment (baseline) and 15 min into the ongoing stimulation. Itch intensity was also recorded directly upon terminating the conditioning stimulation, as well as 12 min (0.2 h) and 1 h later. Subsequently, the patients went home with another 'itch book' in which they were instructed to mark their itch intensities at regular time intervals (3, 5, 7, 9 and 12 h post-conditioning). Itch books were returned to the experimenters by mail within a few days.

Induction and measurement of alloknesis

Alloknesis was elicited here by tactile stimulation with von Frey monofilaments. Two different calibre (generating a force of 40 mN or 70 mN) von Frey monofilaments²⁶ were used to stimulate cutaneous A β fibres. Each monofilament was applied directly at the centre of the treated area and 8 and 16 cm away

from it. The evoked itch sensation was recorded on separate VAS for each calibre and site.

Statistics

One-way repeated measures ANOVA with Dunnett's *post hoc* test was used for multiple matched comparisons within a treatment group. Wilcoxon's signed ranks test was used for single matched comparisons within a group. The Mann-Whitney U test was used for comparisons between treatment groups. Significant differences were assumed at a level of significance of $P < 0.05$. Unless otherwise stated, mean and SEM are reported.

Results

To allow direct comparison between the two treatment groups, all data were normalized with respect to the baseline measurement recorded just prior to commencing treatment.

Effects on itch during ongoing conditioning stimulation

On average, patients treated with CFS indicated increased intensity of itch sensation 15 min after the onset of CFS treatment (239.6% of baseline \pm 24.4 SEM, $P < 0.01$) (fig. 2). TENS patients, however, indicated a significantly larger increase of itch compared to CFS patients (409.7% of baseline \pm 69.3 SEM, $P < 0.01$).

Post-conditioning effects of CFS and TENS on chronic itch

All but one patient treated with CFS reported clear inhibition of itch that lasted for at least 7 h (fig. 3). The inhibition was

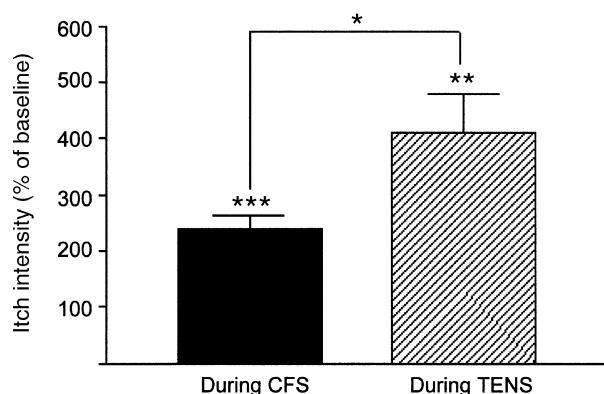


fig. 2 Itch intensity recorded during ongoing stimulation with CFS and TENS. Mean sensory intensities after CFS (black bar, $n = 15$) and TENS (hatched bar, $n = 12$) are shown here. Error bars indicate + SEM. Wilcoxon's signed ranks test was used for matched comparisons within treatment groups and the Mann-Whitney U test was used for comparison between the two treatments; ns, not significant; * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$.

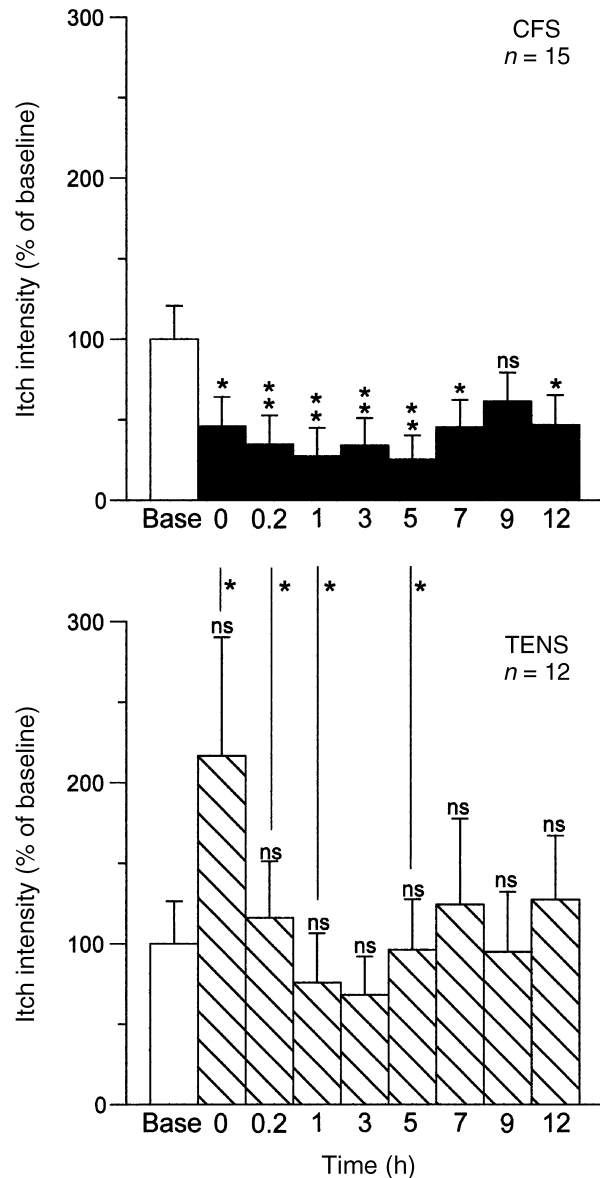


fig. 3 Effects of CFS (top diagram) and TENS (bottom diagram) on chronic itch over a 12-h period. The mean sensory intensities after CFS (black bars, $n = 15$) and TENS (hatched bars, $n = 12$) are shown. Error bars indicate + SEM. ANOVA repeated measures with Dunnett's *post hoc* test was used for matched comparisons within a group, whereas the Mann-Whitney *U* test was used when comparing effects of the two treatments; ns, not significant, * $P < 0.05$, ** $P < 0.01$.

evident directly after cessation of the treatment and reached peak 1–5 h post-conditioning (peak 25.2% of baseline \pm 14.9 SEM, $P < 0.01$). By contrast, TENS treatment induced no significant inhibitory effects at all. In fact, the itch sensation recorded directly after terminating TENS tended to be stronger, compared to baseline itch intensities (216.5% of baseline \pm 73.8 SEM, $P > 0.05$). Differences between the effects induced by CFS and TENS were also significant on measurements taken directly, at 0.2, 1 and 5 h post-conditioning (fig. 3).

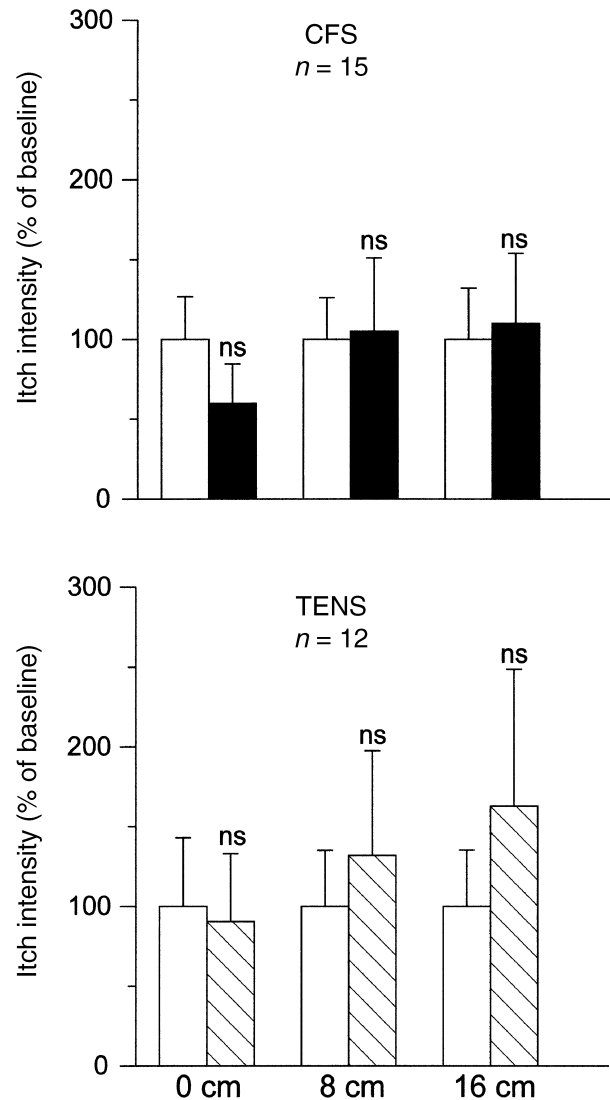


fig. 4 Effect of stimulation with CFS or TENS on allodynia. Mean sensory intensities after CFS (black bars, $n = 15$) and TENS (hatched bars, $n = 12$), at indicated distances from the centre of itch, are shown. Error bars indicate + SEM. Wilcoxon's signed ranks test was used to compare itch intensities within the same treatment group; ns, not significant.

Effects of CFS and TENS on allodynia

Neither CFS nor TENS resulted in any significant effect upon allodynia, regardless of which monofilament was used to evoke allodynia (40 or 70 mN, fig. 4). However, a tendency for increased allodynia was noticeable after TENS treatment, especially as measured at 8 cm (131.9% of control \pm 65.7 SEM, $P > 0.05$) and 16 cm (not reaching the level of statistical significance: 162.9% of control \pm 85.9 SEM, $P > 0.05$) away from the centre of itch. In contrast, CFS tended to reduce allodynia but the effect did not reach statistical significance (Mann-Whitney *U* test, $P > 0.05$).

Discussion

The present study demonstrates that stimulation with CFS, preferentially activating A δ and C fibres, induces a profound inhibition of chronic itch lasting for up to 7 h, thus confirming previous results obtained on acute experimental itch. Both CFS and TENS induced an augmented itch sensation during treatment, this effect being significantly higher for TENS. None of the two conditioning stimulations had any significant immediate impact on alloknesis. Only one itchy skin area per patient was stimulated in the present study. In clinical practice one would have to stimulate more than one area.

On possible placebo effects induced by the treatments

Virtually any type of treatment can induce a placebo effect.^{27–29} In previous studies with healthy subjects, placebo effects of CFS were typically small.^{9,10} In the present study we applied TENS on patients as a control treatment. Identical procedures were employed when using CFS and TENS. In addition, the apparatuses look alike and induce similar sensation intensities. Furthermore, the patients could not anticipate that one of the two treatments would be better than the other. It is therefore reasonable to conclude that any placebo effect would be of equal size in the experimental and control groups. A highly significant inhibitory effect of CFS – but not TENS – on chronic itch was obtained here, just as in healthy subjects in previous studies.^{9,10} This differential effect between the two treatments cannot but correspond to the actual effect of CFS treatment.

On the effect of TENS on itch

Conventional TENS is known to predominantly stimulate coarse afferent fibres^{24,25} usually resulting in a small and temporary inhibition of experimental itch.^{9,30} It has previously been suggested that TENS does not give sufficient relief from itch for practical clinical purposes.^{30,31} The present study supports this suggestion and, in addition, shows that chronic itch may considerably worsen during and after application of TENS.

Altered sensory processing in patients suffering from chronic itch

There are several indications of an altered sensory processing in patients with chronic itch compared to healthy subjects. First, in healthy subjects, TENS induces a tingling sensation. In chronic itch patients, the itch intensity was dramatically increased during TENS, overshadowing any other sensations including tingling, while alloknesis was easily evoked by light tactile stimulation. These findings indicate that in chronic itch

patients tactile A β fibres, which are not normally involved in the transmission of itch, have acquired the capacity to signal information that is perceived as itch. Second, CFS in healthy subjects, which preferentially stimulates A δ and C fibres, causes a pricking and somewhat burning sensation that quickly fades during continuous stimulation. Ongoing CFS in chronic itch patients caused an increased itch sensation. This is an indication that the central processing of information from thin fibres may also be altered in the chronic itch patient. Third, after cessation of CFS, peak inhibitory effect was attained within the first hour in healthy subjects⁹ but as late as 5 h post-conditioning in the chronic itch patient group, suggesting a delayed onset of these inhibitory mechanisms. In fact, in a pilot study where CFS was repeated daily, the abnormal itchy state disappeared entirely after a few days; CFS was consecutively felt as pricking and somewhat burning (Schouenborg, unpublished observation).

In summary, the condition of chronic itch studied here appears to result in an altered sensory processing of information carried by both large and small cutaneous afferent fibres. It is conceivable that this 'itch state', possibly a reflection of alloknesis, initially interferes with or weakens the inhibitory mechanisms induced by CFS and that CFS eventually resets alloknesis. Further studies are needed to evaluate the latter possibility. It should be kept in mind that there may also be differences in the peripheral mechanisms, such as in the chemical mediators involved in acute and chronic itch.

On possible antipruritic mechanisms employed by CFS

We have previously suggested that CFS, by stimulating thin afferent fibres, mimics the itch inhibitory effects of scratching the skin. Several findings indicate that this inhibition is due to an active inhibitory process in the central nervous system. First, the itch inhibition greatly exceeds the duration of CFS and is not followed by after sensations.⁹ Second, it has previously been shown that the flare reaction in the skin following iontophoretically administered histamine is not affected by CFS, indicating that the impulse transmission in thin fibres is not blocked in the periphery.⁹ This point is corroborated by the fact that CFS produces an inhibition at least 10 cm away from the histamine-stimulated skin area.⁹ Third, it is known from animal experiments that stimulation of thin fibres in the dorsal roots at frequencies that inhibit itch in humans¹⁰ can induce an inhibition of transmission in the dorsal horn of the spinal cord lasting for several hours.^{32–36} Taken together, these findings suggest the presence of a central itch inhibitory mechanism, possibly in the spinal cord. It may be worth noting that since coarse fibre stimulation was not efficient (see section 'On the effect of TENS on itch' above), the mechanisms involved in the central itch inhibition differ from those assumed to be involved in the gate theory.³⁷

Conclusions

CFS results in a profound and reproducible depression of chronic itch for over 7 h. This finding confirms previous findings on acute experimental itch. The relief from itch may also break the vicious itch–scratch cycle, thereby increasing the chances of healing. CFS may therefore be a powerful therapeutic method to treat clinical itch. A study clarifying the value of CFS on long-term treatment of itch is ongoing.

Acknowledgements

This project was supported by the Swedish Medical Research Council projects 10569 and 1013, the Medical Faculty of Lund, Alice and Knut Wallenberg's foundation, ASTRA Hässle Inc., Elsa and Thorsten Segerfalk's foundation, Crafoord's foundation, and Greta and Johan Kock's foundations. The skilful assistance of Susanne Rosander-Jönsson is gratefully appreciated.

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