Dinitrochlorobenzene (DNCB) Treatment of Viral Warts
A 5-year Follow-up Study

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A series of 43 patients with therapy-resistant viral warts of long-duration were treated with dinitrochlorobenzene (DNCB). Of the 37 patients, who completed the treatment, 19 were cured, including five of seven patients with hyperkeratotic tumor-like warts. The majority of the patients showed a depressed cell-mediated immune response. 25 patients were re-examined 5 years later and 8 additional patients answered on inquiry. Six (18%) of these patients had warts. Eight of the 21 primarily tuberculin-negative patients had developed immunity to tuberculin, and none of them had warts. Five of the 6 patients with warts were still tuberculin-negative. The reaction to DNCB had reverted to negative in 17 (68%) out of 25 tested patients and in the majority of the remaining cases a weak reaction only was seen. The study does not tell if the cure is a consequence of the DNCB treatment or a function of time. However, it shows that cure is associated with normalization of the cell-mediated immune response. The DNCB hypersensitivity seemed to disappear with time and late complications were not documented. Key words: Viral warts; DNCB; Cell mediated immune response.

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Warts are benign epidermal tumours of viral origin. In most cases they regress spontaneously within a few months, but in some cases they remain for years and prove resistant to all treatment modalities. In the healing process both humoral and cell-mediated immune responses are of importance (1, 2, 3, 4).

Viral warts have been reported to disappear after induction of delayed hypersensitivity with potent contact sensitizing agents, i.e. with DNCB (5, 6, 7, 8, 9, 10). So far no follow-up study has been reported. In the present study the rate of disappearance of warts is evaluated in correlation to the cell-mediated immune (CMI) response of the patients. In addition, the aim of the present study is to report the results of the follow-up of patients and to pay special attention to possible late complications attributable to cross sensitization with DNCB-related substances (11, 12).

MATERIAL AND METHODS
The original series consisted of 46 patients with recalcitrant viral warts treated at the Department of Dermatology, University Central Hospital, Helsinki, during 1975-1978. The re-examination of the patients was carried out in 1980-1983.

Of the 46 patients, three did not develop hypersensitivity to DNCB. The remaining 43 patients (24 females and 19 males) aged 14 to 70 years (mean 28.6 years) were included in the study. All of the patients had multiple warts of long duration (on the average 4.8 years, range 14 months to 30 years). Initially treatment with different keratolytics, curettage, electrocoagulation or cryotherapy had been tried without success. Seven of the patients had large, hyperkeratotic, tumour-like warts on their hands and soles of the feet. Of these seven patients, two had systemic lupus erythematosus (SLE), treated with steroids, and one patient had idiopathic thrombocytopenic purpura. One of the patients had Morbus Hodgkin. The remaining 36 patients had warts of more common type and 5 patients had
plane warts in addition. Of the 43 patients, 14 had warts on their hands as well as on their feet and 29 had warts only on either site, mostly on their feet (20 cases). DNBC sensitization was carried out according to the method described earlier (12, 13) but slightly modified by us. A total of 600 µg of DNBC dissolved in acetone to 1% was applied for 24 hours on the back of the patients, using large Finn Chambers (12 mm in diameter, volume 60 µl) and a filter disc. A challenge test was performed three weeks later with normal Finn Chambers (14) and DNBC concentrations of 0.25, 0.15, 0.05 and 0.005% in acetone (DNBC amounts 30, 30, 10 and 1 µg respectively). None of the 43 patients showed a spontaneous flare, graded as 4+ response by Catalona and coworkers (13). Subsequently the patients were divided into weak reactors with the challenge test positive to 30 and 50 µg corresponding to 1+ and moderate reactors with positive responses to 10 and 1 µg corresponding to 2+ and 3+ reactions.

Delayed hypersensitivity tests

Before starting the DNBC treatment, quantitative Mantoux, candidin and trichophytin tests were performed with the same methods as has been previously described by Johansson et al. (15).

Altogether 18 patients showed negative results in the Mantoux tests. Three patients responded only to 100 TU, while the remaining patients responded to 1 or 10 TU. Of the 21 patients with lowered TU response 18 had a negative result in the other two tests as well.

Treatment

Patients were treated weakly, at the outpatient clinic, with a cotton-tipped swab soaked in the DNBC solution (acetone) and the surrounding skin was protected with zinc paste. The nurse who carried out the treatment was instructed to wear protective gloves and she developed no adverse reactions. The concentrations of DNBC were adjusted according to the patient’s response to the challenge test. The concentrations were gradually increased from 0.1% to 3% and in a few instances up to 10% in patients with hyperkeratotic tumour-like warts. The reaction obtained was considered satisfactory when there was a slight or moderate reaction appearing as mild erythema, slight scaling and itching lasting for 2 to 3 days.

Adjunctive therapy with 40% salicylic acid plaster was used only on patients with hyperkeratotic plantar warts and in the seven patients with hyperkeratotic tumour-like warts.

RESULTS

Of the 43 patients at the beginning of the study, 37 completed the treatment. Two patients discontinued because of personal reasons and four patients because of side effects. Of the 37 patients 19 (51%) were cured during the treatment period, varying from 1 to 6 months. Most of the patients were cured during the first three months of treatment (on average 2.3 months). In five of these patients with wide-spread warts, both untreated and treated warts healed. Of the seven patients with hyperkeratotic tumour-like warts, altogether five were cured, including two of the patients with an auto-immune disease treated with steroids.

In three cases the warts were partly cured so that warts on the hands and glabrous skin were healed while warts on the soles persisted, and in two cases new warts appeared while

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| Warts                                           | Delayed hypersensitivity tests                    |                                                 |                                                 |                                                 |                                                 |
|                                                 | Mantoux - T- /C-                                 | Mantoux - T- /C+                                | Mantoux + T+ /C+                                | Not done                                       | Total                                           |
| Healed                                          | 11                                               | 3                                               | 5                                               |                                                 | 19                                              |
| Non-healed                                      | 7                                                | 3                                               | 6                                               | 2                                               | 18                                              |
| Total                                           | 18                                               | 3                                               | 9                                               | 7                                               | 37                                              |
the treated ones healed. In one case the warts healed already after two applications of DNCB. These 6 patients were not included in the 19 totally cured. In 12 (32%) there was no response to the DNBC treatment.

The cure rate of warts in the 37 patients was evaluated in correlation to the CMI response (Table I). The majority of the patients (21 out of 30 tested) showed a depressed CMI response. Of these 21 patients, altogether 11 were cured.

Follow-up study
We were able to re-examine 25 of the 37 patients who completed the study and 8 additional patients answered on inquiry. Of the 25 patients, 6 had warts at the time of the re-examination. In two of them warts had recurred 3 to 6 months after the therapy, and one patient had recently developed new warts. Three patients belonged to the non-healed group and they had warts on their soles. None of the 8 patients who answered on inquiry reported warts. The 25 patients who showed up for re-examination were re-tested with DNBC and Tuberculin (Table II). Of the 21 primarily tuberculin-negative patients 8 had developed immunity to tuberculin and none of them had warts, while 5 out of the 6 patients with warts belonged to the tuberculin-negative group. Four of them showed also a negative result to the DNBC test.

Of the 25 patients re-tested with DNBC solution containing 50, 30, 10 or 1 µg DNBC 8 (32%) showed a positive response while 17 (68% of the patients) gave a negative result to all of the concentrations tested.

Complications
Side effects were documented in 6 cases and 4 of them discontinued the treatment. Slowly healing tender vesicles developed on the surrounding skin associated with widespread eczema in three patients. One patient developed an erythematous rash with sudden fever, and another patient developed generalized urticaria. The remaining sixth patient complained of a burning sensation and local pain lasting for 2–3 days after each application. The excessive reactions did not correlate with the strength of the DNBC solution neces-

Table II. Occurrence of warts and correlation to the CMI response in the 25 patients retested for DNBC and tuberculin sensitivity 5 years after finishing the DNBC treatment

<table>
<thead>
<tr>
<th>Before treatment</th>
<th>After treatment</th>
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<tbody>
<tr>
<td>TU-positive</td>
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<td>Warts</td>
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1. Moderate DNBC reactors 17 1a 5 8 3 0 3 0 0 3
2. Weak DNBC reactors 8 0 0 3 5 0 3 1 1 5
3. DNBC-negative 0 0 0 0 0 1a 7 4b 5 17
Total 25 1 5 11 8 1 13 5 6 25

a This patient had large hyperkeratotic tumour-like warts in his soles.

b One of these patients was primarily cured with DNBC therapy but had a recent relapse.
sary to provoke a reaction in the challenge test, or with that used for treatment. On re-examination, the excessive reactions in the 6 patients had healed without scars or further complications.

Cross sensitivity
None of the 25 patients re-examined, or of the 8 patients who answered on inquiry reported contact sensitivity to sensitizing agents known to cross-react with DNCB. On the other hand, none of the patients had occupations which could be considered as belonging to a risk group.

DISCUSSION
In our series the cure rate of warts was rather low (51%) compared to the cure rate of most of the other reported series (5, 6, 7, 9, 10). This may be explained by the selection of patients. In our study most of the patients had wide-spread recalcitrant warts of long duration, mostly on their soles. In addition, patients with systemic autoimmune diseases under steroid treatment were included in the series. Furthermore it appeared that the majority of our patients showed a depressed cell-mediated (CM1) response, especially in the tuberculin tests. Because about 95% of Finnish infants are vaccinated, the immunity to tuberculin is generally high in Finland. It has been reported that patients with a lowered tuberculin response tend to have multiple, longstanding warts (16) as do those with e.g. systemic lupus erythematosus (17). However, we found that also the patients with initially lowered CM1 response were cured during the DNCB treatment, as did the patients with systemic autoimmune disease, but simultaneously tuberculin-negativity turned to tuberculin-positivity. None of these patients had recurrence of warts.

In previous studies it has been pointed out that the lowered CM1 response is connected with a poor response to DNCB therapy (5) and that the cure rate does not correlate to the strength of the DNCB reactivity. In our series the majority of patients healed had a rather high DNCB reactivity, while 5 out of 6 with recurrent or persistent warts belonged to the tuberculin-negative group, and four of them had also turned negative in the DNCB test. Furthermore the follow-up study showed that altogether 8 of the patients had become tuberculin reactive when re-tested five years later. None of these patients had recurrence of warts.

Previously, a heightened CM1 response after healing of warts has been demonstrated by in vitro tests (3) and intradermal tests with purified human papilloma virus from plantar warts (18). Our results, particularly as to tuberculin sensitivity, point into the same direction.

The risk of late complications attributable to DNCB seemed to be small, as none of the patients reported any sign of cross sensitivity and as the reactivity to DNCB did not seem to persist. Altogether 17 (68%) of the 25 patients re-tested showed a negative result and in the majority of the remaining patients the reaction was weak. The side effects attributable to DNCB during the treatment period were temporary. The mechanism by which DNCB induces curing of warts is not known. DNCB has both irritating and contact-sensitizing properties. The irritant effect does not explain why also untreated warts are cured and why most of the cases heal with weak DNCB solutions. It has been proposed that warts are cured as "innocent bystanders" to the inflammation without any wart-specific reaction (2, 10).

In conclusion it must be pointed out that even if the cure rate of warts in this selective series was not high, DNCB therapy can be considered as an alternative especially in cases with depressed cell-mediated immunity and when other treatments have failed.
REFERENCES


