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Source: *Occupational and Environmental Medicine*, Vol. 53, No. 4 (Apr., 1996), pp. 276-280

Published by: [BMJ Publishing Group](#)

Stable URL: <http://www.jstor.org/stable/27730530>

Accessed: 06/02/2011 14:36

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# Local cold exposure of the hands from cryosectioning work in histopathological and toxicological laboratories: signs and symptoms of peripheral neuropathy and Raynaud's phenomenon

G Wieslander, D Norbäck, C Edling

## Abstract

**Objectives**—To study relations between cryosectioning work, skin temperature, early signs of neuropathy in the hands, and vasospastic and neurological symptoms. Microtome work is carried out at histological and toxicological laboratories all over the world. It implicates local cold exposure of  $-20^{\circ}\text{C}$  on the hands of exposed laboratory technicians.

**Methods**—Thirty nine laboratory technicians who use microtomes at the preclinical and clinical laboratories at the University of Uppsala, Sweden were studied. An equal number of non-exposed laboratory technicians served as controls, matched for workplace, sex, age, and smoking habits. Information on symptoms, type of work, and personal factors were assessed by means of a self administered questionnaire. Two point discrimination ability was tested, and vibration perception thresholds were measured for both hands by a bio-thesiometer. Also, skin temperature was measured during cryosectioning work in those 15 technicians performing cryosectioning work during the study period.

**Results**—Most laboratory technicians did not use any gloves during cryosectioning work, and direct contact with frozen materials sometimes occurred and resulted in a rapid cooling of the skin. In six of 15 exposed subjects (40%), the mean skin temperature during microtome work was below  $20^{\circ}\text{C}$ . A later rise in skin temperature, due to a compensatory vasodilation, was found in two subjects. The group exposed to cold had signs of early neuropathy on the right hand, indicated both by vibrometry and two point discrimination test. Significant work related differences in clinical signs within the group exposed to cold was also found. No differences between exposed and non-exposed people were found for symptoms of Raynaud's phenomenon, numbness, or musculoskeletal complaints.

**Conclusion**—Our study shows that cryosectioning laboratory work may cause adverse health effects—for example, peripheral neuropathy—and measures should be taken to protect the hands from the local cold exposure.

(*Occup Environ Med* 1996;53:276–280)

**Keywords:** cryosectioning; neuropathy; frostbite; laboratory workers; skin temperature

Occupational exposure to cold may occur in various occupations, outdoors<sup>1</sup> or indoors.<sup>2</sup> Contact cooling can quickly result in frostbite, especially when handling frozen material with unprotected hands.<sup>1</sup> Exposure to local cold on the hands has been studied mainly in the food industry—for example, handling frozen fish in the fishing industry and frozen food in cold stores.<sup>3,4</sup> Cryosectioning is a technique used to prepare tissue preparations in many histopathological or toxicological laboratories, and implies cold exposure ( $-20^{\circ}\text{C}$ ) locally on the hands when working with a microtome. A laboratory cryosectioning worker referred to the University Hospital in Uppsala initiated this study. He had worked for seven years with animal preparations for research purposes without any gloves. Exposure time varied, but between four and six hours a day he was busy with cryosectioning. The symptoms he had were increasing loss of skin sensibility on the fingertips on his right hand and hyperaesthesia in the same skin area. Sensory nerve conduction velocities were normal in the arms and hands.

We could not find any information in the scientific literature on physiological reactions or health impairments related to this type of local cold exposure, so this epidemiological study in laboratory workers who carried out cryosectioning was performed.

The aims of the study were to elucidate if local cooling of the hands when working with microtomes could damage the nerve endings (neuropathy) in the hands, and if Raynaud's phenomenon or other symptoms of the hands were associated with such exposure. Another aim was to study changes of skin temperature during cryosectioning with a microtome.

## Material and methods

### STUDY POPULATION

All laboratory personnel involved in cryosectioning work at the laboratories of the preclinical and clinical departments at the University of Uppsala were identified, and were invited to participate in the study. For each exposed participant, one unexposed control subject was

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Accepted 8 December 1995

randomly drawn from the same workplace. The controls were thus laboratory workers from the same workplace who did not perform cryosectioning work. None of the controls had a history of cryosectioning work. None of the exposed or control workers had ever worked with hand held vibrating tools. Exposed and control workers were matched for age (five years), sex, and smoking (smoker or non-smoker). In total, 40 laboratory workers involved in cryosectioning work were identified in the survey, and 39 of these exposed people and 39 unexposed controls (98%) participated in the study. In the exposed group, 39 participated in the vibrametry, 38 in the two point discrimination test, and 35 had their skin temperature taken. In the control group, 39 participated in the vibrametry, 38 subjects in the two point discrimination test, and 38 had their skin temperature taken.

#### ASSESSMENT OF EXPOSURE

Present and previous occupational exposures to cold, and hand held vibrating tools were reported. Information on exposure time, type of microtome, wearing gloves, and room temperature was also recorded.

#### ASSESSMENT OF SYMPTOMS

All subjects were asked to answer a self administered questionnaire, which was posted to their home addresses. The questionnaire was designed to get information on symptoms of fractures, frostbite, surgical operations of the hands or arms, medical drugs, smoking habits, and 12 months prevalence of Raynaud's phenomenon and numbness. It also requested information on chronic disorders. Questions on the 12 months' prevalence of symptoms of pain in the hands, arms, neck, and shoulders were also included. The same questionnaire was given in the medical interview performed by an occupational physician before the clinical investigation and included questions on chronic disorders (diabetes, metabolic diseases, or other systemic disorders) that could involve the peripheral nervous system.

#### ASSESSMENT OF PHYSIOLOGICAL SIGNS

Skin temperature, two point discrimination test, and vibratory perception thresholds were measured in the morning for both exposed and control subjects before they started any cryosectioning work. Also, the change of skin temperature over time was monitored in subjects performing various types of cryosectioning work. To avoid possible disturbance of one test by another, different fingers were used for different neurological tests.

#### *Skin temperature and room temperature*

In all subjects, skin temperature was measured before any cryosectioning work began, by a calibrated thermistor placed on the right ring finger (digit IV). Also, measurements of the skin temperature were taken during cryosectioning work with a thermistor taped on the finger. The temperature was recorded before, each second minute during, and 30 minutes after cryosectioning. The same equipment was

also used to register room temperature before all clinical investigations. For practical reasons, measurements on skin temperature response during cryosectioning work could only be performed once on each subject, and only on subjects performing such work in the two months of the study period.

#### *Two point discrimination test*

The tactile discrimination test or two point discrimination test tests the ability to recognise separately two compass points simultaneously applied to the skin.<sup>5</sup> A compass with not too sharp points was used. The person had to consider if the two points could be distinguished. The legs of the compass were then gradually brought together. The accuracy of the registration was 1/4 mm. For each person three tests were made and the arithmetic mean was used in the statistical calculations.

#### *Vibratory perception thresholds*

Vibratory perception thresholds were measured on digits II and V of both hands, covering both medianus and ulnaris innervated areas. The test was done when the person was in a relaxed position, to minimise the effect of high muscular tone. The instrument used was a bio-thesiometer (Biomedical Instruments Company, Ohio, USA), and the procedure to determine vibration perception threshold has been already described.<sup>6</sup> A vibrator button vibrating at 120 cycles a second is used for stimulation of the examined fingertip. The instrument was calibrated by the manufacturer. The vertical movement from the 13 mm stimulator head (plastic probe) is recorded as a signal by an accelerometer. The amplitude of the vertical movement is measured in  $\mu\text{m}$ , and is directly proportional to the square of the applied voltage which can be varied continuously. The vibration threshold is measured by increasing the stimulus strength from zero to the point where the vibratory sensation is first perceived. The vibration stimulus is then increased to a higher level and then decreased to the point where the sensation disappears. The test was done three times, and the arithmetic mean of the three measurements was used in the statistical calculations.

#### *Statistics*

Differences in mean values were calculated by Mann-Whitney *U* test. Differences in proportions were calculated with a two tailed  $\chi^2$  test for  $2 \times 2$  contingency tables. Odds ratios (ORs) with 95% confidence intervals (95% CIs) were calculated. Paired comparisons of continuous variables were made with Wilcoxon matched pairs signed rank test. Paired comparisons of dichotomous variables were made with the McNemar test. Methodological error for vibrametry and two point discrimination test was calculated as described previously.<sup>7</sup> The standard error (SE) of variation between three readings was calculated from the formula:

$$SE = (((\Sigma a^2 - (\Sigma a)^2/n) + (\Sigma b^2 - (\Sigma b)^2/n) + (\Sigma c^2 - (\Sigma c)^2/n))/6(n - 1))^{0.5}$$

Table 1 Cumulative incidence of some hand disorders in subjects with and without cryosectioning work ( $n = 78$ )

Characteristics	Cryosectioning group ( $n = 39$ ) (%)	Matched controls ( $n = 39$ ) (%)
Ever had a fracture in the arm, hand, or fingers	13	21
Ever operated on hands or the arms	13	15
Ever had a frostbite in the hands	5	8

No significant differences between exposed and controls by McNemar test for paired comparison.

where a = difference between readings 1 and 2; b = difference between readings 2 and 3; c = difference between readings 1 and 3,  $n$  = number of triplicate readings.

## Results

Mean age was 37.3 years in the group exposed to cold, and 37.5 years in controls. Both exposed and control groups had the same mean duration of employment (7.5 years). Because of the matching, the prevalence of current tobacco smokers (36%) and women (82%) were also similar in both groups. One of the non-exposed controls, but none of the cryosectioning workers exposed to cold used snuff. Mean height was similar in exposed and control subjects (167 and 168 cm, respectively), as was the mean body weight (63 and 66 kg, respectively). One of the exposed workers, and two controls were left handed. None of the exposed or control workers had diabetes, metabolic diseases, or other systemic disorders involving the peripheral nervous system. A history of fractures and operations in the upper extremities was relatively common; reports on a history of frostbite were less common and not significantly different between exposed and control workers (table 1).

## EXPOSURE

The mean (range) duration of employment in cryosectioning work was 7.5 (2–33) years in the exposed group. As cryosectioning was only a part of the work in the exposed group, the mean (range) cumulative cryosectioning work time was 3.7 (0.1–25) years. Twenty five people (64%) had a cumulative duration of exposure to cryosectioning work that exceeded one year. In total, 22 exposed subjects (56%) worked with animal preparations. Most of these preparations were on organs, but seven subjects also performed preparations for whole body radiography on frozen rodents. At other laboratories, cryosectioning was mainly used to prepare tissues for microscopic diagnostic work where the amount of frozen material was

limited. Most exposed subjects did not use gloves when they worked at the microtomes, and direct contact with the frozen material occurred only for short periods. Four subjects used thin cotton gloves, one used rubber gloves, and one used leather gloves. The following types of microtomes were used; Leitz cryostate 1720, Tissutec II Milles cryostate, PMW type 400, 250, 450, 5000 and American Cryo Cut Optical cryostate.

## SYMPTOMS

The questionnaires did not show any difference in the 12 months' prevalence of Raynaud's symptoms or numbness of the fingers in the cryosectioning group compared with the controls (table 2). In all members of the exposed and control groups the prevalences of white fingers at exposure to cold were 7% in men and 18% in women, a non-significant difference. Pains in the neck, shoulder, and arms were common, but the prevalence did not differ between exposed and control groups. All subjects reported the same symptoms in the initial self administered questionnaire and in the medical interview performed before the clinical investigation.

## Skin temperature and room temperature

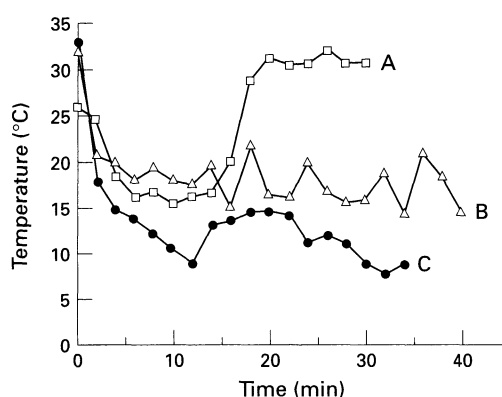
Room temperature and initial skin temperature before any work exposed to cold did not differ significantly between exposed and control groups (table 3). Moreover, no relation was found between initial skin temperature and age, tobacco smoking, or room temperature. In all of the 78 subjects, however, some relation between Raynaud's symptoms and skin temperature was found. Subjects who reported hypersensitivity to cold in the fingers had significantly lower mean initial skin temperature than subjects without such complaints ( $27.5^{\circ}\text{C}$  v  $29.7^{\circ}\text{C}$ ,  $P < 0.05$ ). Because cryosectioning work was not performed each month in all workplaces, skin temperature measurements during cryosectioning work could only be performed in 15 subjects. The other 24 exposed subjects did not perform any cryosectioning work during the two months study period. For most of the exposed subjects, the skin temperature was rapidly reduced in the initial phase of the cold exposure. After two minutes of cryosectioning work, the mean temperature in all 15 subjects was significantly reduced from  $29.4^{\circ}\text{C}$  to  $24.6^{\circ}\text{C}$  ( $P < 0.01$ ), but the continued cold exposure did not induce any significant further reduction of the mean skin temperature. There were, however, large individual differences in the skin temperature responses. Three types of reactions are shown in the figure. Two subjects showed a rapid initial decrease in the temperature curve (curve A) followed by a vasodilatation known as the Lewis effect.<sup>8</sup> Seven subjects had a rapid decrease in finger temperature, followed by a constant low skin temperature of about  $15^{\circ}\text{C}$  (curve B). Two subjects had a rapid decrease of skin temperature, and a further small decrease in skin temperature (curve C). Finally, four subjects were not affected by the

Table 2 Twelve months' prevalence of symptoms from the upper extremities in subjects with and without cryosectioning work ( $n = 78$ )

	Exposed subjects ( $n = 39$ ) (%)	Matched controls ( $n = 39$ ) (%)	OR (95% CI)
White fingers on exposure to cold	15	19	0.6 (0.2–2.2)
Cold hypersensitivity in the fingers	29	27	1.1 (0.4–3.0)
Numbness in the hands	24	30	0.7 (0.3–2.0)
Weakness of grip	15	11	1.2 (0.3–5.0)
Pain in the neck, shoulder, or arms	44	35	1.4 (0.6–3.6)

No significant differences between exposed and controls by McNemar test for paired comparison.

Finger skin temperature curves during cryosectioning with a microtome. Three types of reactions shown by curves A, B, and C.



cold exposure, and had a constant skin temperature around 28°C (not shown in the figure). In six cases the mean skin temperature during cryosectioning was below 20°C, and five of them performed whole body animal cryosectioning work. No significant relation was found between the minimum or the mean skin temperature during cryosectioning and a history of Raynaud's phenomenon in the medical interview.

#### Clinical signs

The relative standard error (SE) was 1% for the two point discrimination test and 6% for the vibration perception threshold measurements. Age was a significant confounder for the clinical signs. Both two point discrimination test values and vibration perception thresholds on all four fingers increased significantly with age ( $P < 0.05$ ). All the exposed and control subjects who reported numbness had a significantly increased two point discrimination value ( $P < 0.05$ ). In contrast, no

significant relation was found between numbness and vibration perception threshold. The two point discrimination test differed significantly between the exposed and the unexposed group (table 3). Also, the vibration perception threshold in the pointing finger (digit II) of the right hand were significantly higher in the group exposed to cold (table 3). Work related differences in vibration perception threshold within the group exposed to cold was also shown. Subjects working with the larger animal preparations had significantly higher vibration thresholds on all measured fingers than those handling tissue preparations (table 4). For the two point discrimination test, no such work related differences could be found. No significant difference in age was found between subjects handling human tissue preparations at the University Hospital, and subjects working with animal preparations at the research laboratories at the University.

#### Discussion

We found signs of neuropathy among subjects exposed to cold during cryosectioning work. There was also a large difference between workers in skin temperature response to cryosectioning work. Subjects who reported cold sensitivity in the hands had a lower initial skin temperature before the cold exposure. A cross sectional study has certain drawbacks due to the selection processes and the number of available employees, which may limit the validity of the study. There could also be a possible underestimation of the true effect if people with pronounced symptoms have left a poor environment, so there is the possibility of health based selection of employees. A selection bias can occur, because of incorrect study design or as a result of low response rate. This study included all laboratory workers who carried out cryosectioning in the preclinical and clinical departments. No selection on the basis of prevalence of symptoms occurred. To obtain comparable subjects without occupational cold exposure, matched subjects from the same workplaces were used as controls. Also, the non-response rate was low, both among exposed subjects and controls (2%), and the employment time was similar in both groups.

A confounder is defined as a variable that may cause or prevent the outcome of interest, but is not an intermediate variable and should be controlled for. Matching for sex, age, and tobacco use was performed in our study as these factors could be potential confounders for Raynaud's phenomenon.<sup>9</sup> We showed that age is a significant confounder for both vibration perception threshold and two point discrimination test, suggesting that age should always be controlled for in epidemiological studies on neurological symptoms and signs.

Another problem with a bearing on the validity of the study is response bias due to the awareness of exposure. In this study, the investigator, the exposed subjects, and unexposed subjects were aware of the purpose of

Table 3 Room temperature, skin temperature, and clinical neurological signs in subjects with and without cryosectioning work ( $n = 78$ )

Variable	Exposed subjects ( $n = 39$ ) mean (range)	Matched controls ( $n = 39$ ) mean (range)
Room temperature (°C)	23.0 (18.4–25.7)	22.9 (20.6–26.0)
Initial skin temperature (°C)	29.2 (18.5–35.0)	28.4 (22.0–35.5)
Two point discrimination (mm):		
Digit IV right hand	2.9** (1.0–9.0)	2.5 (1.0–8.0)
Vibratory perception threshold (amplitude (μ)):		
Digit II right hand	7.3* (3.5–10.5)	6.5 (3.5–12.0)
Digit V right hand	7.1 (3.0–13.0)	6.7 (4.0–12.0)
Digit II left hand	6.4 (3.0–10.0)	6.3 (4.0–10.5)
Digit V left hand	6.4 (3.5–10.0)	6.3 (4.0–11.0)

\*  $P < 0.05$ ; \*\* $P < 0.01$  exposed *v* controls, by Wilcoxon matched pairs signed rank test.

Table 4 Difference in room temperature, skin temperature, and clinical neurological signs between subjects with low exposure cryosectioning of human tissue ( $n = 17$ ) and high exposure cryosectioning of animal tissue ( $n = 22$ )

Variable	Low exposure subjects ( $n = 17$ ) mean (range)	High exposure subjects ( $n = 22$ ) mean (range)
Room temperature (°C)	23.1 (21.5–25.3)	22.9 (18.4–25.7)
Initial skin temperature (°C)	27.8 (18.5–35.0)	28.2 (20.6–34.2)
Two point discrimination (mm):		
Digit IV right hand	2.7 (1–4)	3.0 (2–9)
Vibratory perception threshold (amplitude (μ)):		
Digit II right hand	6.6* (3.5–10.5)	7.8 (5.0–10.0)
Digit V right hand	6.5* (3.0–9.0)	7.6 (4.0–10.0)
Digit II left hand	5.7* (3.0–12.0)	6.9 (5.0–13.0)
Digit V left hand	5.4** (3.5–8.5)	7.1 (5.0–10.0)

\*  $P < 0.05$ ; \*\* $P < 0.01$  low exposure *v* high exposure group by Mann-Whitney *U* test.

the study, so the study was not blinded. We found, however, no significant excess of symptoms in the exposed group, only a significant difference in clinical signs, which are less likely to be influenced by response bias. The investigator made the clinical tests in a standardised manner. We do not think that the aspects discussed of internal validity of the results of our study have been unduly affected by response bias, or selection bias. The cross sectional design, however, could entail an underestimation of the true effect of the local cold exposure.

We found a prevalence of 18% of white fingers in women and 7% in men, similar to earlier studies. The prevalence of Raynaud's phenomenon in the general population has been studied in different countries. Leppert<sup>9</sup> studied 3000 women 18–59 years old in Sweden and found a prevalence of 15.6%. Heslop *et al* found that 18% of the women and 8% of the men had symptoms of Raynaud phenomenon.<sup>10</sup> In 1978, Olsen and Nielsen reported a 22% prevalence of Raynaud's phenomenon among women in the general population.<sup>11</sup>

Most of the studies on the physiological effect of cold exposure have been performed in situations where the whole body is exposed to cold.<sup>1,3,8,12</sup> In contrast, cryosectioning work results in a local cold stress in the hands only. Most of the laboratory workers did not use any gloves during the cryosectioning work, and direct contact with the frozen material occurred only for short periods. The skin temperature curves during cryosectioning work showed a rapid cooling effect during the first minutes. In a few cases, individual break points where the skin temperature rises were also found. This is due to a well known physiological reaction sometimes called the Lewis effect.<sup>8</sup> It is a vasodilatory reaction and works as a safeguard against frostbite and cold induced damage.

Contact cooling can quickly result in frostbite, especially when handling goods with unprotected hands.<sup>1</sup> Signs of an early peripheral neuropathy of the right hand in the cold exposed group were found both by vibrometry and two point discrimination test. Skin temperature was dependent on the type of cryosectioning, and the lowest average skin temperatures were measured for whole body preparations of rodents at the University laboratories. Moreover, work related differences were found, as vibration perception values were higher among subjects preparing whole body preparations of rodents at the University laboratories than human tissue cryosectioning in the University Hospital.

We found large differences in the individual skin temperature responses to cryosectioning work. Individual differences in response to cold exposure have earlier been reported, in experimental studies and in occupational field investigations.<sup>4,13</sup> Individual differences in

reactions to cold have also been described in different ethnic groups in Arctic areas of Canada.<sup>1,14</sup> Adaptive responses to local cooling of the hands have been shown experimentally,<sup>15</sup> and might occur in our laboratory personnel. As expected, we showed a significant relation between skin temperature and a history of cold fingers. In contrast, we found no relation between room temperature and initial skin temperature. This could be due to the small variation of the indoor temperature in the buildings, and homeostasis, or differences in physical work before the measurement of skin temperature. The clothing was, however, very similar in all subjects. Finally, we showed a relation between symptoms of numbness and signs of early neuropathy, measured by the two point discrimination test. This indicates that the clinical signs measured in our study had a medical relevance, to the extent that they were related to neurological symptoms.

In conclusion, laboratory personnel who cryosection are exposed to a rapid cooling of the skin, particularly during work with larger frozen animal materials. There might, however, exist large individual differences in the response to such local cold exposure, as shown by our temperature curves, and the cooling of the skin was sometimes followed by a compensatory vasodilatation, the so called Lewis effect. We also conclude that this type of laboratory work may cause adverse health effects—for example, peripheral neuropathy—and measures should be taken to protect the hands from the local cold exposure.

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