widespread use for about 20 years and, because of the 20-year latency period expected for human cancer (*18*), we would not expect cancer incidence among machinists to be related to NDElA. However, machinists may have been exposed to relatively large amounts of NDElA by skin absorption and inhalation. We suggest that epidemiological studies be initiated to screen workers who have been subjected to NDElA for prolonged periods. Until now, *N*-nitrosamines have not been directly associated with human cancer because no population groups had been identified that were inadvertently exposed. Cutting fluid users have the dubious honor of being the first such population group to be identified.

Note added in proof: Zingmark and Rappe initially reported NDElA to be absent from grinding fluid (*2*). Since submission of this manuscript, we were informed by Rappe of a second manuscript (*19*) reporting the presence in grinding fluid stored for 4 to 6 months of a compound which was claimed to be NDElA.

TSAI Y. FAN, JOHN MORRISON
DAVID P. ROUNBEHLER
RONALD ROSS, DAVID H. FINE
Thermo Electron Cancer Research Center, Waltham, Massachusetts 02154
WALTER MILES, N. P. SEN
*Health Protection Branch,
Food Research Division,
Ottawa, Ontario, Canada*

References and Notes

1. W. Linjinsky, L. Keefer, E. Conrad, R. Von de Bogart, *J. Natl. Cancer Inst.* **49**, 1239 (1972).
2. P. A. Zingmark and C. Rappe, *Ambio* **5**, 80 (1976).
3. H. Druckrey, R. Preussmann, S. Ivankovic, D. Schmahl, *Z. Krebsforsch.* **69**, 103 (1967).
4. D. H. Fine, F. Rufeh, D. Lieb, *Nature (London)* **247**, 30 (1974).
5. D. H. Fine, D. P. Rounbehler, A. Silvergleid, R. Ross, in *Second Symposium on Nitrite in Meat Products* (Central Institute for Nutrition and Food Research TNO, Zeist, Netherlands, in press).
6. The recovery of NDElA after this procedure was 100 percent.
7. A 0.1-ml portion of cutting fluid (brand C) was extracted with 30 ml of diethyl ether or ethyl acetate in the presence of 10 g of magnesium sulfate. The extract was filtered through 20 g of sodium sulfate. The filtrate was concentrated with a stream of nitrogen to approximately 300 μl and loaded onto a silica gel column (1 by 5 cm), which was washed with 50 ml of diethyl ether and then eluted with 50 ml of ethyl acetate. The eluate was concentrated to approximately 300 μl as the final isolated sample. An aqueous solution containing 5 percent each of sodium nitrite and triethanolamine was treated by the same isolation procedure used for the cutting fluid. No artifact formation of NDElA was found during the procedure.
8. The solvent system was 3 percent methanol and 97 percent methylene chloride for the μ Bondapak NH_2 column, and 30 percent acetone and 70 percent hexane for the μ Porasil column. The flow rate for both columns was 2 ml/min.
9. The column (6 feet by ⅛ inch) was packed with 5 percent Carbowax 20 M on 100- to 200-mesh Chromosorb W High Performance and used isothermally at 180°C. The flow rate of helium carrier gas was 25 ml/min. The mass spectrometer was operated to monitor the molecular ion of *N*-nitrosomorpholine at a resolution of 10,000.
10. N. P. Sen, W. F. Miles, S. Seaman, J. F. Lawrence, *J. Chromatogr.*, in press.
11. The column was packed with 25 percent Carbowax 20 M containing 2 percent NaOH on 80- to 100-mesh Chromosorb P. The temperature of the column was maintained isothermally at 140°C for 3 minutes and then programmed to 180°C at a rate of 10°C per minute. The flow rate of the helium carrier gas was 25 ml/min.
12. D. H. Fine, R. Ross, D. P. Rounbehler, S. Fan, paper presented at the American Chemical Society meeting, San Francisco, September 1976.
13. P. Bogovski and E. A. Walker, *N-Nitroso Compounds in the Environment* (International Agency for Research on Cancer, Lyon, France, 1974).
14. D. N. D. Cruickshank and J. R. Squire, *Br. J. Ind. Med.* **7**, 1 (1950); R. Tourenc, *Presse Med.* **72**, 2009 (1964); J. E. H. Milne, *Med. J. Aust.* **2**, 13 (1970).
15. H. Desoille, M. Philbert, G. Ripault, A. Cavigneaux, H. Rossignoli, *Arch. Mal. Prof. Med. Trav. Secur. Soc.* **T34**, 669 (1973).
16. E. Mastromotteo, *Br. J. Ind. Med.* **12**, 240 (1955).
17. International Agency for Research on Cancer, *Evaluation of Carcinogenic Risk of the Chemical to Man. Certain Polycyclic Aromatic Hydrocarbons and Heterocyclic Compounds* (Lyon, France, 1973), vol. 3, p. 30.
18. R. J. Waxweiler, S. Stringer, J. K. Wagoner, J. Jones, H. Falk, C. Carter, in *Occupational Carcinogenesis*, U. Saffioti and J. K. Wagoner, Eds. (New York Academy of Sciences, New York, 1976), p. 40; J. D. Gilliam, J. M. Dement, R. A. Lemen, J. K. Wagoner, V. E. Archer, H. P. Blejer, in *ibid.*, p. 336.
19. C. Rappe, *Ambio*, in press.
20. We thank R. Carrigan and G. Gordon of the National Science Foundation for valuable discussions, and F. Benoit of the Health Protection Branch, Ottawa, for carrying out the chemical ionization mass spectrometry. The work at Thermo Electron was supported by NSF grant ENV75-20802.

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Perception of Impossible Limb Positions Induced by Tendon Vibration

Abstract. *When the wrist flexor muscle is vibrated and the wrist is passively extended to a position close to its anatomical limit, the hand is felt to be bent to a position about 29° beyond its maximum operating range. The mechanism of position sense must in this case be operating on the basis of extrapolation. Ambiguity of sensed position can occur in this situation. Some subjects, when opposing the vibration-induced contraction of biceps, report experiencing multiple forearms.*

Until recently, position sense in limbs was thought to be due solely to the receptors associated with the joint capsule and pericapsular tissue (*1*). However, evidence now strongly suggests a role for muscle receptors, especially the primary endings of muscle spindles (*2*). In this report I present evidence that vibration of muscle tendons can result in errors of position sense as great as 54° when the muscle is passively stretched. Furthermore, the size of this effect is not restricted by the anatomically given limits of flexion and extension.

Cat spindle primary endings are highly sensitive to periodic stretch of small amplitude while secondary endings are not (*3*). In humans, vibration of a tendon causes a predictable increase in the contractile activity of the agonist, caused by autogenous reflex excitation of the alpha motoneurons and reciprocal inhibition of the antagonist. This leads to involuntary movement (*4*). When this movement is stopped by an external agent, the subject reports a persistent illusion of movement in the direction appropriate to extension of the vibrated, and contracting, muscle. This is associated with an error of position sense, also in the direction of extension, the size of which has been reported as being between 5.5° (*5*) and 8° (*2*) when the biceps tendon is vibrated at 100 hertz. McCloskey (*5*) argues that these position signals are not merely the integration of those responsible for the persistent movement illusion, for the size of the position error does not increase with vibration time. Furthermore, procedures that lower or abolish the movement illusion do not similarly affect the size of the position error. This makes the existence of the position illusion of considerable theoretical importance, for it implies that some of the afference from the muscles could be used by the brain as a source of positional information, as distinct from the notion that vibration merely biases position analysis by virtue of the volume of movement information.

Some properties of the muscularly derived position mechanism were studied in right-handed subjects 6 to 40 years of age. The majority were university students and faculty. The apparatus consisted of a vibrator with a piston 15 mm in diameter which was driven sinusoidally at 80 hertz with stroke, under load, of 2 mm. This piston was applied to various sites on the left arm. Objective measurement of the position of the left wrist or hand was achieved by asking the subject, whose vision was occluded, to make a mark with a pen held in the right hand on a vertically mounted Plexiglas sheet adjacent to the left arm. This task used only the position sense of the two arms. Precise localization of wrist or hand of the experimental arm was aided by the experimenter touching one or the other with a slender pointed rod. The effect of vibration on the position sense of the left arm or hand was determined by testing the subject for the accuracy with which he or she could point with the right hand to the left wrist or hand, both before and during vibration.

Vibration of nontendinous areas around the joint does not give rise to the illusion of movement (*2*); however, it is still desirable to show that the joint about which the vibrated muscle acts plays no part in bringing about the position error. Thus, one object of the first experiment was to dissociate the experimentally induced position error from contamination due to joint vibration. The procedure consisted of vibrating a muscle tendon which is remote from its site of action, thereby minimizing the power of standing waves transmitted to the relevant joint.

The second objective was to determine the limiting magnitude of the vibration-induced error. Vibrating the tendon of a muscle that is being maintained at a fixed length while supporting a load of 6.8 kg increases the position error by a factor of 2 when compared with the effect of vibration alone (*5*). This raises the possibility that the muscularly derived afferent barrage responsible for position information may be further increased by stretching the reflexly contracting muscle, and that consequently larger positional errors may be exhibited.

Twenty subjects were used. Each was seated with his supinated left arm raised about 65° from the vertical and with the elbow joint almost fully extended. The whole arm was supported on a dense foam-plastic pad. Pretreatment judgments of both arm and hand position were collected, the experimenter providing the subject with punctate position information by touching the skin over the pisiform bone and on the medial side of the little finger. The skin over the tendon of flexor carpi radialis was then vibrated in the region of the elbow, at a point about 40 mm from the medial epicondyle. This muscle is a wrist flexor, and the vibration caused unintentional flexion of the wrist. This reflex contraction of the muscle was allowed to continue until moderate flexion had been achieved. The experimenter then moved the subject's hand, against the contraction of the muscle, into a randomly chosen position of flexion or extension and maintained it in this position. The subject was then asked to make judgments of the position of his arm and hand during this vibration.

Table 1. Mean differences and standard deviations (S.D.) of localizing the hand before and during vibration. All deviations are in the direction of extension. The mean difference in localization was 22.11°; the standard deviation of differences was 14.15°. The within-subject standard deviation before vibration was 7.29°; that during vibration was 4.76°. The mean hyperextension was 28.52°.

Subject	Difference (deg)		Subject	Difference (deg)	
	Mean	S.D.		Mean	S.D.
1	17.3*	6.4	9	7.8	4.5
2	11.2	3.4	10	29.4*	5.2
3	48.7*	3.9	11	12.9	4.1
4	17.8*	7.6	12	28.6*	5.3
5	54.2*	11.6	13	31.6*	5.4
6	14.6*	6.4	14	7.2	4.8
7	28.5*	7.3	15	14.5*	5.1
8	6.1	5.2	16	28.5*	13.0

*The difference is sufficient to represent a position of the hand attainable only by hyperextension of the wrist.

Although the vibrator was close to the elbow, there was no significant difference in the judged position of the forearm ($t = 0.32$, d.f. = 19, $P > .1$). That is, the elbow joint was not affected by the treatment. However, all subjects displayed an error in judged hand position in the direction of extension of the wrist (sign test of direction of differences in localization before and during vibration: $\chi^2 = 0.077$, d.f. = 1, $P > .7$ for forearm; $\chi^2 = 10.00$, d.f. = 1, $P < .01$ for hand).

The mean error of hand localization was 22.7°, with all subjects showing unidirectional errors in the direction of extension. The between-subject variability was high [standard deviation (S.D.) = 15.1°], but within-subject variability was much lower (S.D. = 5.8°). A control condition in which various sites around the wrist were vibrated directly yielded no position illusion.

These observations allow me to conclude three things. (i) There is a substantial position error accompanying the vibration of muscle when the associated joint is largely unaffected by the vibration. (ii) These data are consistent with the notion that stretching the muscle makes it more sensitive to vibration and there is consequently a larger irrelevent position signal to the brain. These direct measures of position error are a factor of 2.8 larger than the greatest of those previously reported, in which the muscle was not stretched in opposition to its own contraction (*2*). (iii) Since the effect is unidirectional and occurred for all subjects and in all tested positions, it is reasonable to suggest that the irrelevant positional information that stems from the vibrated muscle and that from the joint receptors in the wrist (and possibly from other structures) are being analyzed conjointly, and together contribute to the final sensation of position.

The next problem concerns the rules of interpretation which the brain uses when it inspects this afferent bombardment from the vibrated muscle. Suppose that there is a vibration-induced error of 20° about the elbow joint, and that the forearm is made to move toward and steadily beyond a point 20° from the limit of extension; how will the brain interpret the available information? If it is assumed that the brain adds the nonveridical position information from muscles to the position derived from joint information, then there are only two possible outcomes. Either the internal scale for sensed position will define the limit for the registration of position, or the limb will be sensed to be in an impossible position, beyond the limit normally set by the anatomical configuration of the joint.

The following experiments examined the effect of vibration of biceps and triceps tendons when the related muscle was stretched against its contraction. The magnitude of the induced position error was measured in 16 subjects by asking them to judge when they had attained the position of maximum extension or flexion of the elbow. The subject sat with left arm pronated and raised to 65° from the vertical and comfortably supported at the elbow. During vibration of the biceps tendon the experimenter opposed the reflex contraction of the muscle by slowly moving the forearm in the direction of extension. The subject's task was to report when the arm felt fully extended. When the triceps was being vibrated the procedure was similar; the arm was flexed by the experimenter, and the subject had to report when the arm felt fully flexed. Eleven of the subjects displayed substantial position errors when making one or both of these judgments (with vibration of triceps, mean error = 12.8°; with vibration of biceps, mean error = 32.7°). The difference between these two effects cannot yet be explained, but their respective magnitudes are larger by factors of 1.6 and 4.1 than those previously reported (*2*). This again suggests that stretching the vibrated muscle can make available a large irrelevant position signal. Three subjects, however, did not display position errors.

Some subjects are unsure how to interpret the sensations from their arm; one subject reported "heaviness" of the arm and another maintained that the forearm was curving. In an identical pilot experiment, one subject claimed that the arm was "flicking up and down," another that there was "a double image," and a third that the arm was "in two places at once."

The eleven subjects who showed unambiguous position errors in the previous experiment were vibrated in the same sites and asked to report on the sensation accompanying actual movement of the limb beyond the point previously reported as the limit of extension or flexion. All of these subjects reported varying degrees of hyperextension or hyperflexion of the joint (*6*). For many subjects these reports were vivid; their reports contained phrases such as "the arm is being broken," "it is being bent backwards," "my hand is going through my shoulder," and "it cannot be where it feels." Although no pain is involved in the procedure, subjects displayed the overt signs which often accompany pain, such as writhing, sweating, and gasping. Once again, vibration of the biceps yielded the greatest effect. This experiment indicates that there is no set limit for the internal scale of sensed position.

In the next experiment the magnitude of the sensation of hyperextension and hyperflexion was quantified for the wrist joint. Sixteen subjects were studied under the same experimental arrangements as in the first experiment. With the left arm resting on its pad, the subject was asked to move the hand until maximum wrist extension was attained. A reference mark of this position was made on the adjacent vertical sheet of Plexiglas. The position closest to this which could be comfortably maintained was then ascertained and a further reference mark made; the experimenter then held the hand in this position. The blindfolded subject was then asked to mark with his right hand the position of the left little finger on the Plexiglas. Punctate stimulation of the little finger was provided by the experimenter as an aid to localization. Ten readings were collected. The subject was then asked to move his hand to a slightly flexed position and vibration of the flexor carpi radialis commenced. As soon as the experimenter observed reflexive movement of the hand he slowly moved it into the position previously defined as a comfortable maximum. The subject was then asked to point to the little finger a further ten times.

All subjects felt the hand to be bent backward toward the dorsal surface of the forearm (Table 1). Although there are wide individual differences in the magnitude of the effect, the within-subject standard deviations during vibration are significantly smaller than those for the before-vibration data ($t = 2.42$, d.f. = 15, $P < .05$), which suggests that the position signals from muscle are fairly precise. Informal tests of the effects of vibrating extensor carpi radialis longus follow the same pattern, with subjects demonstrating up to 40° of apparent hyperflexion of the wrist.

The fact that subjects can demonstrate that their hands feel to be in impossible positions supports the idea that position information from muscle and conventional position sensors, such as joint receptors, is contributing to the final sensation of position under these conditions. Furthermore, it seems likely that the brain is functioning as an extrapolator to achieve this sensation.

In the next experiment, 30 subjects were asked to report their sensory experience when they voluntarily overcame the reflex contraction of their biceps, and to indicate, by pointing, the position of the limb. Ten subjects could not move their arm at all; of these, six correctly reported their immobility, and four claimed that they experienced movement into extension. The remaining subjects could move their arms, but with difficulty. Of these, six knew the position of their arm fairly accurately and nine reported that they were moving the arm downward rapidly when the limb was moving slowly. Of the remaining subjects, one reported that his forearm was curving down from the elbow and four reported double or multiple images of their forearm.

All difficulties in moving the arm may be interpreted as weakness of the triceps caused by reciprocal inhibition. The errors of localization were in the direction of extension and ranged from 0° to about 50°; this may be due to the varying degrees of the voluntarily imposed stretch of the biceps. The report of multiple forearms suggests that for some subjects muscle and joint position information is not perfectly integrated and that each gives rise to a separate sensory experience.

The experiments reported here allow me to conclude that the joint about which the position error occurs is not itself responsible for the position illusion. Furthermore, stretching the reflexly contracting muscle greatly increases the magnitude of the position error. However, the limiting magnitude of the effect has not been determined. The position error reported here is larger than any bias of the position senses caused by other forms of experimental manipulation, but its magnitude might be further increased by more powerful stretching of the muscle or greater amplitude of impressed vibration.

The sensory experience of position accruing from vibrated muscle is referred unambiguously to the joint about which it acts. The subject apparently cannot differentiate between muscular and other sources of limb position information. When an irrelevant position signal from muscle is present, it will apparently be analyzed together with the normal position input associated with the objective joint angle. Thus at least two sources of information are involved in position sense (*7*). However, the report by some subjects of double or multiple forearms when the contraction of the vibrated muscle is overcome suggests that integration of this information may occasionally be imperfect.

Both the elbow joint and the wrist can be perceived to be hyperextended or hyperflexed under the conditons reported here. The anatomy of these joints has precluded the subject from previous experience of these positions. It follows that the sensory limit is not set by the limits of joint excursion. There is evidence that the position sense of a limb has to be calibrated before it can be used in any meaningful way (*8*). If this is so, then it is reasonable to suggest that under these experimental conditions the brain is deriving position information by extrapolating from the previously calibrated position domain.

BRIAN CRASKE

Department of Psychology,
Memorial University of Newfoundland,
St. John's, Newfoundland,
Canada A1C 5S7

References and Notes

1. S. Skoglund, in *Handbook of Sensory Physiology*, A. Iggo, Ed. (Springer-Verlag, New York, 1973), pp. 111–136.
2. G. M. Goodwin, D. I. McCloskey, P. B. C. Matthews, *Brain* **95**, 705 (1972).
3. P. Bessou and Y. Laporte, in *Symposium on Muscle Receptors*, D. Barker, Ed. (Hong Kong Univ. Press, Hong Kong, 1962), p. 105; R. Bianconi and J. P. Van Der Meulen, *J. Neurophysiol.* **26**, 177 (1963).
4. K. E. Hagbarth and G. E. Eklund, in *Muscular Afferents and Motor Control*, R. Granit, Ed. (Almqvist and Wiksell, Stockholm, 1966), p. 177.
5. D. I. McCloskey, *Brain Res.* **63**, 119 (1973).
6. Hyperflexion and hyperextension are defined here as the sensation that the joint has taken up a position of flexion or extension which is beyond that attainable when the subject uses maximum voluntary effort.
7. The joint receptors provide the primary source of limb position sense (*1*). These would seem to be the obvious candidates for the veridical position information required. The experiments reported here, however, do not specifically identify these structures.
8. R. Held and J. A. Bauer, *Science* **115**, 718 (1967).
9. Supported by grant AO268 from the National Research Council of Canada.

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