# A STUDY OF RECEPTION WITH THE USE OF FOCUSED ULTRASOUND. I. EFFECTS ON THE SKIN AND DEEP RECEPTOR STRUCTURES IN MAN

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(Accepted February 10th, 1977)

#### SUMMARY

The possibility of use of focused ultrasound (focused beam of high-frequency mechanical waves) for stimulation of nerve structures was investigated. The stimulation of human hand resulted in various sensations: tactile, temperature, pain etc. The corresponding thresholds were determined and characteristic features of ultrasonically induced sensations were studied. The modality of temperature sensation (warmthcold) was found to depend on the environmental temperature. The character of pain was dependent upon the type of tissue stimulated. Effective factors in ultrasonic stimulation are discussed.

## INTRODUCTION

Ultrasound has been successfully applied in various domains of biology and medicine for the past decades<sup>8,9</sup>. Focused ultrasound, however, holds as yet a rather modest place restricted, in the main, to its ability of rupturing the tissue within a given volume and depth without injuring the surrounding tissues. Meanwhile, the use of the focused ultrasound to stimulate nerve structures looks like offering a promising method. It would supply an investigator with a method of non-contact stimulation capable of affecting both surface and deep nerve structures, with precise quantitative characteristics, adjustable over a wide range of intensities, action times and volumes of a region stimulated.

In this investigation, under study was the possibility of the use of focused ultrasound for stimulation of nerve structures. The experimental object chosen was the hand of man, i.e. an object possessing the receptor structures whose stimulation produces diversified sensations: touch, tickling, pain, warmth etc. Some earlier results are available elsewhere<sup>2,3</sup>.

### **METHODS**

To obtain the ultrasound stimuli, focusing irradiators made on a basis of the concave piezoceramic plates of barium titanate or lead zirconate-titanate were used. The resonant frequencies were 0.48, 0.887 and 2.67 MHz, with the diameter of the focal regions, respectively, 6.4, 3.4 and 1.1 mm, and the maximal ultrasonic intensities: 1300, 8000 and 30,000 W/sq.cm. Stimulus durations were 1, 10 and 100 msec, in some cases being shorter than 1 or longer than 100 msec.

The irradiator and the hand of a subject were submerged in a bath of water (Fig. 1), the water temperature being 30, 35 or 40 °C. To effect fixation the hand was placed in a special fixer of silumin cast into its shape. The position of the irradiator with respect to the hand was adjusted with a coordinating device allowing a movement of the irradiator to  $\pm$  0.01 mm. The focal length of the irradiator being 70 mm, it was possible

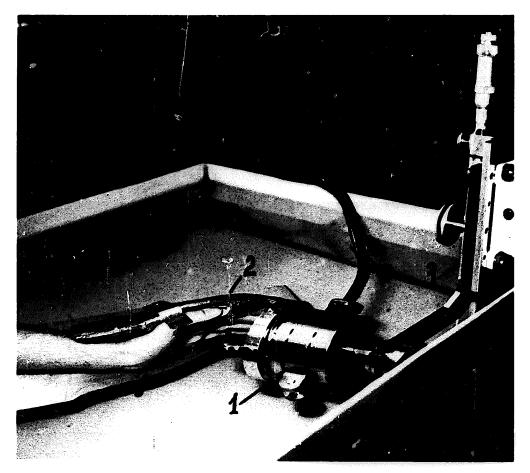


Fig. 1. The focusing irradiator (1) and silumin casting for fixation of the forearm (2) in a water bath. A part of coordinating device (3) is also seen.

to advance the focal region from on the palm surface deep into the palm till it came out onto the back of the hand.

Experiments were performed on 7 subjects, aged 23-45 years, spots on the skin of the fingers, the palm, and forearm being examined. Altogether more than 600 experiments were made, including repeated tests in one and the same spot to know the variation in responses between experiments, and experiments with immersion of the focal region deep into the hand tissue. The depth of stimulation was practically constant when the centre of the focal region was set on the skin surface.

In the course of an experiment (20–25 min) the subject reported the presence or absence of sensation when skin or deep tissues were stimulated by ultrasound. Each time a stimulus was given the subject was warned by the phrase: 'Attention, please'. When the sensation appeared the subject was asked to describe its character, and the associated thresholds were measured. Stimuli of a given duration were applied at irregular intervals, the intensity rising from stimulus to stimulus. As a rule an experiment included stimuli first for 1 msec, followed by stimuli 10 and 100 msec long. The experiment was stopped immediately after a first expressed feeling of pain appeared. After the spots on the skin had been examined they were marked on the hand with a special device and later the marks were redrawn onto a 'chart' which was a life-size



Fig. 2. A 'chart' of the hand of one of the subjects with spots examined.

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photograph of the subject's hand (Fig. 2). Such charts allowed repeated experiments to be made in one and the same spot.

In a special series of experiments the appearance of cavitation in soft tissues was checked with registration of subharmonic components of the acoustic noise which appeared with ultrasonically induced cavitation in the medium. The set-up used comprised a miniature piezoreceiver (a piezoceramic cylinder 1.2 mm long, 0.8 mm in bore diameter and 1.2 mm in outside diameter) placed in water 2–3 cm from the centre of the tocal region; a selective amplifier tuned to half ultrasonic frequency, and an oscilloscope. The appearance of cavitation resulted in an impulse on the screen of the oscilloscope, the impulse amplitude depending on the degree of development of cavitation. The intensity of ultrasound at which the impulse amplitude exceeded by 40 dB the noise level was taken as a conventional minimum intensity to induce cavitation.

## RESULTS

When the focal region was on the skin surface the subject felt diverse sensations depending on the location of the focal region, water temperature, intensity and duration of a stimulus. As a rule, stimulation of one and the same spot with the focused ultrasound of ascending intensities resulted first in tactile, then in temperature and, finally, in pain sensations. When the ultrasound frequency was 2.67 MHz, the pain sensation appeared less frequently than it did at the lower frequencies. This effect may be due to a smaller focal region or to the fact that the maximum stimulus associated with this frequency was not enough for pain sensation. Stimulation of some spots on the palm and, much more frequently, on the forearm resulted in sensation of no more than one or two modalities, e.g. tactile or tactile and temperature or only pain sensations, etc. In the deep tissues, of the above sensations it was possible to cause only the pain or sensations fore-running the pain. A shift of the centre of the focal region with respect to a sensitive spot was accompanied by disappearance of sensations or by higher thresholds. As a rule, the tactile sensations were repeatedly produced with repeated stimulation while temperature and pain sensations were not. When a sensitive spot was able to respond to ultrasound stimulus with several different sensations, the shortest latency was observed for tactile and longer, respectively, for temperature and pain sensations. Repeated stimulation which failed to give repeated temperature or pain sensation did repeatedly produce the tactile sensations.

## Tactile sensations

Of all the sensations the tactile ones were associated with stimuli of lowest intensity. The subjects described them as a 'local touch', a 'slightly sensed stroke', a 'burst of a falling water drop', a 'slight push' and could well distinguish them from the temperature, tickling, itching and pain sensations. Occasionally, with the focal region in tissues under the skin layer, the sensations were described as 'unpleasant tactile' or 'fore-running the pain' differing from those arising within the skin layer.

The threshold for tactile sensation was taken to be a minimum intensity of stimulus to cause the sensation. The threshold intensity increased with frequency of the ultrasound.

**TABLE I** 

Thresholds for tactile sensations obtained from 4 spots in finger skin

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Abbreviations: *t* is the Student criterion for 95% probability; m, Standard Error.

Water	l msec			10 insec			100 msec		
temperature °C	I, M ± tm W/sq.cm	A, µm	<b>⊿</b> 7, °C	I, M ± tm A, µm W/sq.cm	A, µm	ΔT, °C	I, M ± tm W/sq.cm	A, µm	AT, °C
8 S 04	<i>Subject 1</i> 208 ± 28 196 ± 22 160 ± 15	0.1 0.1 0.09	0.027 0.025 0.02	214 ± 30 213 ± 18 160 ± 15	0.1 0.1 0.09	0.27 0.27 0.2	240 ± 40 225 ± 54 203 ± 29	0.11 0.105 0.1	2.4 2.3 2.1
30 35 40	Subject 2 240 ± 33 210 ± 31 200 ± 16	0.11 0.1 0.1	0.03 0.027 0.025	260 ± 23 200 ± 10 197 ± 18	0.11 0.1 0.1	0.33 0.25 0.25	250 土 30 210 土 14 193 土 19	0.11 0.1 0.1	5 5 5 5 5 5

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Effects of the focused ultrasound on tissues can be due to a variety of some phenomena related to particular parameters of ultrasound. From the measured value of intensity and the use of a relation for a plane wave<sup>1</sup> it is possible to calculate the displacement amplitude in the focal region (A,  $\mu$ m), the sound pressure amplitude (P, atm), the particle velocity amplitude (V, m/sec) etc. With a formula<sup>5</sup> fitting well to experimental data it is possible to calculate the temperature rise ( $\Delta$ T, °C) in the focal region.

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In Table I are given the results obtained from two subjects. The frequency was 2.67 MHz. Listed are the displacement amplitudes (A,  $\mu$ m) and temperature rise in the focal region ( $\Delta$ T, °C) associated with the threshold intensities of ultrasound. Increasing stimulus duration from 1 to 100 msec failed to reliably change the thresholds. Increasing water temperature from 30 to 40 °C resulted in a moderate decrease of the thresholds. The threshold increased with the moving of the focal region (within the skin layer) from fingers to forearm.

When the centre of the focal region was moved into the tissues under the skin layer the threshold rose. The tactile sensations disappeared when the whole of the focal region was in the soft tissues. However, if the focal region happened to be projected onto the skin layer of the opposite surface of the hand, for example, through soft tissues between the thumb and the forefinger, the tactile sensations appeared again but with higher thresholds. They were localized in the place of projection of the centre of the focal region.

With stimuli longer than 100 msec the tactile sensations appeared in response to both the beginning and the end of the stimulus. Thus, a sensation produced by two stimuli 10 msec duration spaced by 380 msec failed to differ from that produced by a threshold stimulus 400 msec long.

## Temperature sensations

In some spots within the skin layer, increasing the intensity of the focused ultrasound resulted in warmth or cold sensations. The sensations irradiated in a circular pattern or in one direction. Thus, a cold sensation evoked in a spot on the skin of a finger tip could irradiate along the finger skin, the palm and the distal third of the forearm. The temperature sensations disappeared when the focal region was submerged under the skin layer. Similar to the tactile ones, the warmth sensations could be evoked in the skin of the opposite side of the hand if the focal region was projected there through soft tissues. The cold sensations failed to appear in this case.

The threshold temperature sensation was taken to be a sensation of warmth or cold reproduced by repeated presentation of the associated stimulus or a stimulus with a slightly higher intensity. The thresholds for temperature sensations, as those for tactile ones, increased with the moving of the focal region from finger to forearm. If stimuli of the same or higher intensity were repeatedly sent to the same spot the temperature sensations, as a rule, were reproduced. On different days, however, repeated stimulation of the same spot could fail to result in temperature sensation. The number of experiments where there were reported, if only once-through, sensations of warm or cold (n) and the total number of experiments (N) are given in Tables II

Thresholds for	Thresholds for warmth sensation														
Water	l msec					10 msec					100 msec				
temperature °C	I, M ± tm W/sq.cm	A, µm	4, µm 47, °C n	2	2	I, M ± tm W sq.cm	A, μm	A, μm ΔT, °C n		2	I, M ± tm W/sq.cm	A, μm	A, μm ΔT, °C n	=	2
40 33 30	Subject 1 Subject 1 12,000 12,400 16,800 ± 2803	0.77 0.78 0.9	1.52 1.57 2.1		15 19 19	5600 3400	0.52 0.41 0.6	7.1 4.3 9.4	445	15 19 19	1400 ± 240 1000 ± 100 1050 ± 80	0.26 0.22 0.22	14 10 10.5	10 15	14 18 18
30 35 40	<i>Subject 2</i> 4900 ± 800 5500 ± 1000 14,500 ± 1600	0.44 0.52 0.83	0.5 0.7 1.8	20 م 20	5 19 24	3700 ± 800 3300 ± 400 5200 ± 400	0.43 0.4 0.5	4.7 4.2 6.6	14 16 19	19	$1000 \pm 140 440 \pm 20 900 \pm 120$	0.22 9.15 0.21	10 4.5 9	17 15	19 19

TABLE II Thresholds for wormth son

Water	1 msec					10 msec			ĺ		100 msec				
°C	I, M ± tm W/sq.cm	А, µт	А, µт ДТ,°С п N	2	2	l, M ± tm W sq.cm	A, µm	A, µm AT, °C n N	2	2	I, M ± 1m W/sq.cn	A, µm	A, µm 4T, °C n	2	2
30	Subject 1 21,800	1.03	2.8	7	15	13,000 ± 1000	0.79	16	13	15					4
40 83	$14,000 \pm 2600$ $18,000 \pm 2600$	0.83 0.94	1.8 2.3	Ś	61 <u>61</u>	8000 ± 1600 0 11,800 ± 2400 0	0.63 0.76	10	<b>1</b> 4 6	61 61	2800	0.37	ا ۲	-	18
30 35 40	<i>Subject 2</i> 17,000 ± 1800 12,900 ± 2000 —	0.91 0.8	2.2 1.7	13	21 24	10,400 ± 700 8300 ± 600 —	6.71 0.64	13.5	251	19 19 24	1600 ± 160 640 	0.28 0.18	16 8.1	e –	24 19

TABLE III Thresholds for cold sensation

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and III. In each experiment stimuli of 1, 10 and 100 msec were presented. Also listed are the mean values of the threshold stimulus intensities (W/sq.cm), the corresponding displacements of the medium (A,  $\mu$ m) and temperature rise ( $\Delta$ T, °C) in the focal region. The frequency was 2.67 MHz. The data presented were obtained from four spots on the pads of finger tips, excepting the thumb (two subjects examined). As can be seen from Tables II and III, mainly for stimuli 1 and 10 msec long, depending on water temperature around the hand, stimulation of the same sensitive spots mostly evoked the feeling of cold (at a temperature of 30 °C) or warmth (at 40 °C). In Fig. 3 are presented the data obtained from 17 experiments on one and the same subject in a spot on the skin of the tip of the forefinger. The ultrasound frequency was 2.67 MHz, the stimulus duration, 10 msec. It will be seen that at a temperature of 30 °C both cold and warmth sensations, and at a temperature of 40 °C only the warmth sensations were found. It should be noted that if both types of sensations appeared the warmth 3ensation always preceded the cold one.

A special series of experiments was done where, at a room temperature of 21-23 °C a thermode, with a tip diameter of about 1 mm, was used to find 'warm' and 'cold' spots on the palm skin. The temperature of the water circulating in the thermode was, respectively, 50 or 10 °C. When the points found by the thermode were stimulated with ultrasound stimuli (frequency 0.887, 1.95 and 2.67 MHz; duration 1 and 10 msec: water temperature 34-36°C) cold or warmth sensation appeared independent of whether a point under study was previously determined as 'warm' or 'cold'. For example, a 'warm' point was determined on the palm skin of subject 2 by making use of a warm thermode. Stimulation with the ultrasound stimuli happened to arouse sensations of both cold and warmth. In another case, a 'cold' point determined on the palm skin of subject 3 by the thermode gave a warmth sensation when stimulated with ultrasound.

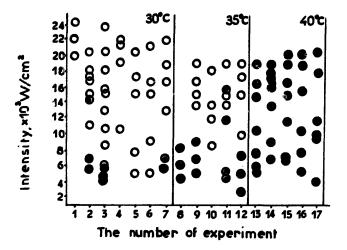


Fig. 3. Relationship between the character of temperature sensation (cold-warmth) and the temperature of surrounding medium.  $\bigcirc$ : cold sensation;  $\bigcirc$ : warmth sensation;  $\bigcirc$ : warmth sensation followed by cold one. At the top: the temperature of surrounding medium (water in the bath). Subject 2; ultrasonic frequency 2.67 MHz; stimulus duration 10 msec. Data from 17 experiments done in different days on the same spot of the forefinger skin.

The regularities observed in these experiments were similar to those presented in Tables II and III, i.e. irrespective of whether a point determined with the thermode was 'cold' or 'warm' it could produce either cold or warmth sensations in response to ultrasound stimuli of a duration of 1 or 10 msec. As above, the cold sensations appeared at a temperature of 30 °C, while at 40 °C the warmth sensations appeared.

## Pain sensations

With increasing stimulus intensity and action on some spots there appeared a feeling of pain.

Depending on which spot in the skin was stimulated, the pain sensation could either be preceded by other sensations or not; it could also fail to appear even with a maximum intensity of stimulus injuring the skin.

Unlike the other sensations, the pain appeared not only with the centre of the focal region within the skin but also when it was shifted into the tissues under the skin layer. While checking the pain sensations produced by directing the focal region into different tissues it was found possible to compare, according to their associated subjective colouring, the degree of 'unpleasantness'. The pain sensations from deep tissues were characterized by the subjects as 'more unpleasant', 'much more unpleasant', or 'the most unpleasant' as compared with those from the skin layer.

According to the location of the centre of the focal region, four types of pain sensation could be separated. (1) Within the ckin layer: the sensation of a surface pointlocalized pain similar to a sharp pain from pricking a hand with a needle but with a burning component. (2) In soft tissues: pain sensation in depth, slightly irradiating in a circular pattern, the pain being 'more unpleasant' than that of type 1. (3) In the bone: pain sensation in the bone. The pain of this type is admittedly due to the periosteum, since it is known from surgical experience that manipulations directly involving the bone tissue are painless. This sensation is even less localized than that in soft 'issues, irradiates over a long distance along the bone and is concentrated again at the place of stimulation, with a 'far more unpleasant feeling'. (4) In the joint: a sensation similar to the pain in the bone but irradiating only within the joint. It is assessed by the subject as 'the most unpleasant'.

The types of sensations were independent of frequency. When the focal region covered two or three types of tissue, as could easily be the case on the finger tip, there appeared a mixed pain sensation. The subjects trained to differentiate each pain sensation were able to sort out such a sensation into its separate components.

The threshold intensity was taken to be the intensity of a stimulus to produce, with gradually increasing intensity from stimulus to stimulus, the first sensation of pain.

In Table IV are given the lowest thresholds obtained from two subjects (water temperature, 35 °C). (It was assumed that the lowest thresholds are associated with certain most optimal conditions for stimulus effect, due to a more exact coincidence of the centre of the focal region with a receptor structure. Because of this, the comparison of the lowest thresholds should be preferred to the procedure used in the conventional statistical treatment.) It will be seen that threshold intensities depend

TABLE IV

Pain thresholds with different location of the focal region

-, absence of pain sensation with maximum intensity of ultrasound stimulus; X, not studied.

	•	morbel as sr								A, µm	1							
Duration, msec	-			01			100						10			100		
Frequency	0.48	0.48 0.887	2.67	0.48	0.887	2.67	0.48	0.887	2.67	0.48	0.887	2.67	0.48	0.887	2.67	0.48	0.887	2.67
Location of the focal region																		
Skin																		
fingers	14	140	0006	12	100	3600		80	620	0.14	0.24	0.66	0.13	0.21	0.42	0.14	0.18	0.17
palm	160	680	1700	50	140	3000	45	140	620	0.47	0.54	0.90	0.27	0.24	0.38	0.25	0.24	0.17
forearm	200	1	1	65	١	11,400		340	200	0.99	]		0.30	1	0.75	0.14	0.38	0.10
Soft tissues																		
fingers	120		13,400	28	100	2200	14	80	220	0.41	0.2	0.81	0.20	0.21	0.32	0.14	0.18	0.10
palm	27	820	17,000	42	1380	ł	4	220	1800	0.20	0.6	0.90	0.24	0.77	I	0.24	0.30	0.29
forearm	225	×	1	120	×	×	350	×	1200	0.56	×	I	0.41	×	×	0.70	×	0.24
Bone																		
fingers	12	380	×	13	120	×	13	60	×	0.13	0.4	×	0.14	0.23	×	0.14	0.16	×
palm	8	160	15,000	60		11,600	590	ł	800	0.36	0.26	0.86	0.29	1	0.75	0.37		0.20
Articulatio inter-																		
phalangea of the																		
middle finger	12	36	3000	28	80	3000	×	×	1200	0.13	0.12	0.38	0.20	0.18	0.38	×	×	0.24
Articulatio meta-																		
carpo-phalangea																		
of the thumb	200	×	18,800	140	×	13,000	i 30	×	200	0.53	×	0.98	0.44	×	0.79	0.40		0.18

on the type of pain and the part of the extremity stimulated (fingers, palm, forearm). The thresholds for all types of pain exhibit a tendency to increase with the moving of the focal region in a proximal direction, i.e. from fingers to forears.

A separate series of experiments was made to assess the possible part played by ultrasonically induced cavitation in soft tissues in the appearance of the threshold pain sensation. With stimulus duration of 1 msec, the pain sensation, as a rule, failed to appear, though a well-developed cavitation occurred in tissues. With a stimulus duration of 10 msec, the threshold intensities for pain exceeded the intensities which produced cavitation. Again, with a stimulus duration of 100 msec, in some cases the cavitation appeared at smaller intensities than pain, and in others there was pain and no cavitation. These data indicate that there is no causal relationship between the appearance of cavitation and threshold sensations of pain.

## Other sensations

Aside from tactile, temperature and pain sensations, focused ultrasound was capable of producing the feeling of itching and tickling. Thresholds for tickling sensation were close to (but always lower than) those for warmth sensation. The same relationship holds for thresholds for itching and pain sensations. The feeling of warmth or cold changed sometimes to a feeling of tickling, the feeling of pain in the skin being followed, as a rule, by an itching sensation.

## DISCUSSION

By stimulating the hand with focused ultrasound it was found possible to evoke all the cutaneous sensations that are experienced by man in natural conditions. Sensations were evoked by stimulating separate sensitive spots in the skin. The sensation threshold increased with the moving of the focal region in a proximal direction.

The temperature sensations contrasted with the others by being dependent on the temperature of the surrounding medium: in one and the same spot it was possible, by changing the temperature of the water bath, to cause the feeling of warmth or cold. Different sensations in the same point might have been due to different receptors for cold or warmth sensations. This explanation does not hold, however, for the forearm skin, where receptors are more spaced than on the skin of the fingers or palm (the spacings on the forearm skin are greater than 1.1. mm, which is the smallest diameter of the focal region<sup>6</sup>). Another explanation is that the same receptor may be responsible for both sensations. These suggestions seem to be supported by conventional methods using point mechanical stimulation of the cornea, where there are only the so-called free nerve endings. In this case the appearance of a cold or warmth sensation depends on the air temperature<sup>7</sup>.

When establishing and assessing the effective factors of an ultrasonic irradiation it was found that the sound pressure, the particle velocity, the temperature rise in the focal region and other factors of a stimulus involved in producing sensation of one or another modality undergo changes within several orders depending on ultrasonic frequency. It is only the displacement amplitude of the medium in the focal region that is independent of frequency<sup>3</sup>. This evidence suggests that the mechanical factor plays a major part in stimulating a variety of receptor structures. The appearance of threshold sensations for pain is not related to the occurrence of cavitation (there is no cavitation with other sensations). This indicates that mechanical phenomena associated with cavitation are not essential for the appearance of pain sensation, as compared with displacement of the medium in the focal region. Evidence concerning displacement as the main effective factor in ultrasound stimulus allowed the focused ultrasound to be used in electrophysiological investigations. The results obtained are to be found in the following paper<sup>4</sup>.

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