High intensity therapeutic ultrasound research in the former USSR in the 1950s – 1970s

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Valentin Burov

1934 - 2014

Outline

- Introduction:
  - 2 cycles of intense therapeutic ultrasound research in the former USSR
- A.K. Burov – immune response to ultrasound treatment (*50s)*
- M.G. Sirotyuk, L.R. Gavrilov –
  - brain, neurology, other applications *(70s)*

Leonid Gavrilov

Andrey K. Burov – architect and scientist

Head of the Laboratory of Anisotropic Structures, Academy of Sciences of the USSR;

Doctor of technical sciences

Corr. Member of the Academy of Architecture of the USSR

1900 - 1957

S.-E. Le Corbusier, C.M.Eisenstein, A.K. Burov. 1927

Published for the 100th anniversary of A.K. Burov by Physics Faculty of MSU, 2000 (in Russian)

Andrey Burov - architect

Examples of his projects in Moscow

House of Architects

1938 - 1941

Apartment building

Tverskaya, 25

1936 - 1950

Open-work House

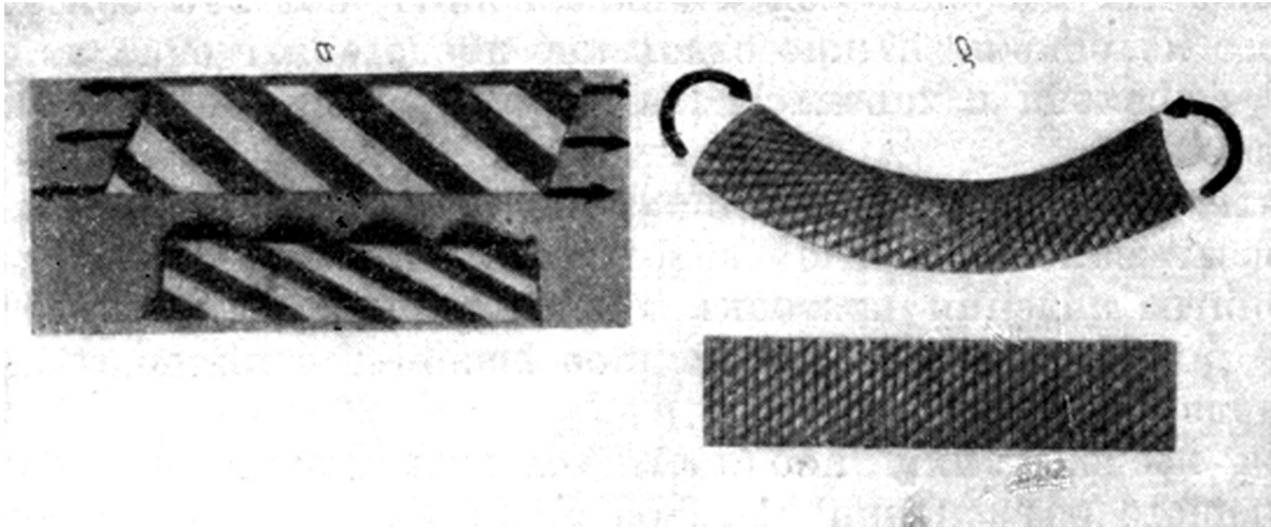
Leningradsky Avenue, 27

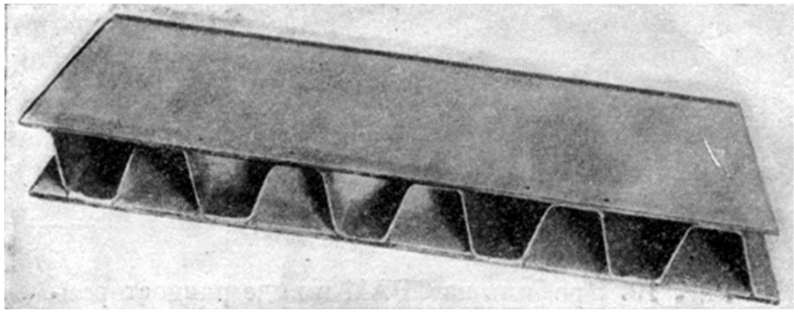
1936-1940

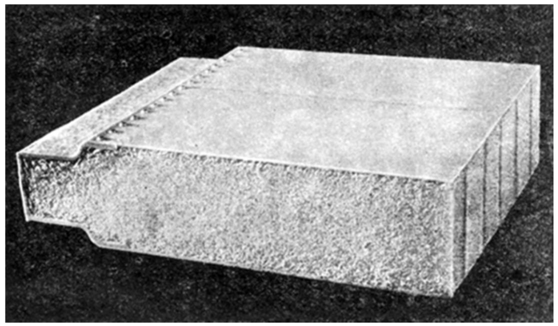
Andrey Burov – development of new materials for lighter constructions

Laboratory of Anisotropic Structures, Academy of Sciences of the USSR

Composite fiber-glass and polymer materials







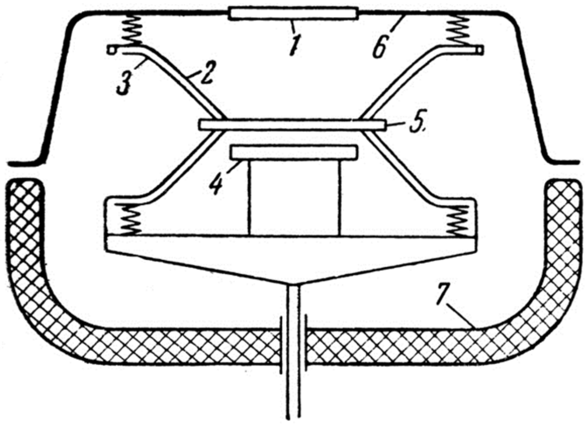
1950s

Ultrasound treatment of malignant tumors

Development of high-intensity ultrasound sources

unfocused US beams, quartz transducers: f = 1.5 MHz,
intensity I = 200 W/cm^2 cw, up to 500 W/cm^2 in a pulsed regime

ultrasound transducer and its diagram



1. output window; 2. main contactor; 3. preserving contactor; 4. reflector; 5. quartz plate; 6. metallic crankcase; 7. plastic crankcase

ultrasound beam mapping

Melting and boiling: diffraction beam pattern at the plexiglass plate in water

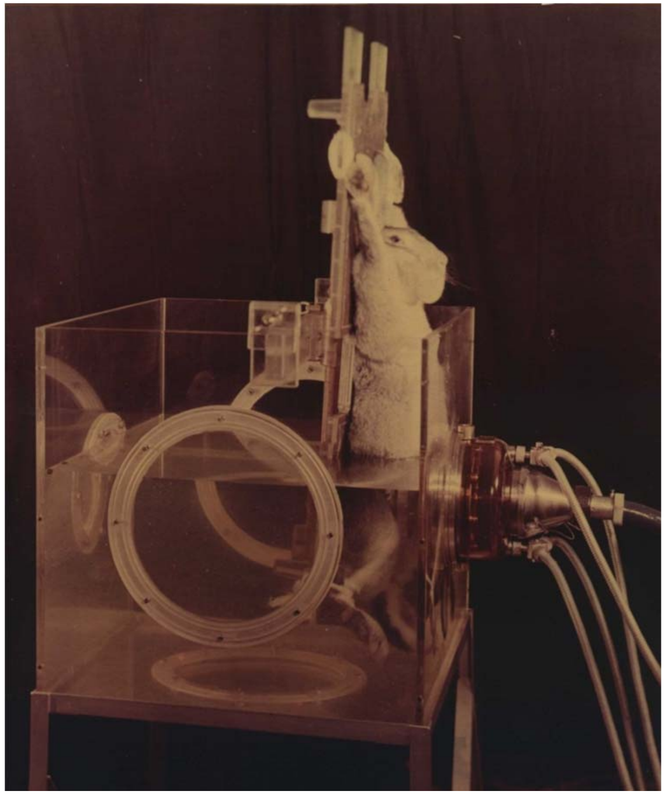
Burov, A.K., Dokl. Akad. Nauk SSSR, 106, no. 2, 239–241 (1956);
Burov, A.K. and Andreevskaya, G.D., Dokl. Akad. Nauk SSSR, 106, no.3, 445–448 (1956);
Burov, A.K., Sov. Phys.Acoust., 4, no. 4, 326–330 (1958).

1950s

Ultrasound treatment of malignant tumors

Short irradiation time: thermal effect was assumed to be negligible

unfocused US beam, f = 1.5 MHz, I = 100 - 200 W/cm^2, exposure 1-2 s



- high-malignancy strain of Brown–Pearce tumor model
- tumor transplanted in a rabbit testicle
- ultrasonic irradiation after 8 – 11 days
- tumor grows to volume about 40 cm^3

In 40–80% of cases, the tumor resolved completely several months later, the resulting cicatrix was often calcified, clearly pronounced immune response was reported

1950s

Ultrasound treatment of malignant tumors

Hypothesis: nonthermal therapeutic effect to induce immune response

unfocused US beam, f = 1.5 MHz, I = 100 - 200 W/cm^2, exposure 1-2 s of testicle

disappearance of metastasis in the rabbit eye

N.P. Dmitrieva. On the resorption of metastases following treatment of Brown-Pearce tumor by ultrasound of high intensity in rabbits, Bull. Exp. Biol. Med., 11, 81–85 (1957).
N.P. Dmitrieva. The effect of supersonic waves of high intensity on the growth and metastasis of transplantable Brown-Pearce's tumors in rabbits, Bull. Exp. Biol. Med., 11, 97–102 (1958).

1950s

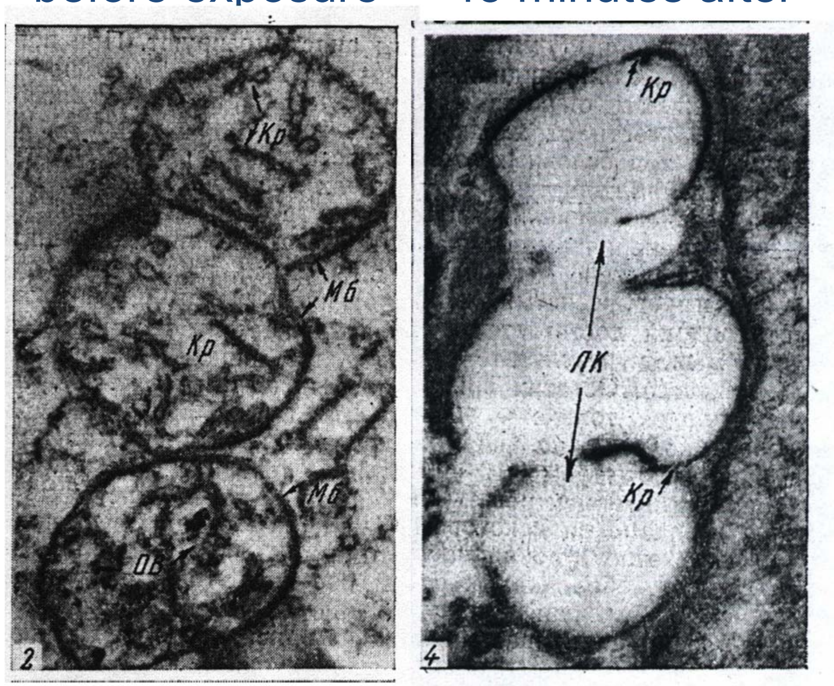
Ultrasound treatment of malignant tumors

multiple transplantation of tumor suspension to recovered rabbits did not cause the disease relapse

Hypothesis: nonthermal therapeutic effect to induce immune response

Mitochondria of Brown-Pearce tumor

before exposure 45 minutes after



Optical microscopy:

- no observable changes in cell structure of insonified tumor tissue during the first hours or days after sonification.
- clear signs of distrophy, further degeneration, and resorption of tissues at later stages.
- no similar processes in healthy tissues.

Electron microscopy:

- changes in the structure of mitochondria:

at early stages - membrane laceration and stratification,

at later stages - modification of inner mitochondrial structure

Dmitrieva, N.P., "Histologic chances in the Brown-Pearce tumor under the action of ultrasound of high intensity", Vopr. Onkol., 3, no.6, 688–693 (1957).

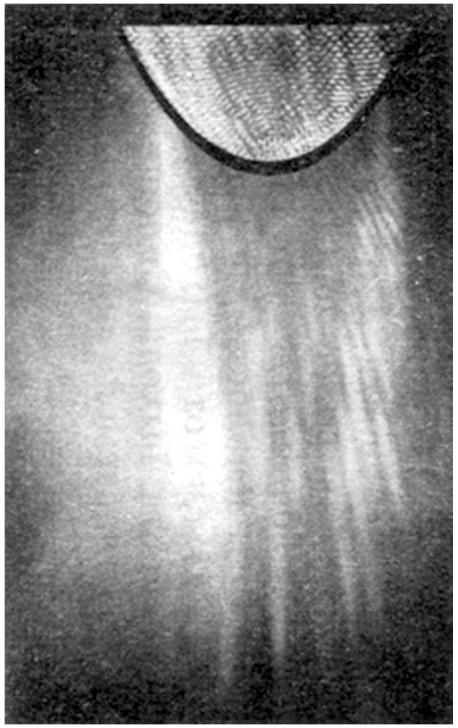
Dmitrieva, N.P., Dokl. Akad. Nauk SSSR, 132, no.1, 210–212 (1960).

1950s

Ultrasound treatment of malignant tumors

Development and testing of experimental anti-tumor autovaccine
Laboratory of Anisotropic Structures (1956–1957)

- Sonications were performed in parabolic reflector-concentrator;
- Homogenized and sonicated tumoral mass was centrifuged;
- The resulting liquid fraction was injected back to the same animal;
- The autovaccine inhibited malignant process and caused recovery of the experimental animals



1950s

Ultrasound treatment of malignant tumors

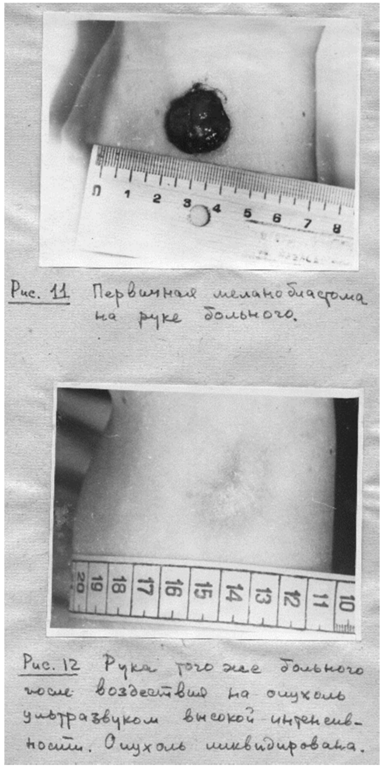
Clinical trials of melanoma treatments at the N.N. Blokhin Institute of Experimental Pathology and Therapy of Cancer

ten patients, mainly with the terminal stage of melanoma

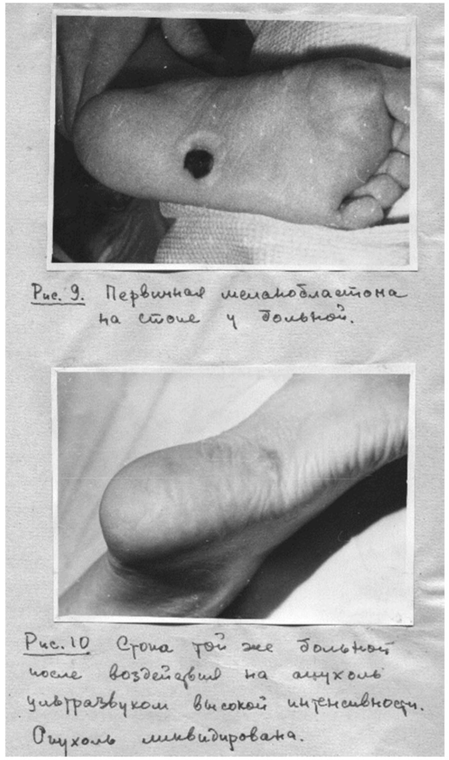
Patients preparation for sonication of the melanoma on the shoulder

Primary melano-blastoma

arm



foot



Although, in some cases, positive results were not obtained (several patients died of severe concomitant diseases), complete resorption of melanoma was observed in some patients

The studies stopped after sudden death of V. Burov in 1957

1970s

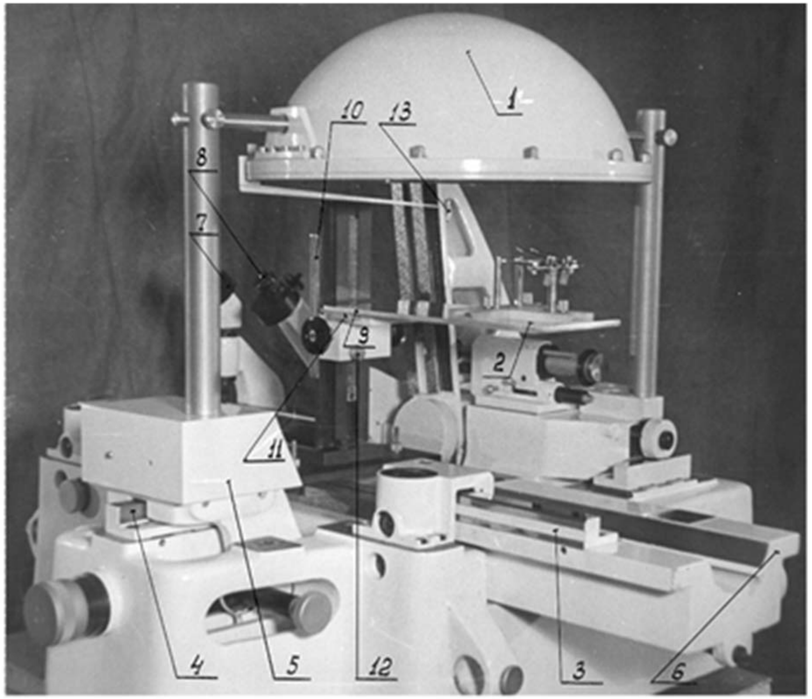
HIFU in the USSR in 1970s

N.N. Andreev Acoustics Institute, Moscow

Development of super high-intensity focused systems of 0.5 and 1 MHz

Prof. Lasar D. Rozenberg
Ultrasound Department (founder)
Acoustics Institute

1908 - 1968



Frequency 1 MHz, power 870 W, focal length 18.3 cm, surface area 1560 cm^2, convergence angle 75°, max intensity 146 kW/cm^2, average - 43.5 kW/cm^2

Assumed to be used for neurosurgery in animals

L. D. Rozenberg, Sound Focusing Systems (1949) [in Russian].
Editor (Plenum Press, New York): *I. Sources of High-Intensity Ultrasound,* 1969
Part 3 written by Rozenberg: *Ultrasonic Focused Radiators;*
***II. High-Intensity Ultrasonic Fields,* 1971; *III. Physical Principles of Ultrasonic Technology,* 1973**

1970s

Initial goal of the HIFU project

develop ultrasound instrumentation and transfer it to several Medical Centers in the USSR for research on a number of applications

Head of the HIFU project – M.G. Sirotyuk, key person – L.R. Gavrilov (head from 1973)

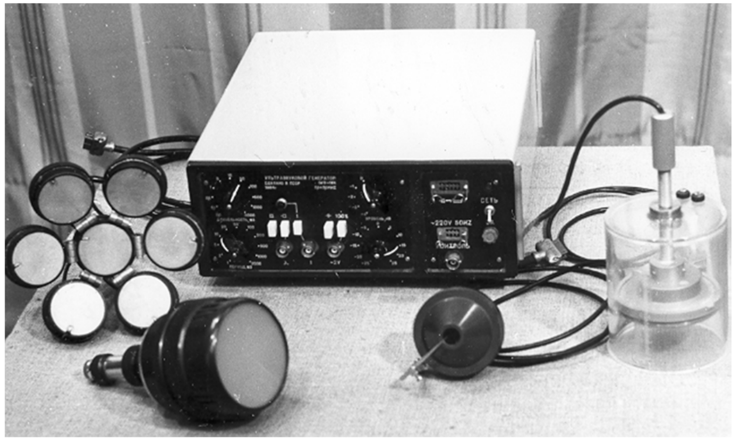
High power ultrasound generators

electrical power
1000 W

electrical power
250 W

portable generators

electrical power
up to 300 W



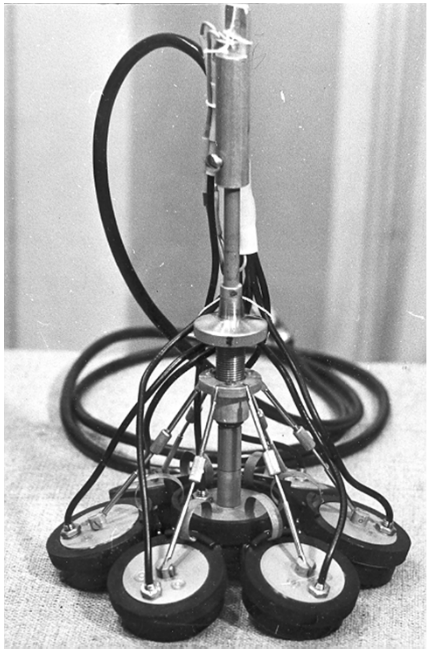
Described in:
L. R. Gavrilov, E. M. Tsirulnikov,
Focused Ultrasound in Physiology and Medicine, Nauka, Leningrad, 1980

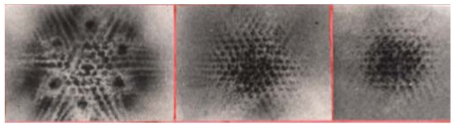
Initial goal - develop ultrasound instrumentation and transfer it to several medical Institutes for research on a number of applications

Head of the HIFU project – M.G. Sirotyuk, key person – L.R. Gavrilov (head from 1973)

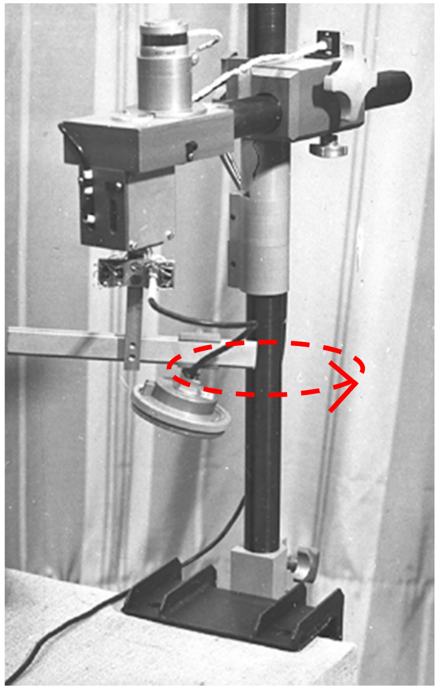
Ultrasound (US) transducers

7-element system with varying focal length *f* = 1 MHz

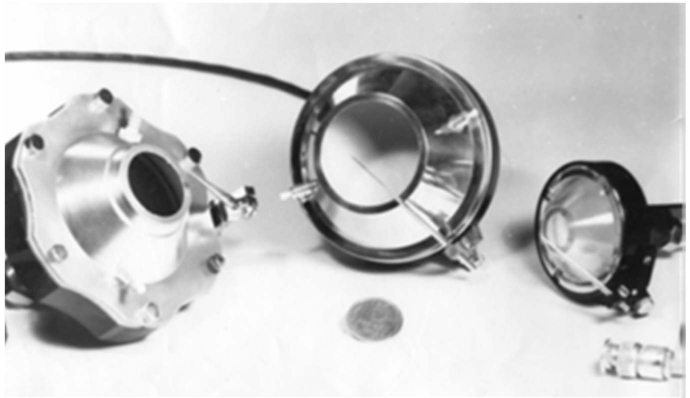




Rotary transducer to induce ablations of annular geometry f = 1 - 2 МГц

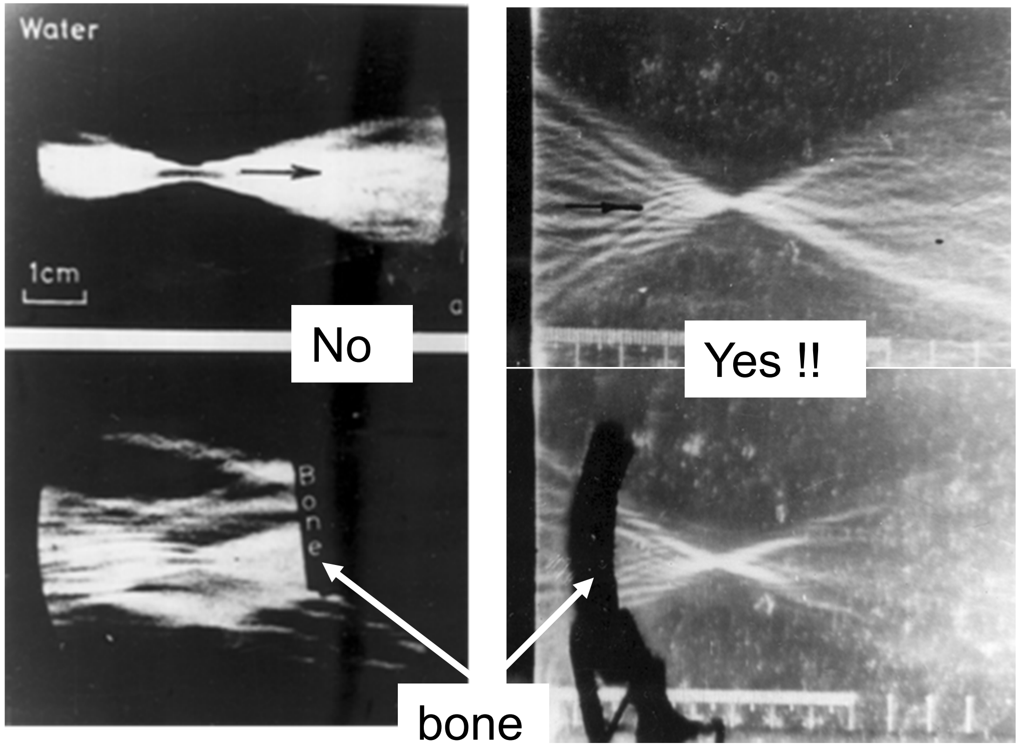


***f* = 0.5 - 3 MHz**
***D* = 6-8 cm, *F* = 5-7 cm**



Major results

Feasibility of US focusing through the skull



Prof. P.P. Lele, Ultrasonics, 1967

Bulletin of Experimental Biology and Medicine, 1971, 1973

Patent, 1970

СОЮЗ СОВЕТСКИХ СОЦИАЛИСТИЧЕСКИХ РЕСПУБЛИК

ГОСУДАРСТВЕННЫЙ КОМИТЕТ СОВЕТА МИНИСТРОВ СССР ПО ДЕЛАМ ИЗОБРЕТЕНИЙ И ОТКРЫТИЙ

АВТОРСКОЕ СВИДЕТЕЛЬСТВО

№ 412891

На основании полномочий, предоставленных Правительством СССР, Государственный комитет Совета Министров СССР по делам изобретений и открытий выдал настоящее авторское свидетельство

ГАВРИЛОВУ Леониду Рафаиловичу и другим, указанным в описании

на изобретение "Способ воздействия на заданные участки ткани головного мозга в эксперименте"

в соответствии с описанием изобретения и приведенной в нем формулой,

по заявке № 1434033 с приоритетом от 6 мая 1970г.

заявитель изобретения: Центральное конструкторское бюро с опытным заводом Академии медицинских наук СССР

Зарегистрировано в Государственном реестре изобретений Союза ССР

5 октября 1973 г.

Действие авторского свидетельства распространяется на всю территорию Союза ССР.

Bull. of Exp. Biol. & Med. 1971

УДК 616.831-085.837.3

ИССЛЕДОВАНИЕ ВОЗМОЖНОСТИ ЛОКАЛЬНОГО ВОЗДЕЙСТВИЯ ФОКУСИРОВАННЫМ УЛЬТРАЗВУКОМ ЧЕРЕЗ УЧАСТКИ ЧЕРЕПА ЖИВОТНЫХ И ЧЕЛОВЕКА

Ю. С. Инин, М. Г. Сиротюк, С. И. Тюрина

Центральное конструкторское бюро с опытным заводом АМН СССР и Акустический институт АН СССР, Москва

(Поступила в редакцию 5/VIII 1970 г. Представлена акад. В. В. Париным)

Эксперименты по визуализации ультразвукового поля при прохождении фокусированного ультразвука через участки черепа животных и человека показали принципиальную возможность локального воздействия ультразвуком на структуры мозга без вскрытия черепа (Бюлл. экспер. биол., 1971, № 4, с. 120).

In 1970 it was first shown that ultrasound can be focused through the intact skull (Acoustics Institute and Central Designing Bureau of the Academy of Medical Sciences of the USSR)

Experiments in animals and human cadavers (1973-77)

Acoustics Institute and Central Designing Bureau of the USSR Academy of Medical Sciences

Bulletin of Experimental Biology and Medicine, 1973

USE OF FOCUSED ULTRASOUND FOR LOCAL DESTRUCTION OF BRAIN STRUCTURES WITHOUT DAMAGE TO THE SKULL

S. I. Tyurina, F. A. Brazovskaya, Yu. S. Inin, D. I. Paikin, M. G. Sirotyuk, and L. R. Gavrilov

UDC 612.82-089:615.837.3

By means of a special technique it is possible to produce local destruction in the deep structures of the brain by irradiation with focused ultrasound through the intact skull. Histological investigations revealed no pathological changes in the brain along the path-way to the lesion, in which a focus of coagulation necrosis was observed.

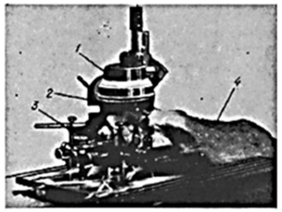


Fig. 1. The use of focused ultrasound in a stereotaxic apparatus: 1) generator; 2) rubber bag filled with distilled water; 3) stereotaxic apparatus; 4) rabbit.

Fig. 2. Focus of destruction in hypothalamic region of a rabbit's brain (arrow), Nissl, 15×.

achieved through distilled water or mineral oil, contained in a hollow on the skull formed after removal of an area of skin. To secure better wetting of the skull with water or mineral oil and, consequently, better acoustic contact, the skull in the zone of irradiation was exposed on the day before the operation. During the operations areas of the brain located at a depth of 16-20 mm from the surface of the skull in the region of the hypothalamus and mesencephalon were irradiated [5]. The animals were killed 3-6 days after irradiation.

The brain was extracted from the skull of the experimental animals and examined morphologically. Thin frontal sections were cut and examined in reflected light by means of the MBS-1 stereoscopic microscope with a magnification of 4-8 times (ocular 8, objective 0.6-2). The foci of destruction were located at different levels of the segmental portion of the mesencephalon or in the hypothalamic region. After a single irradiation foci 0.2-1 mm in diameter and 1-3 mm long were observed in the brain. The zone of brain destruction was much smaller than the focal spot of the generator in water [1], presumably because of the considerable losses of acoustic energy during passage through the skull. The foci were elongated in shape, repeating the geometry of the focal spot in water. This showed that defocusing of the sonic beam during passage through the cranial bond was negligible. In the case of repeated ultrasonic irradiation of the brain, when the focal spot in the brain was displaced (by ±0.5 mm) the foci of destruction were elongated in a direction perpendicular to the spread of the sonic waves, showing that foci of destruction of the brain of any desired shape and size can be obtained by repeated irradiation.

Histological investigations of frontal sections of the brain of the experimental animals revealed a focus of coagulation necrosis in the zone of irradiation (Fig. 2). Nerve cells with gross destructive changes were seen in the perifocal zone. The size of the focus of necrosis in a dorso-ventral direction in sections treated with celloidin in both cases was 0.25 mm, and together with the perifocal zone the region of pathological changes extended to 0.85-0.90 mm. No pathological changes could be found anywhere along the path of the sonic waves to the focal spot.

This investigation demonstrates that focused ultrasound can be used in principle to produce local destruction of the deep structures of the brain without injury to the skull.

Human cadavers (1977)

МИНИСТЕРСТВО ЗДРАВООХРАНЕНИЯ СССР

I МОСКОВСКИЙ ОРДЕНА ЛЕНИНА И ОРДЕНА ТРУДОВОГО КРАСНОГО ЗНАМЕНИ МЕДИЦИНСКИЙ ИНСТИТУТ ИМЕНИ И. М. СЕЧЕНОВА

ПРИМЕНЕНИЕ УЛЬТРАЗВУКА И НОВЫХ ВИДОВ ЭНЕРГИИ В ДИАГНОСТИКЕ, ТЕРАПИИ И ХИРУРГИИ

Сборник научных трудов

Под ред. профессора В. И. Петрова

МОСКВА—1977

РАЗРАБОТКА МЕТОДА ЛОКАЛЬНЫХ РАЗРУШЕНИЙ В ГЛУБИНЕ МОЗГА ПУТЕМ ОБЛУЧЕНИЯ ФОКУСИРОВАННЫМ УЛЬТРАЗВУКОМ ЧЕРЕЗ ИНТАКТНЫЕ ВОЛОСЯНОЙ ПОКРОВ, КОЖУ И ЧЕРЕП

(Экспериментальное исследование)

А. С. Корсаков, С. И. Тюрина, Л. Р. Гаврилов, Ф. А. Бразовская

Нами была поставлена задача разработать метод, позволяющий с помощью фокусированного ультразвука создавать локальные разрушения в мозге трупа без вскрытия кожи и черепа. Эксперименты выполнялись на извлеченном мозге, черепе и целых трупах. Работа проводилась на кафедре судебной медицины I-го Московского ордена Ленина и ордена Трудового Красного Знамени медицинского института им. И. М. Сеченова (зав. кафедрой — проф. А. П. Громов).

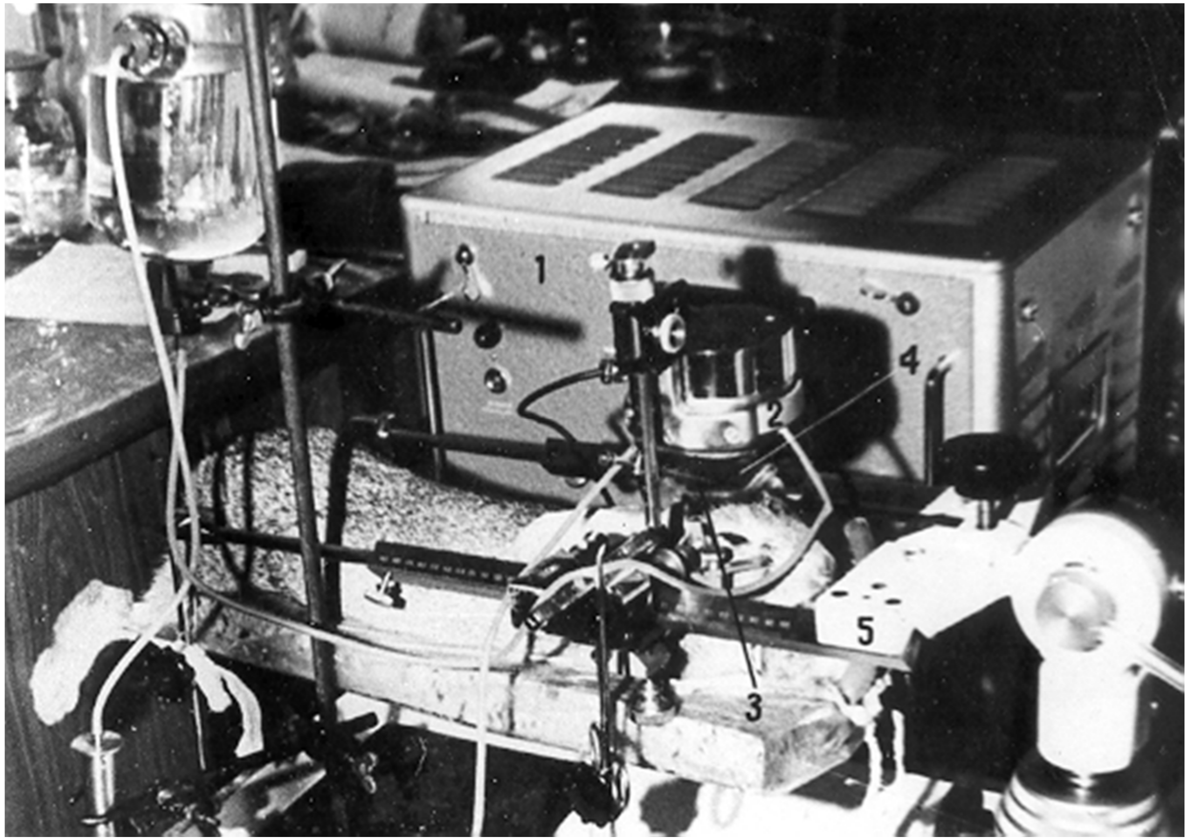
Выполненная работа продемонстрировала принципиальную возможность использования фокусированного ультразвука в клинической нейрохирургии для операций, не требующих вскрытия кожи и черепа.

Classic work which is usually referred to as the first in this field: Fry F.J., Goss S.A. Ultrasound in Med. and Biol. 1980. V. 6. P. 33–38

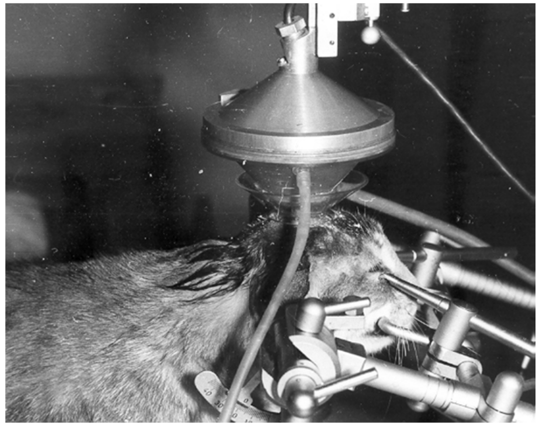
Major results

Measurement of cavitation thresholds in brain *in vivo f* = 0.5 - 3 MHz

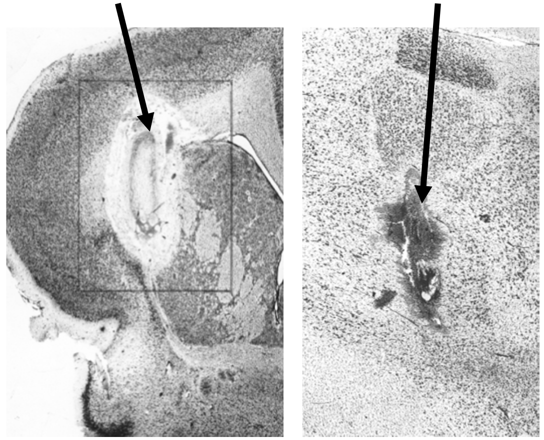
Irradiation of brain in rabbits using HIFU
I_F = 100 - 10 000 W/cm^2, exposure = 0.1-5 seconds



Irradiation of brain in cats



HIFU-induced lesions:
thermal *cavitational*

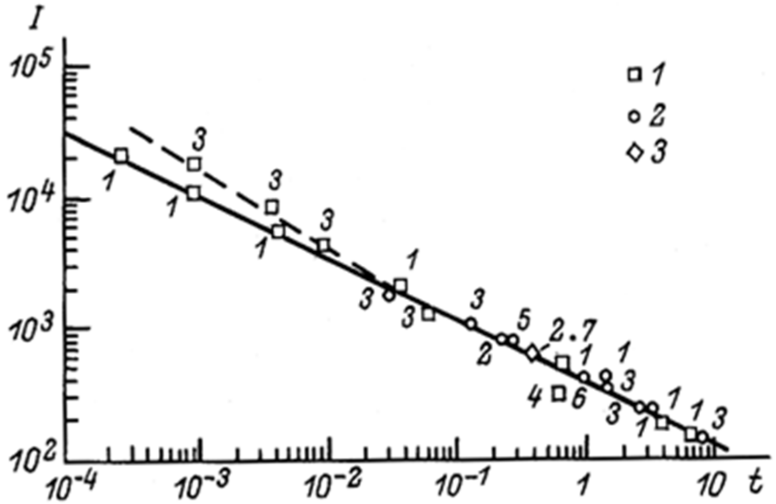


Courtesy of N. Vykhodtseva

Measurements of cavitation thresholds in animal brains *in vivo* (1973-74)

Acoustics Institute and Institute of Brain of the USSR Academy of Medical Sciences

Threshold ultrasonic dosages for structural changes in mammalian brain. Fry F. *et al*. JASA, 1970



Measurements of cavitation thresholds
L.R.Gavrilov, Sov.Phys.Acoust. 1974

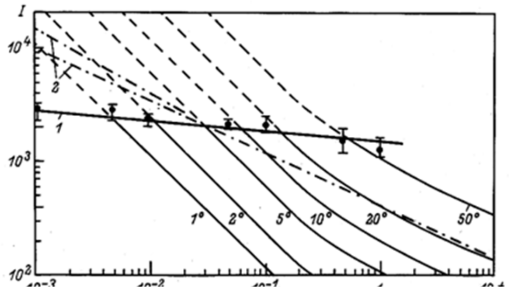
Physical mechanism of the lesion of biological tissues by focused ultrasound

L. R. Gavrilov

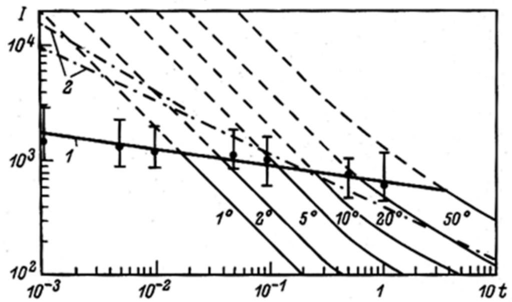
Acoustics Institute, Academy of Sciences of the USSR

(Submitted October 27, 1972)
Akust. Zh., 20, 27-32 (January-February 1974)

The physical mechanism of the lesion of biological tissues by focused ultrasound is investigated. The results of measurements of the cavitation thresholds in the brain tissues of experimental animals are given. A method is proposed for determining the ultrasonic dosages corresponding to the cavitation and thermal regimes of biological tissue destruction.

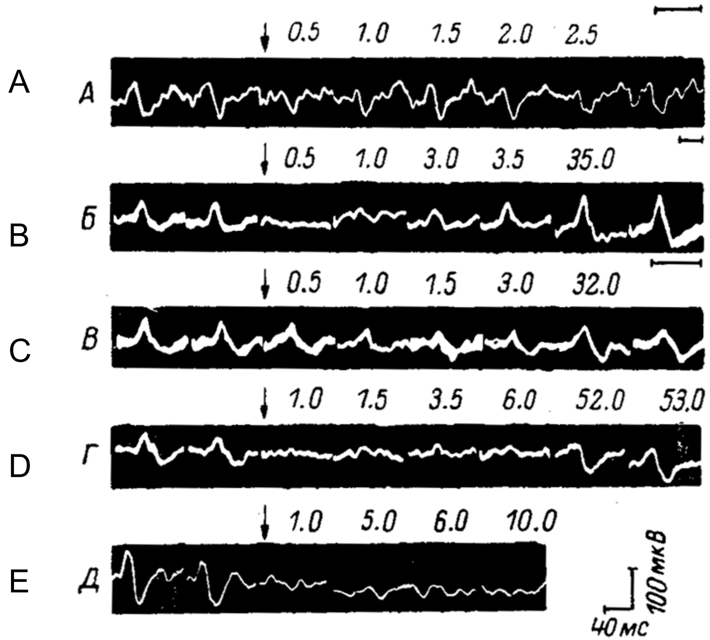


f= 1.72 MHz



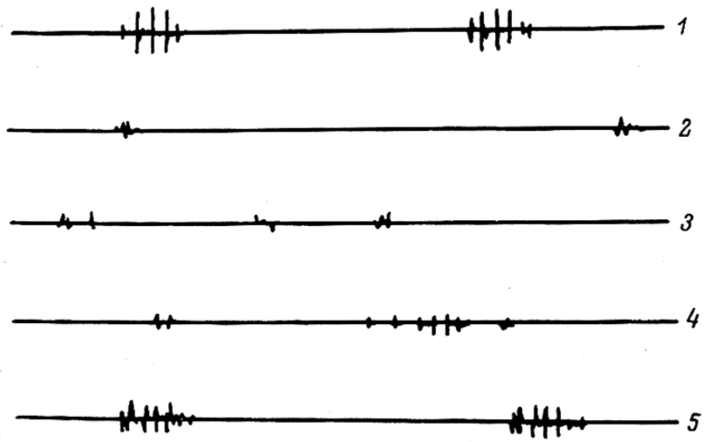
f= 0.94 MHz

Reversible effects on brain neural structures



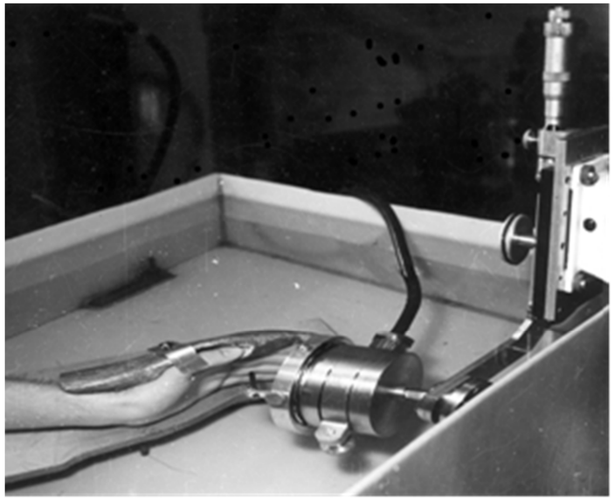
Changes of the action potential induced by short illuminations of the cats' retina after the action of HIFU at the optic tract in the brain. Numbers – time in minutes after ultrasound irradiation.
A, C - partial inhibition of evoked potential;
B, D - complete reversible suppression;
E - irreversible inhibition.
Calibration 100 mV, 100 ms (Adrianov *et al*. 1977).

Courtesy of N. Vykhodtseva



Voice reactions of a frog recorded on a tape recorder.
1 – before ultrasound irradiation of the brain;
2 - 1 hour after ultrasound irradiation;
3 – after 2 h; 4 – after 3 h; 5 – after 5 hours
(Tsirulnikov et al, 1977)

Neurostimulation effects of focused ultrasound

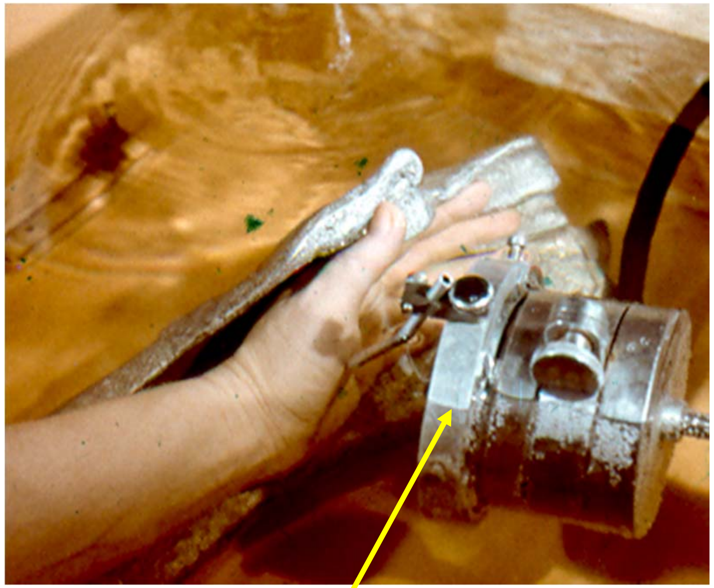


Stimulation of somatic sensations by focused ultrasound

**Acoustics Institute and Institute of Evolutionary Physiology,
USSR Academy of Sciences**

**Frequency from 0.5 to 3 MHz; pulses from 0.5 to 100 ms;
intensity from units to hundreds of W/cm^2**

3-D positioner



Focused transducer

It was shown that pulsed focused ultrasound can induce different somatic sensations (tactile, warmth, cold, pain, etc.) in humans

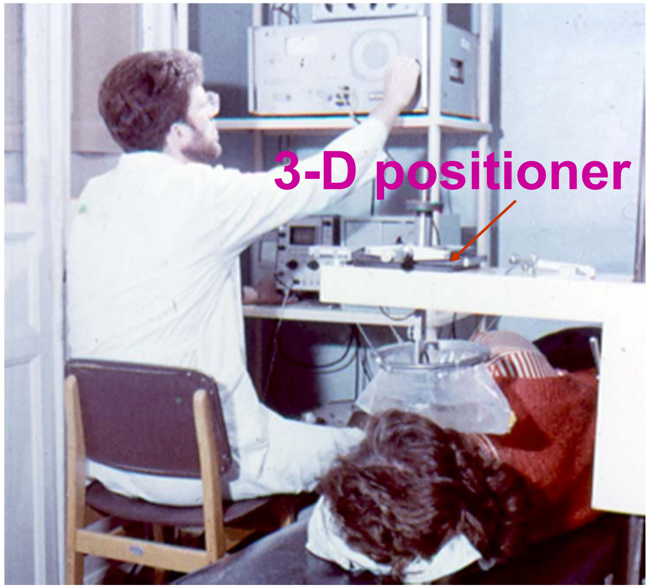
L. R. Gavrilov, G. V. Gershuni, et al., "Stimulation of human peripheral neural structures by focused ultrasound", Sov. Phys. Acoust. 19, 332-334 (1973).

L. R. Gavrilov, G. V. Gersuni, O. B. Ilyinski, E. M. Tsirulnikov, "A study of reception with the use of focused ultrasound. I. Effect on the skin and deep receptor structures in man", Brain Res. 135, 265-277 (1977).

L. R. Gavrilov, E. M. Tsirulnikov, "Focused Ultrasound in Physiology and Medicine" (Nauka, Leningrad, 1980)

Stimulation of hearing effects by focused ultrasound

Acoustics Institute and Institute of Evolutionary Physiology,
USSR Academy of Sciences

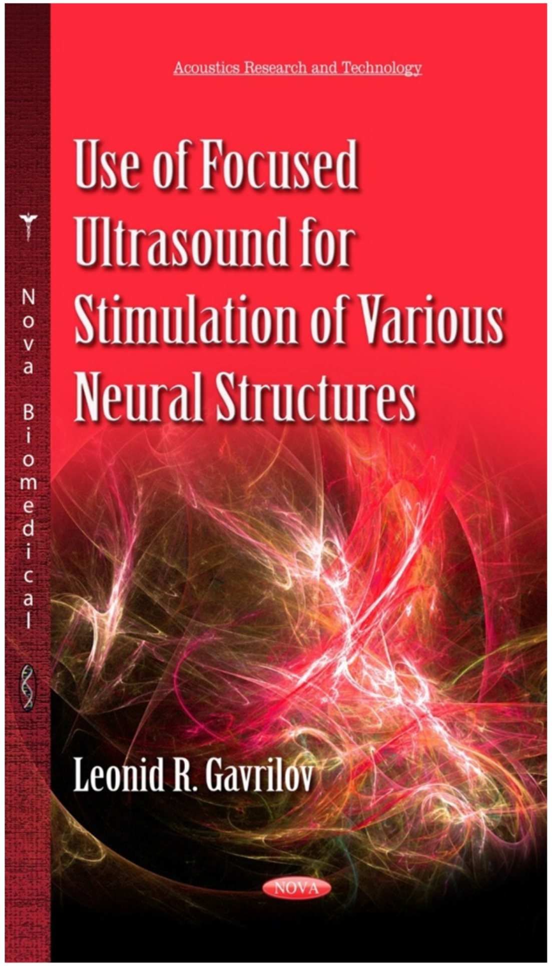


It was shown that US modulated by sound signals (tone, speech, music, etc.) induce hearing sensations corresponding to the character of modulation. Thresholds of HIFU-induced sensations can be measured with high accuracy and used to diagnose neurological, skin and hearing diseases

Proposed mechanism – acoustic radiation force

L.R. Gavrilov, E.M. Tsirul'nikov, "Focused Ultrasound in Physiology and Medicine" (Nauka, Leningrad, 1980)
L.R. Gavrilov, "Use of focused ultrasound for stimulation of nerve structures", Ultrasonics 22, 3, 132-138 (1984).
L.R. Gavrilov, E.M. Tsirulnikov, I. Davies, "Application of focused ultrasound for the stimulation of neural structures", Ultrasound Med. Biol. 22, 179-192 (1996)

These investigations became a basement for the development of a new field of medical acoustics related with neuromodulation of neural structures.

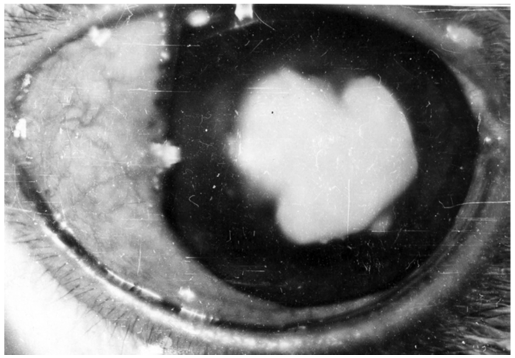


Contents

Gavrilov L. R. Use of Focused Ultrasound for Stimulation of Various Neural Structures. Nova Science Publishers. 2014. P.182.

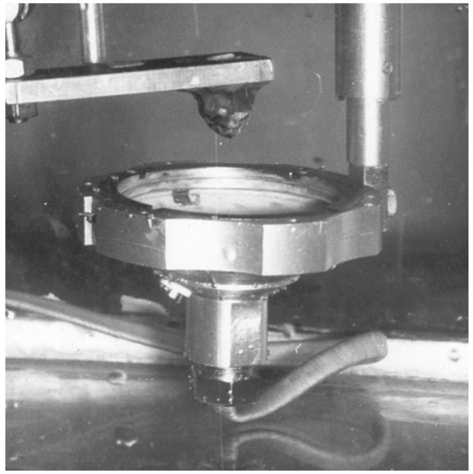
Other clinical applications:

Ophthalmology:
maturation of cataract



Gavrilov L.R., Narbut N.P., Fridman F.E.
Use of focused ultrasound to accelerate the
"maturing" of a cataract. Sov. Phys.-Acoust., 1974

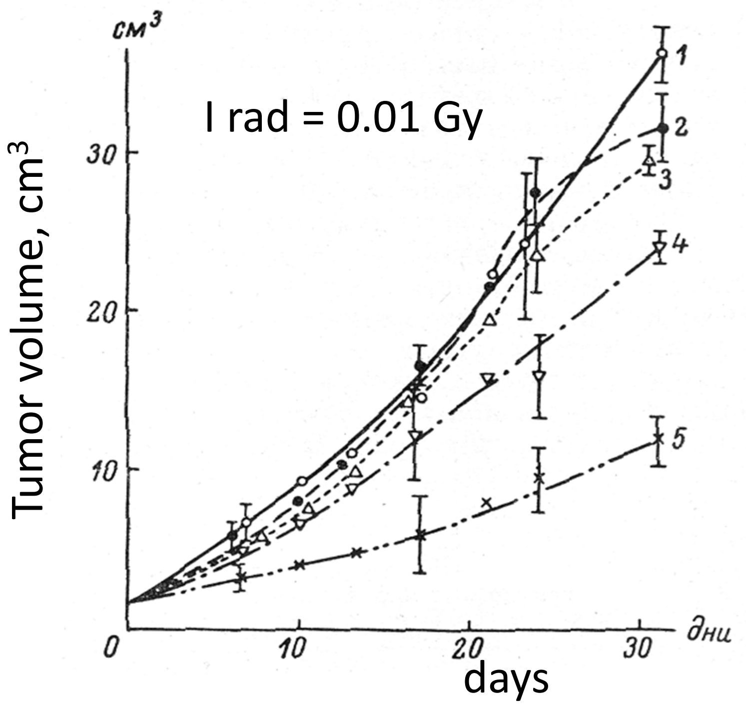
Urology:
fragmentation of stones in gallbladder



Galkin *et al*. Patent № 602180,
priority 1976

Ultrasonic enhancement of the gamma-irradiation of malignant tumors (1975)

50 animals, 10 animals in each group, total 450 animals used in experiments



1- control

2- γ-irradiation 350 rad

3- 0.5 W/cm² 3 min

4- 0.5 W/cm² 3 min + after 3 min γ 350 rad

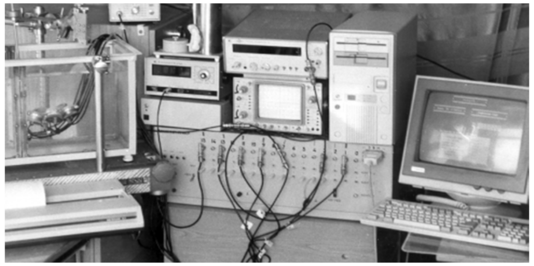
5- 0.5 W/cm² 3 min + after 7 min γ 350 rad

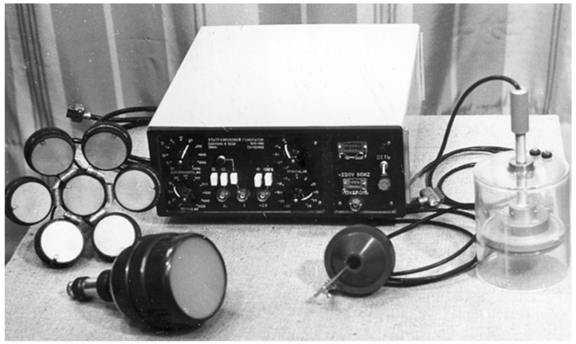
Combined US and γ irradiation with certain delay (7 min) resulted in stronger therapeutic effect

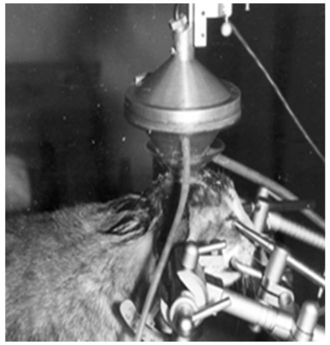
***Proposed mechanism**: stimulation of vital processes in the tumor cells by low intensity ultrasound leads to reduction of tumor resistance to the ionizing radiation. Time interval between stimulation and destruction was shown to be of importance.*

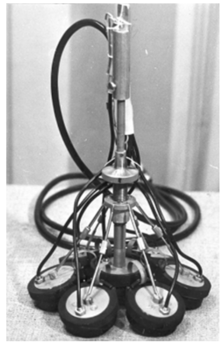
Gavrilov L.R., Kalendo G.S. *et al*. Sov. Phys.-Acoust., 1975

In the beginning of 1980s research on hyperthermia of tumors of brain and eye tissues started at the Acoustics Institute and other medical Institutes









…but this is another story and a topic of another presentation…

THANK YOU

FOR YOUR ATTENTION