14

Recent Developments in Ultrasound at the Biophysical Research Laboratory and Their Application to Basic Problems in Biology and Medicine

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Introduction by Dr. Weissler

Professor Francis Fry will now discuss the recent progress of the ultrasound research program here at the Biophysical Research Laboratory. For those of us who attended the previous symposia, it is a great pleasure to have the opportunity to learn about the current research and compare it with the status of the work at the time of the previous meetings. The progress in this field has been most stimulating.

During the past 5 years a variety of basic biological problems have been investigated and associated instrumentation developments have been pursued in the Biophysical Research Laboratory. The work of the laboratory thus falls into two major categories. First, we are primarily concerned with biological systems and the solution of problems pertaining to them. Therefore, we are involved with the methodology of attack on these problems and thus with the interaction of operating apparatus with these biological systems. Unfortunately, it is quite frequently true that the apparatus desired for a research investigation is not available commercially and a major effort must then be expended on the design of equipment. The second major category of work is, therefore, the development of apparatus, and in conjunction with this, the utilization of existing instruments as auxiliary equipment, for example, computers, to further the research activity.

The biological investigations include: (1) structure and function of the central nervous system of animals, such as monkey and cat, (2) modification of central nervous system of man for treatment of neurological disorders, (3) physical mechanism of action of ultrasound on components of central nervous systems – mouse spinal cord, (4) structure of skeletal muscle, (5) differential modification of the hypophysis, and (6) measurement of basic acoustic properties of tissue, for example, spinal cord, lung, etc. High-intensity ultrasound has been applied as an investigative tool in all of these programs. It should be noted that the specific studies are not, in general, directed at the observation of ultrasonic changes, for example, lesions, per se, but each has a broader scope as will be discussed here and in other papers presented in this symposium.

The application of high-intensity ultrasound to the treatment of human neurological disorders has been performed at the State University of Iowa Hospitals, and this work is a joint research program between the Biophysical Research Laboratory of the University of Illinois and the Division of Neurosurgery of the State University of Iowa Hospitals, of which Dr. Russell Meyers is chairman (1–6).

Under apparatus development, one can consider three general classifications: (1) mechanical, (2) electrical and electronic, and (3) electromechanical. In order to insure reproducible results in the use of high-level focused ultrasound as applied to tissue, it is necessary to control precisely the sound field parameters, as well as the parameters which determine the state of the tissue and consequently which determine the type of interaction. This applies not only in the case of irreversible changes in tissue, in which the selective action of ultrasound on various tissue components is desired, but also in the case of reversible interactions, in which tissue is not permanently affected. Control of the sound field parameters begins with the construction of reasonably stable transducers, which in turn are driven by appropriate electronic equipment. The problems associated with the design of this electronic apparatus will be discussed in another lecture at this session.

Transducers of a variety of types have been and are being used for the irradiation procedures. The frequency of the ultrasound used initially on animals was 1 Mc/sec and this frequency has continued in use on humans. Since the major fraction of the neuroanatomical investigations on experimental animals of interest to us at the present time demand small lesions, 4 Mc/sec sound has been used for most of this work. Reflecting, multi-beam, and single-beam focused transducers have all been employed in the irradiation procedures. However, for the past 5 years the majority of the animal irradiations have been performed with a single-beam, lens-focused transducer, while the human patients have been irradiated, up to the present, with a focused multi-beam irradiator.

A schematic view of a single-beam, 4-Mc irradiator is shown in Figure 1. A view of one electrode face of the quartz crystal is shown resting against the stainless steel housing, and this face is continuous with the electrical ground. The opposite electrode is in electrical contact with a thin gold foil which lies partially beneath the back-up gasket. The latter maintains the crystal in electrical and mechanical contact with the front part of the housing. The lens, in this case a plastic plano-concave unit, is held at an appropriate spacing distance, one-quarter acoustical wavelength at the operating frequency, from the crystal. Castor oil or silicone oil[1] is the coupling medium

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[1] Dow-Corning Type 7d.

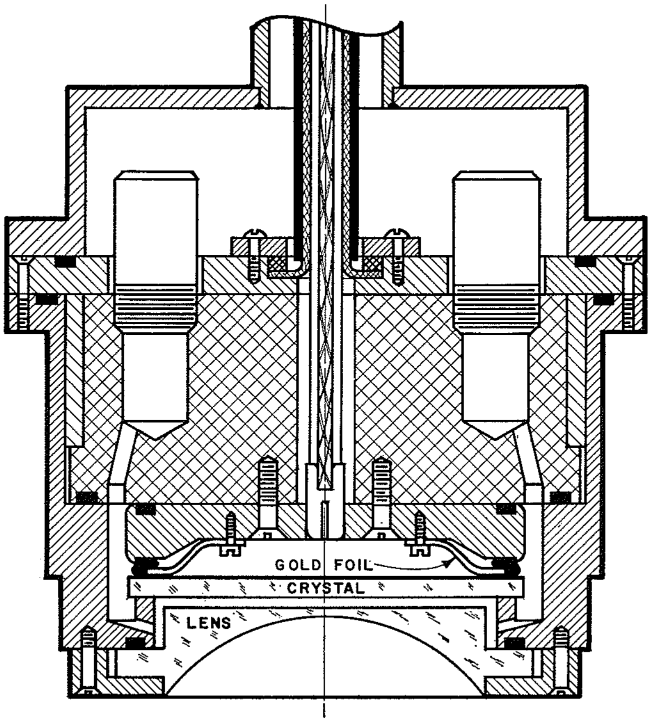

FIGURE 1. A schematic view of a single-beam, 4-Mc irradiator.

between the lens and crystal. Ports provide a free interchange for this medium to flow to the region surrounding the circumference of the crystal, to provide electrical insulation for the applied driving electric field. The lens is held in such a way that it can expand sideways relative to the housing. Thus, it does not flex in the center to produce variations in transducer output due to the differential temperature expansion between the housing and the lens. It should be noted that for calibration of the sound output of this type of transducer we use a thermocouple probe that is calibrated in absolute units by a radiation pressure procedure based on measuring the deflection of small diameter metal balls positioned in the sound field (7, 8). With a transducer of the type described it is possible, by careful assembly and subsequent storage in a constant temperature oven at, for example, 37°C (with the unit immersed in a sterilizing fluid such as benzakonium chloride), to obtain the type of transducer output data illustrated in Figure 2. The ordinate represents the r.f. voltage level on the transducer required to obtain a constant sound level at the focus. The abscissa refers to the time interval, in days, following filling of the space between the lens and crystal with oil. As one can see, the sound output exhibits a relatively slow drift pattern coupled with apparently random, day to day, variations. These random short time variations amount to ±0.7% and are within the limits of the overall accuracy of recording the data.

Accurate geometric placement of lesions in the brain of both humans and experimental animals requires a rigid tie between the skull and irradiator. In our earlier animal research studies, we employed modified Horsley-Clarke head holders, but for our later investigations we designed completely new types of head holders. For humans we designed a rigid head holder utilizing four stainless steel pins which fit hemispherically prepared indentations in the skull bone, two in the front and two in the rear. Each pin is supported by a post which provides three directions of motion, with a repositioning accuracy determined by micrometer readings. The accuracy of repositioning in the holder is such that, in general, ventriculography is *not* done for each irradiation procedure. Figure 3 shows a patient mounted in this type of head holder at the State University of Iowa Hospitals. Figure 4 shows the head holder in use with the apparatus for irradiation clearly visible. A local anesthetic is infiltrated into the tissue at the sites at which the pins penetrate the scalp. Although the forces along the pin axes are of the order of 50 to 75 lb, the patients do not usually complain. A sensation of compression is not a common occurrence, but some patients experience a transient compression feeling which is perhaps suggested by their visual observation of the turning of the pin tightening nuts.

Figure 5 shows a similar type of head holder which we designed and installed at the Medical Center of the University of Indiana. Dr. Robert Heimburger, Head of the Division of Neurosurgery there, is using this instrument. (Lesions are produced electrolytically.) Figure 6 shows a patient in this apparatus.

As one can readily see from an examination of these figures, both the mechanical rigidity of supporting the head of the patient and the accuracy of repositioning his head in the instrument have been prime considerations

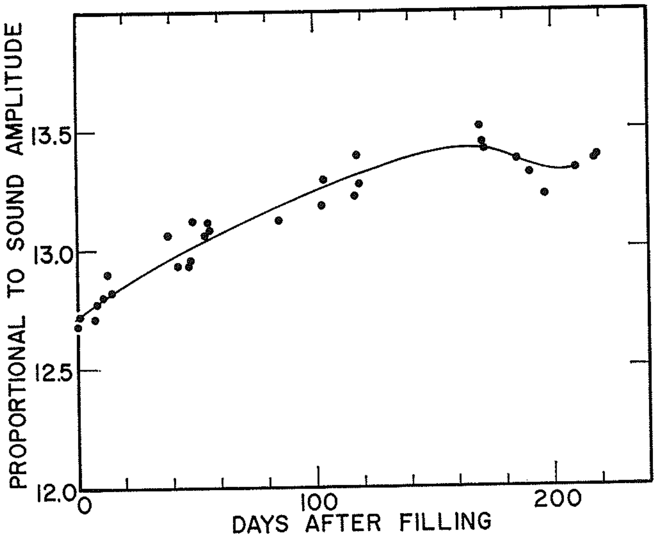

FIGURE 2. Transducer output data obtainable with a transducer of the type described.

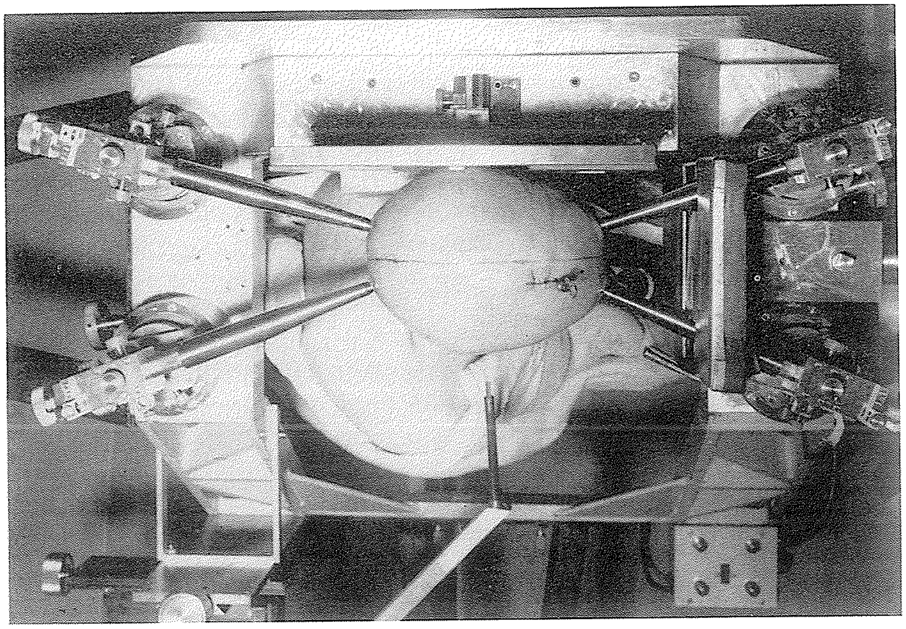

Figure 3. A patient at the State University of Iowa Hospitals mounted in the new type of head holder.

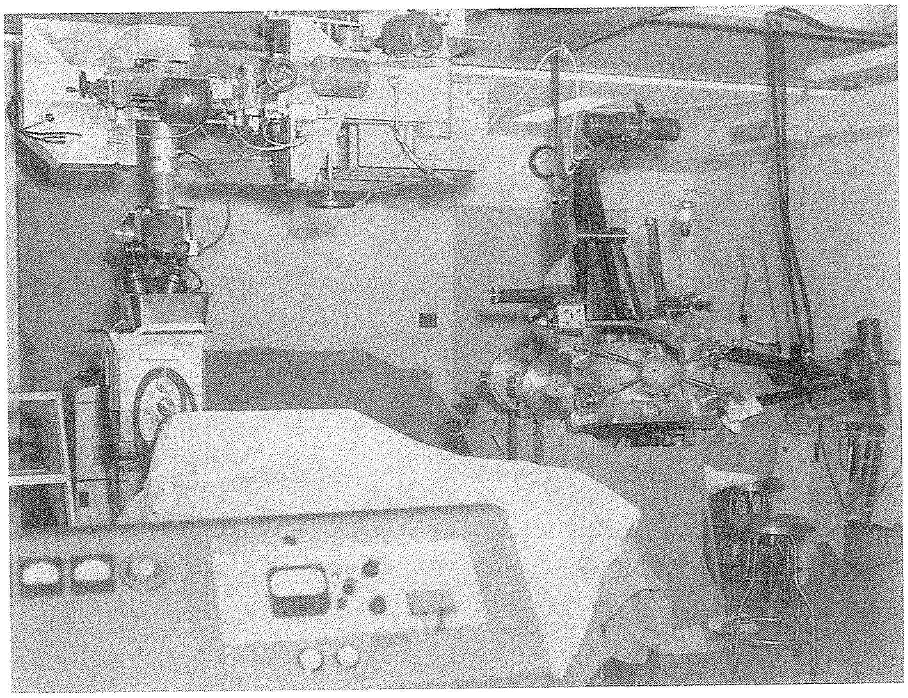

Figure 4. The head holder in use at the State University of Iowa Hospitals with the apparatus for irradiation clearly visible.

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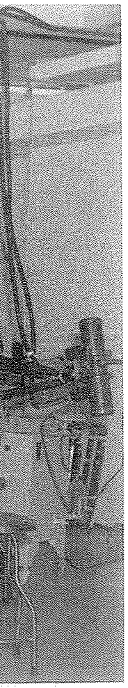

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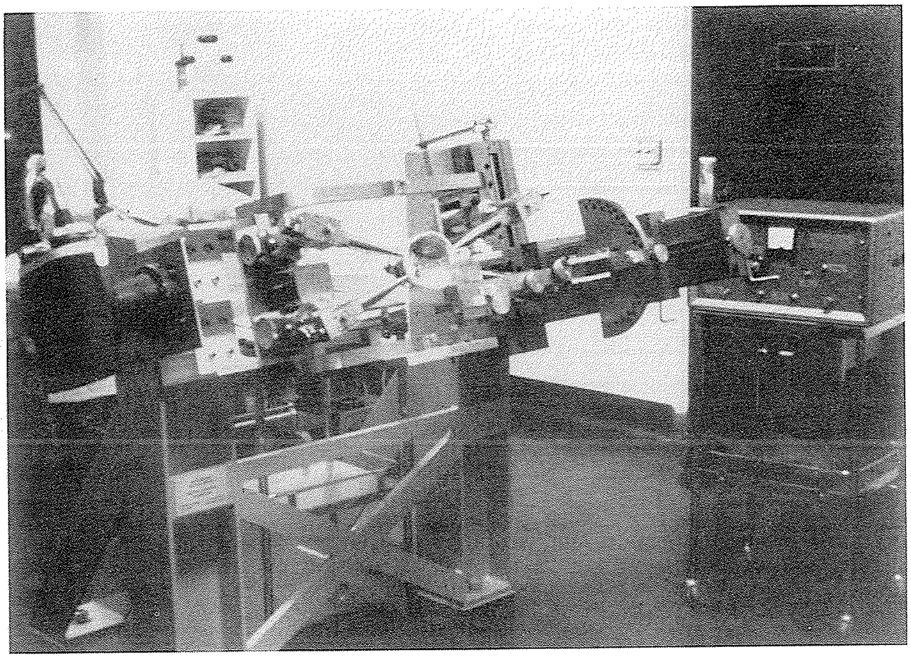

FIGURE 5. A similar type of head holder installed at the Medical Center of the University of Indiana. A piece of skull is mounted in the holder.

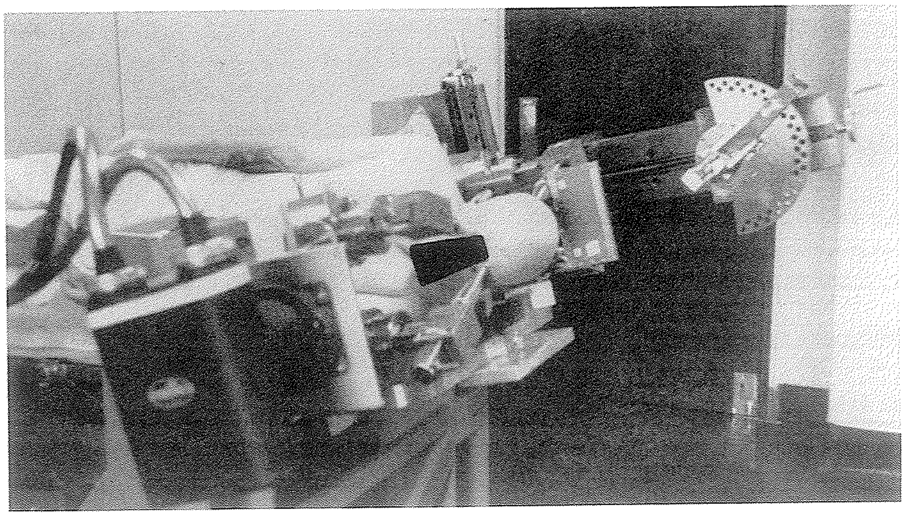

FIGURE 6. A patient shown in the apparatus at the University of Indiana Medical Center.

in the design of these head holders. In order to achieve reasonable accuracy in the determination of the coordinates of prechosen anatomic sites in the brain of the human or experimental animal, internal landmarks must be employed, except in cases where it is possible to localize a structure by reference to bony landmarks alone, for example, the pituitary gland. For the animal studies at the Biophysical Research Laboratory, the techniques have progressed from the simple ear bar zero method to an x-ray procedure employing internal bony landmarks and, finally, to the procedure involving x-ray ventriculography (9). For successful introduction of the x-ray opaque medium into the ventricles of the experimental animal, we have devised an electrical impedance measuring device which indicates by pointer deflection on a meter when the ventricle is entered by the penetrating cannula. Figure 7 shows the concentric arrangement of the cannula and the inner electrical insulated lead. In the lateral view of the cat skull shown in Figure 8, one can see that the needle, oriented vertically downward and driven by a mechanical positioning system, has just penetrated the roof of the lateral ventricle. At this point, the inner conductor is withdrawn and the x-ray opaque medium is introduced into the ventricle. One can see clearly the outlines of the lateral and third ventricles, and the anterior and posterior commissures are readily identified. A vertical view of these same structures is shown in Figure 9. A modified but similar ventricular cannula as that shown in Figure 7 has been devised for human use. Figure 10 shows a patient in a head holder with the ventricular needle held by the associated positioning system. A three-

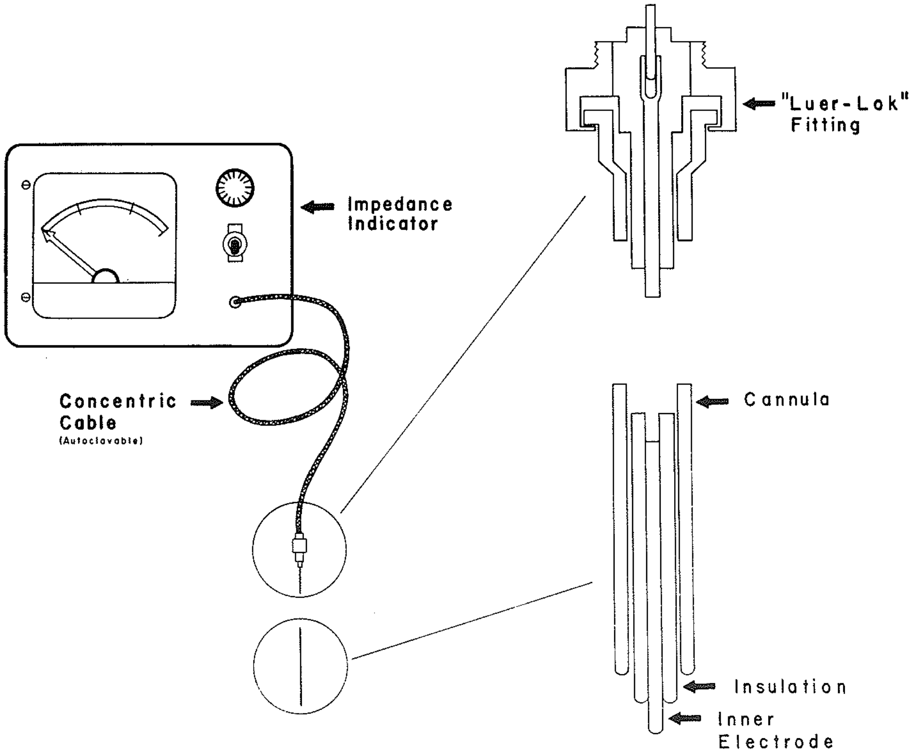

FIGURE 7. A schematic drawing of an electrical impedance measuring device used in the introduction of the x-ray opaque medium into the ventricles to indicate when the ventricle is entered by the penetrating cannula. The concentric arrangement of the cannula and the inner electrical insulated lead is shown.

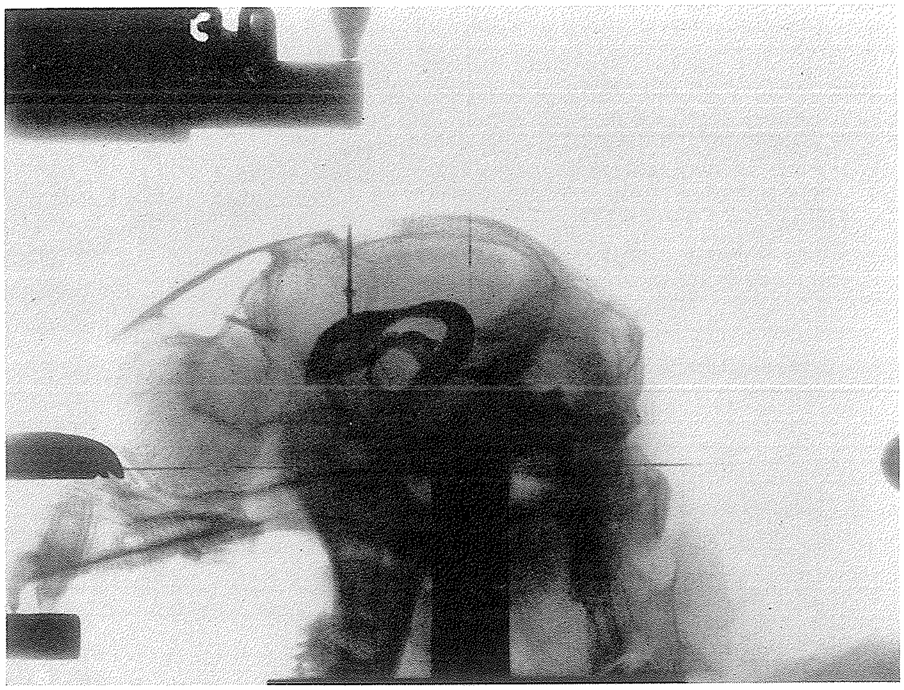

FIGURE 8. Lateral view of a cat skull showing the hypodermic-type needle described in Figure 7 penetrating the roof of the lateral ventricle. The outlines of the lateral and third ventricles are visible.

view x-ray technique is employed to localize the ventricular system of the patient in space: (A) lateral view, (B) anterior-posterior view, and (C) a view along an axis in the direction from the superior frontal sinuses to the base of the neck on its dorsal aspect.

The x-ray opaque medium we used for the earlier ventriculography on the human was Thorotrast, but this is no longer employed for this purpose. Figure 11 shows a group of three x-ray photographs taken with panopaque[2] filling. The anterior and posterior commissures are clearly visible on the lateral view (A). The length of the intercommissural line, which varies from patient to patient, is used for longitudinal scaling. The position of the midline of the third ventricle is based on the anterior-posterior information contained on the two views (B and C). After the x-ray photography is completed, most of the medium can be removed from the patient by draining it out through the cannula in the lateral ventricle.

The irradiation procedure and equipment have undergone continuous modification and evolution during the course of the work on the human. Figure 12 shows a schematic view of the configuration of some of the elements of the equipment used during the irradiation. A patient's skull is shown clamped in a head holder. In this case, a 1-Mc multi-beam transducer is used

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[2] Brand of ethyl iodophenylun decylate, 30.5% iodine, distributed by Westinghouse Electric Corporation, X-ray Division, Baltimore, Md.

FIGURE 9. A vertical view of the same structures pointed out in Figure 8.

and the coupling pan (in which the degassed liquid is held and the transducer partially immersed) does not rest on the patient's head but is suspended from the side. In the first stage of evolution of the technique involving human patients, we employed a procedure in which the bone opening was made on the day of irradiation. The brain was irradiated transdurally, the excised bone was replaced, and the opening closed. The entire procedure was rather long and stressful. It has since been replaced with a procedure in which the bone is removed under general anesthesia during the initial preparation, the scalp is closed over the bony defect, and the irradiation procedures are carried out at a later date under nonsterile conditions, with the radiation traversing the intact skin. A variety of types of patients in the category of the hyperkinesias, for example, Parkinsonism, athetosis, dystonia, and in-

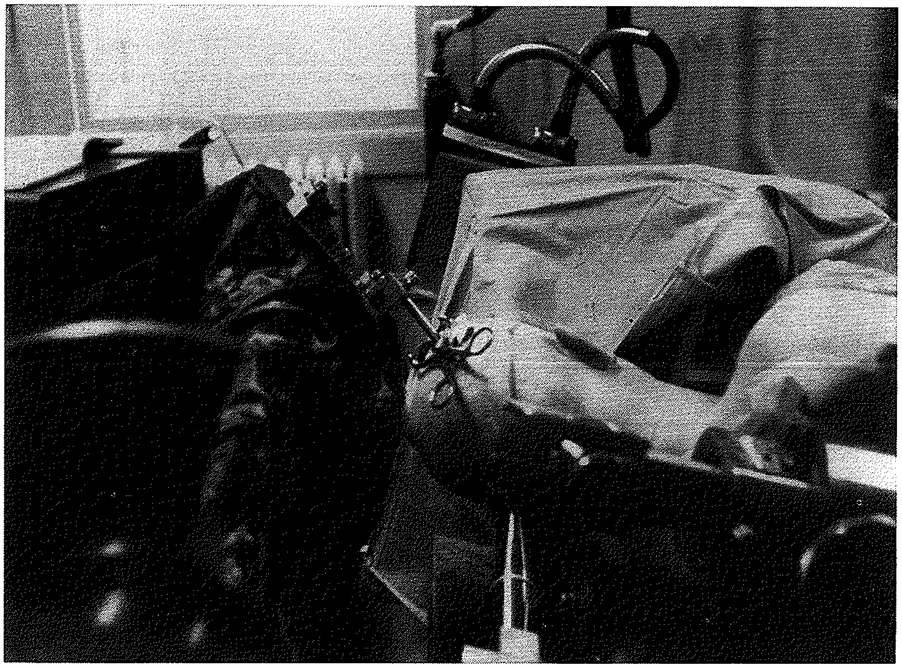

FIGURE 10. A patient in place in a head holder with the ventricular needle held by the associated positioning system.

tention tremor have been treated. Some work has also been accomplished on phantom limb and other intractable pain cases.

With regard to the effects that have been observed in the central nervous system of experimental animals on exposure to high-level ultrasound, it is abundantly clear that the white matter is more susceptible to irreversible damage than is the gray matter. This is shown by the group of pictures in Figure 13. A classic example of this differential susceptibility is shown in the illustration showing the lesion in the subcortical white matter of the cat (A). Irradiation was performed by placing a multiplicity of exposures spaced laterally at equal intervals. The overlying gray matter experienced the same dose received by the white matter. The selective destruction of the compact white matter is strikingly apparent. The figure also shows the mammillothalamic tract selectively destroyed (B), a subcallosal fornix lesion (E), and a lesion in the medial part of the medial mamillary nucleus (D). Part C of this group shows a lesion interrupting fibers of the cingulum, and part F shows a two-step sheet lesion produced in thalamic gray matter with one of the steps extending into the internal capsule. The dimension of the sheets in the anterior-posterior direction is a few tenths of a millimeter. Extensive histological studies have shown that the neural components of the tissue are, in general, more susceptible to the action of the ultrasound than are the nonneural components.

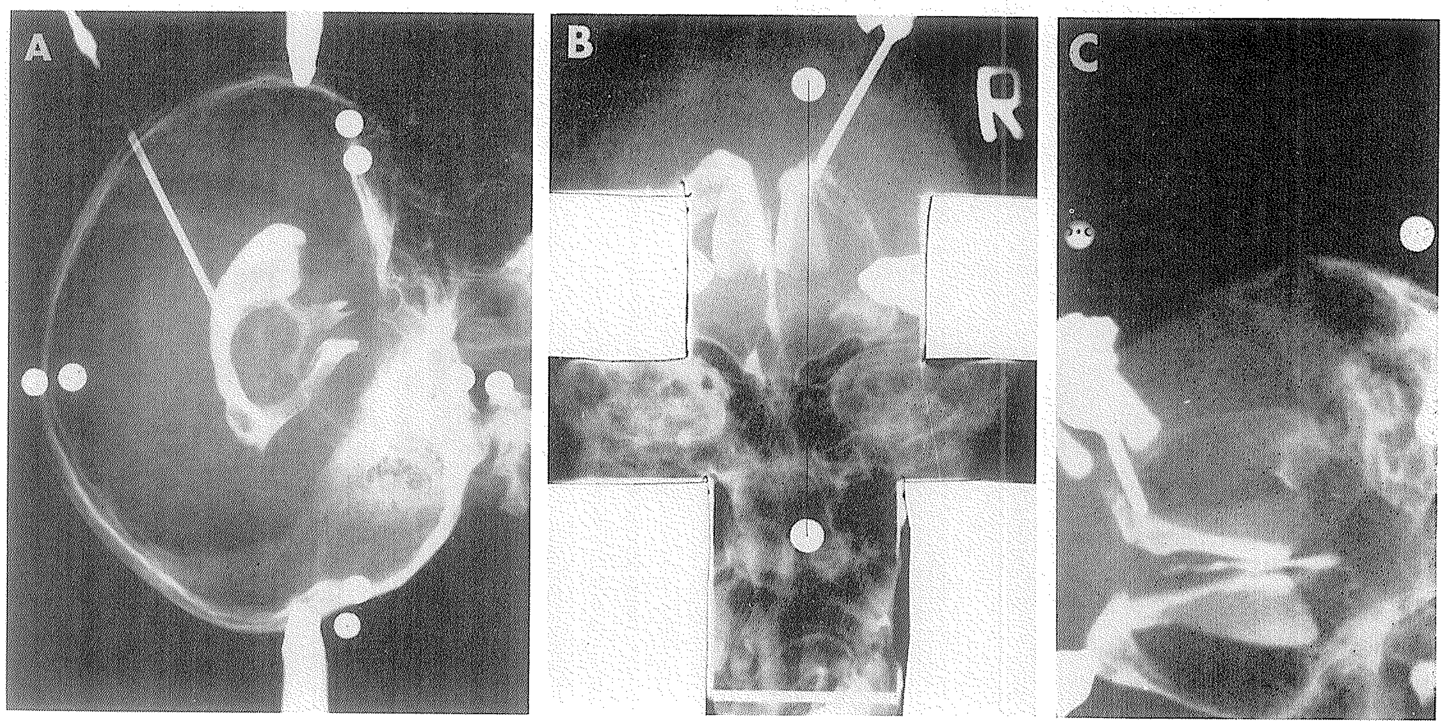

FIGURE 11. A group of three x-ray photographs taken with panopaque filling. A. Lateral view. B. Anterior-posterior view. C. View approximately in the mid-sagittal plane of the brain along an axis in the direction from the superior frontal sinus to the base of the neck on its dorsal aspect.

Unfortunately, it is not possible in the time available to discuss in any detail the many other programs underway. I will, therefore, simply mention some of the other areas in which we have worked. As you probably know, we have investigated the use of high-intensity sound to produce *reversible* effects in the central nervous system (10). In this investigation it was shown that it is possible to markedly affect the evoked potentials in the occipital cortex in response to light flashes at the eye, while focusing ultrasound at various sites in the lateral geniculate nucleus.

In the experimental animal behavioral studies, under the direction of Garth Thomas, the mammillothalamic tract of animals has been severed bilaterally, both totally and partially (11). Ultrasound is also being used to produce the refined lesions required for a comprehensive neuroanatomical study, now in progress, on the mammillary nuclei and associated complex. So far, this study has provided a considerable amount of new anatomic information (12) and the quantitative neuroanatomical studies which will be forthcoming in the future will provide much more.

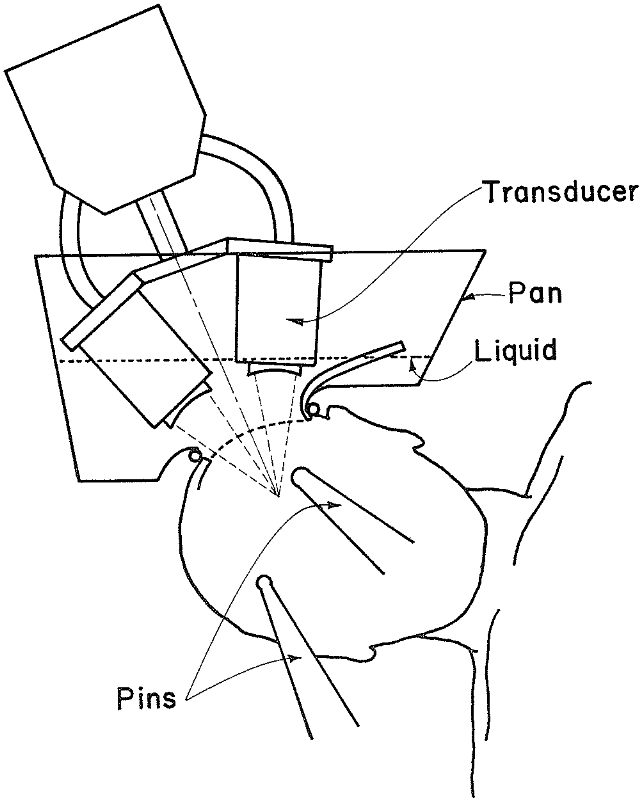

FIGURE 12. A schematic view of the configuration of some of the elements of the equipment used during human irradiation. A patient's skull is shown clamped in the head holder.

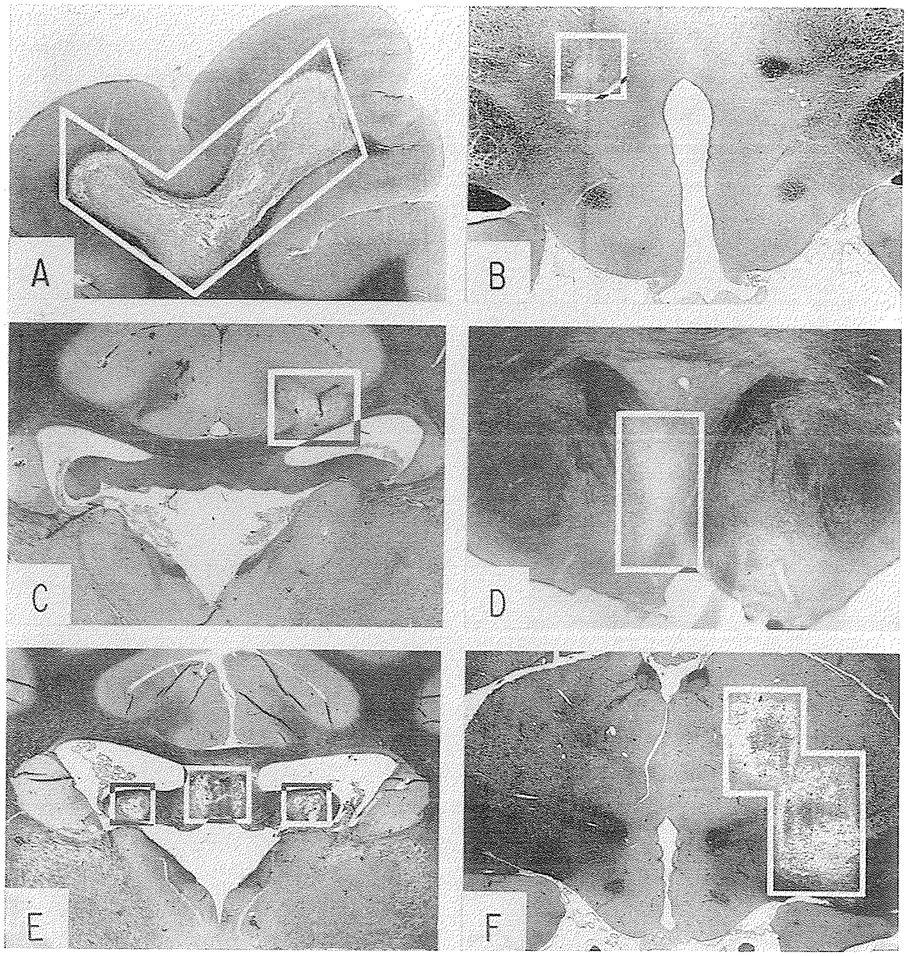

Figure 13. Photomicrographs of stained tissue sections of cat brain illustrating the differential susceptibility of white and gray matter to irreversible damage by high-level ultrasound. A. Selective disruption of subcortical white matter. B. Mammillothalamic tract selectively interrupted. C. Interruption of longitudinally running fibers of the cingulum. D. Destruction of the medial part of the medial mamillary nucleus. E. Three lesions in the subcallosal fornix. F. Two rectangular sheet lesions in thalamic gray and structures ventral to thalamus.

Data on man is being obtained from histological studies of the brains of patients who have succumbed, for a variety of reasons, subsequent to ultrasonic irradiation. Of the 86 patients irradiated, none have died as the immediate result of an irradiation procedure, although two deaths have occurred within 10 days after irradiation.

Dr. Weissler: As part of his paper, Frank Fry has a film to present. Unfortunately, there is insufficient time to show it now, so the film is scheduled for the afternoon session, when Dr. Ballantine will be presiding as chairman.

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FILM

Dr. Ballantine: This afternoon we will hear from several members of the Biophysical Research Laboratory. Professor Francis Fry will show a film presentation which is part two of the paper he presented this morning. It was apparent from part one of Frank Fry's paper that in order to successfully apply high-intensity ultrasound as a research tool, very rigid requirements must be placed on the design of the irradiation instrumentation. Dr. Leichner will enlighten us further on this by discussing the overall electronic design approach required in order to obtain such precise control of the effect of ultrasonic energy on the biological system. For the final presentation we are privileged to hear from our host, Professor William Fry, Head of the

Biophysical Research Laboratory, who will discuss new approaches to the study of biological systems by ultrasound.

A film will now be shown on the application of ultrasound as a neurological procedure. As most of you know, the equipment used for the ultrasonic neurosurgical work was designed and built here in the Biophysical Research Laboratory. The irraditions were performed by a research team consisting of various members of the Biophysical Research Laboratory of the University of Illinois and Dr. Russell Meyers of the State University of Iowa Hospitals. The first patient shown has a Parkinson's syndrome, and the other patient is suffering from a random movement disorder. Since the film does not have a sound track, Professor Francis Fry will explain the procedure during the film.

Dr. F. J. Fry: This is a sweeping view of the operative area (Fig. 14). You see here the ultrasound transducer, calibration tank, head holder, electronic equipment, and x-ray equipment. The patient is mounted in the machine. In preparation for the irradiation procedure, a plastic drape is placed around the suture line, so that the area of the dura corresponding to the area of bone removal is not covered with the plastic. The drape is drawn up through a metallic pan which is supported off the head-pin support posts and degassed saline is introduced into a plastic bag which is supported by the metal pan. All this draping and filling is, of course, done under nonsterile conditions. A heating coil keeps the saline at body temperature. The next view shows the multi-beam transducer being lowered into the coupling pan and medium (Fig. 15). You see here the patient in the head holder just prior to irradiation. The patient is rigidly held at the skull attachment, but otherwise unrestrained. A light indicates the period of irradiation, that is, the sound is on during the interval that the light is on. The first irradiation is of the order of

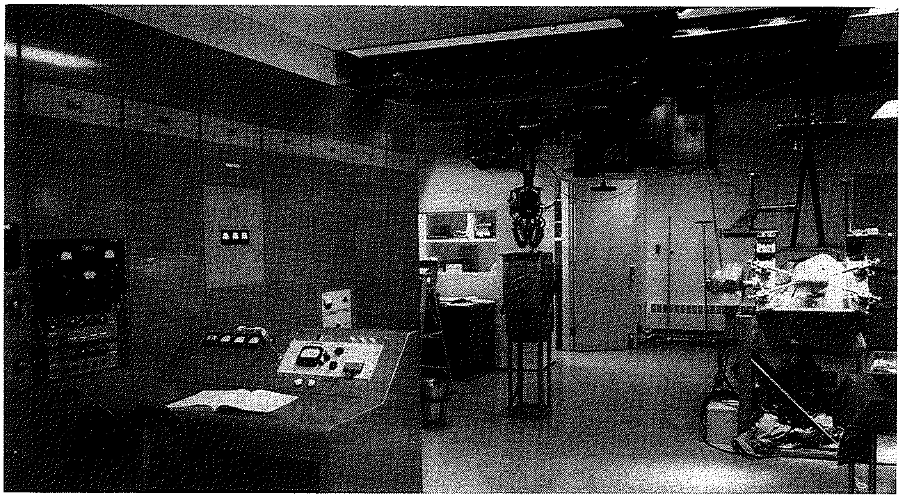

Figure 14. A general view of the operative area for the ultrasound irradiation procedure. The ultrasound transducer, calibration tank, head holder, electronic equipment, and x-ray equipment are visible. A patient is in position in the head holder.

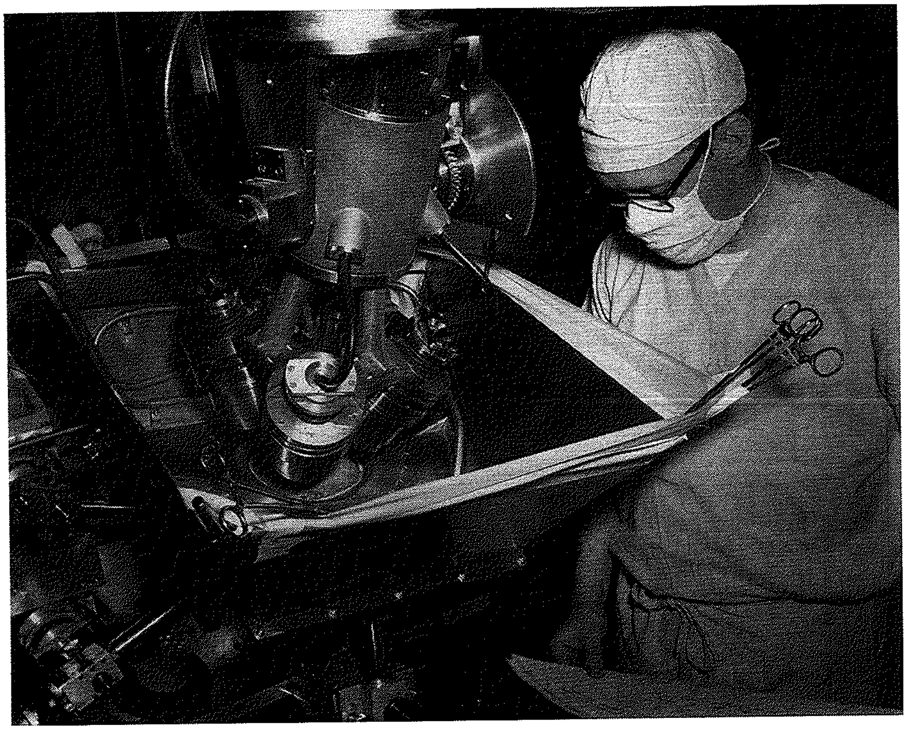

FIGURE 15. Professor W. J. Fry shown checking clearances for various positions of the transducer to be employed during the irradiation procedure.

a few seconds. A time recorder indicates the total time in minutes after the first irradiation. We usually leave a reasonable period of time between exposures for observational purposes. It is now 40 min from time of zero reference, and the sound is now on for the third exposure. In general, of course, these individual exposures have been placed in such a way as to produce some lesions at preselected areas which may or may not be adjacent to each other. The total time is now 1 hr. The total time required, of course, is dependent on the length of the time you want to observe the patient on the operating table. In some cases, the period required for the full procedure is only 1½ to 2 hr. You now see the patient after irradiation. The tremor is gone, and he is demonstrating his muscle control by successfully opening and closing a safety pin with one hand. His irradiation was unilateral with a total of three exposures.

The next patient, a thirty-two-year-old female, shows a nonpatterned intention tremor, primarily in the upper-left extremity. As you can see, she cannot accomplish the simple movement of touching hand to nose. The patient is now in the machine prior to irradiation, and the machine has been padded so she will not injure her arm and hand due to her random movements. The right side of the brain is to be irradiated, the sound is now on. Apparently the amount of tissue involved in the first sound exposure resulted in a reasonable reduction in symptoms. Each of the individual lesions encompasses a volume of tissue which is quite small (of the order of magnitude of 6 or 7 mm long and 1.5 mm in maximal diameter) and is elliptically shaped. This patient was the sort of individual who felt that nothing could ever be done to relieve her symptoms. Here, for the first time during our association with her, she manages a small smile. This view shows the patient the following day after irradiation — and as you can see, she can now perform hand to nose movement quite smoothly.

DISCUSSION

Dr. Gordon: What advantage is there in using ultrasound as opposed to the accepted techniques that are being presently used in my neurological hospital, that is, the injection of Novocain and alcohol at comparable sites? I would be only too pleased to sell an ultrasonic technique to my neurosurgical colleagues but, as the hospital radiologist, I was associated with the treatment of some hundreds of cases of Parkinson's disease which have shown exactly similar cure and benefits by being treated by a small bore hole and an injection of alcohol. I would like to hear about a series of cases showing significant improvement from ultrasound treatment, as against the alcohol injection technique.

Dr. Ballantine: The chairman will exercise his prerogative. Let us illustrate a diagrammatic cross-section of the brain, and let us say you wish to ablate a portion of the thalamus for Parkinson's disease. You place the electrode (which is bare only at its tip) down here. Previously, you put a needle through here into which you injected alcohol and Novocain. Well frankly, I don't know anybody who now injects alcohol and Novocain. Some people inject Novocain first and then alcohol, but most of the chemical techniques for ablation have more or less gone out of style in this country. The reason for this is, Dr. Gordon, that a free-flowing solution will follow planes made by nerve fibers, and so you have no way of knowing where your destructive agent is going to go. If you use an electrode, which, I would say, is one of the very common methods of ablating a certain portion of the basal ganglia, then you run into two difficulties: (1) the vast majority of the complications of this operation are secondary to the tearing of the blood vessels as you introduce your needle, and (2) control over the lesion size and shape associated with methods such as chemical destruction or heat destruction by electrocautery techniques is not as precise as that possible with ultrasound. The final point is that blood vessels are extremely susceptible to the type of heat that an electrocautery produces, and therefore there is grave danger of a hemorrhage at the site of your lesion when you are using such methods for producing lesions. So, these are the advantages of sound: (1) there is no track going down to the area that you wish to destroy, (2) control over lesion size and shape is quite precise — the destruction takes place only where your focal region is placed — and (3) as pointed out in the previous talk, the blood vessels in the lesion region are the least susceptible to the damaging effects of ultrasonic radiations.

Now, balanced against all of these advantages is the disadvantage of the necessity for removal of a large section of bone. This problem has been solved to a certain extent by Fry and Meyers since the bone flap is now removed prior to irradiation. This will strike a great many people as a handicap, however, and it is an objection that you must be prepared to meet. But there is no question, I believe, in the minds of anyone that the ultrasonic technique is the method of choice for making lesions within the central nervous system, if you can get the energy in without having to use a large craniectomy. Would you like to speak on that, Dr. Heimburger?

DR. HEIMBURGER: The only thing I would like to add is that the lesions that you make with electrocautery or with alcohol are roughly spherical, whereas you can make sheets of lesions with ultrasound. The anatomy of the brain is not spherical in any one area. You can interrupt tracts by sheet lesions, something that you cannot do with other methods.

DR. GORDON: I'm well aware of these arguments, and I've done my best to put them to my colleagues and associates, but our results with these alcoholic injections are so obviously good. I want to see a long series of cases treated by ultrasonic techniques that can produce better results than the results at my hospital with other techniques.

DR. BALLANTINE: If you are getting uniformly good results without complications, then I'm going to send all of my cases to England because we do not get uniformly good results without complications. We get paralysis, we get hemorrhages, and we get infection. Those are the three things that occur as complications in such a significant number of cases that we are still searching for a better way to make a lesion.

DR. JOYNER: I would like specific statistics on the exact number of patients irradiated and both the immediate and long-term results of these irradiations. Did these patients survive for 6 mo, and for those that survived, was there a return of symptoms at a later date? I am under the impression that the cases shown in the movie may be isolated cases.

DR. W. J. FRY: In answer to your question, I would like to point out that insofar as neurological results are concerned, it is essential to distinguish between methods of making lesions and between the choice of structures in which lesions are placed. These are completely separate problems. Dr. Ballantine indicated very clearly the advantages of the ultrasonic method as the means of making changes in the brain. The neurological result is dependent upon the specific choice of structures that one modifies. If one doesn't choose a proper structure, then obviously there will not be a favorable neurological result. Now, I can comment very briefly on the latter aspect, but I wanted to clearly differentiate it from the former.

The number of irradiation procedures pertinent to the discussion are over 100. Some patients have undergone as many as four such procedures. The results obtained must be subdivided first on the basis of the various categories of disorders treated – about half a dozen different types. In addition, we modified at least half a dozen different structures in Parkinson patients alone. Therefore, because of the large number of combinations, I cannot answer your question in detail in a few minutes. But I can say that if one considers a Parkinson patient with a tremor, then irradiating or modifying the tegmental field of Forel will result in the elimination of tremor in an extremely large percentage of cases, certainly above 90%, and I suspect that we could accomplish elimination of the tremor in 95% of the cases. This result is not true of modifying, for example, the base of the ventrolateral nucleus of the thalamus. By modifying this region one can affect tremor to some extent, one reduces rigidity markedly, but one does not eliminate tremor in such a high percentage of cases. These constitute examples of the types of results that can now be achieved. One could also, of course, place a coagulating electrode into the tegmental field of Forel and if the lesion included the appropriate region, then one could also eliminate the tremor. Does that answer the question?

Dr. Joyner: I agree with your statements, but I would still like to know how many patients with Parkinson's disease have been irradiated.

Dr. W. J. Fry: We have treated 86 patients – probably 60 Parkinson patients.

Dr. Joyner: And of those 60, how many are now living, and what is the extent of the improvement of their original symptoms?

Dr. W. J. Fry: Of the Parkinson patients that we have irradiated during the five years since the start of the program, four died for various reasons, in addition to the two that were mentioned this morning. The complications – paresis and paralysis – that were produced in some early members of the series when we were working with the medial globus pallidus were the result of impinging on the internal capsule. In addition to Parkinson patients, we worked with a small number of intractable pain cases, seven patients in all. We started the series by modifying the ventroposterior lateral nucleus of the thalamus which receives an input from the medial lemniscus. If one irradiates the basal portion of the ventroposterior lateral nucleus, one may produce anesthesia, and this occurred in the first phantom limb case that we treated. This individual had the right-upper extremity severed midway between the wrist and elbow, and he experienced a phantom of the severed portion, pain in the phantom, as well as pain in the stump. In this case, immediately following the irradiation of the ventroposterior lateral nucleus, the patient exhibited an analgesia over a portion of the corresponding side of the body, and he later developed a thalamic syndrome. In the next patient we moved more medially and had no complications of analgesia and no delayed thalamic syndrome. However, the original discomfort returned within a couple of months postirradiation. In a third phantom limb case irradiated more medially – border zone of the centromedian nucleus – the phantom and discomfort were eliminated and did not return. This is an example of the way the program evolved in the modification of intractable pain disorders. We also worked with several patients exhibiting a thalamic syndrome, and in these we modified the ventrolateral and lateral border region of the centromedian nucleus. In two cases we were able to produce a normal neurological sensory status, but the favorable results obtained were not sustained. Within a few months the symptoms of the thalamic syndrome returned. Are there any other specific points you would like to have discussed?

Dr. Ballantine: I think Dr. Joyner has raised an extremely important point in attempting to obtain an analysis of the results of the irradiation of patients with ultrasound. I may say that I find it a great pleasure to be on the same side of the fence as Bill Fry from time to time. In answer to Dr. Joyner's question, I would like to say that I do not believe that Bill Fry and Russell Meyers are advocating at the present time the ultrasonic method of ablation for the treatment of all cases of Parkinson's disease. I think this would be a gross exaggeration if anyone did say this, because I think there are certain fundamental disadvantages associated with the technique, which incidentally have led us in our laboratory to postpone the use of this in the central nervous system. This is a matter of opinion, but I would feel that if I were going to have "my Parkinson's disease" treated, I would still probably have it done by more conventional techniques. But this does not detract from the potential advantages of the focused ultrasound method. I think that while it would be nice to know exactly what the percentage of complications is in a particular series, or the mortality figures, which is what you were asking for in "X" number of cases, I think you will agree that with cardiac surgery, neurosurgery, and all new methods which have to be developed, the percentage of good results increases with the number of operated cases. If there were 50% complications – I don't think there are, don't misunderstand me – but suppose there were 50% complications in this series of ultrasonically irradiated cases, I would simply say that they were on that portion of the curve which represents the necessity of gaining experience in order to translate a potentially good result into an actually good result. I think that there are many problems that we must overcome in the use of focused ultrasound in the making of lesions. But (I made this statement in conversation here, and I'll make it in public) there is no question in my mind but that if anyone is interested in studying neuroanatomy or neurophysiology by ablation techniques in animals, the ultrasound method is the only method to be used and I wouldn't give a damn for any electrode or chemical introduced into the brain as opposed to the use of ultrasound. This is a proven method, and it eliminates so many of the artifacts inherent in other methods of making lesions that it represents a prime event.

Dr. Joyner: There is no doubt that the advances in localization represent a great improvement, but the point is, if you are to move into the so-called clinical sphere with an experiment of clinical design, then you must have some idea of where you are going as you go along.

Dr. Ballantine: I think this is very important, and I agree with you on that point.

Dr. W. J. Fry: I want to second the comment made that we certainly wouldn't recommend the ultrasonic method for general therapeutic use at this time. We are still in the process of improving our methods. As Frank indicated here this morning, since the start of the human work, the technique has been greatly improved in reducing the total time involved in an irradiation procedure. Formerly, 12 to 14 hr were required to accomplish the craniectomy and irradiation at a single procedure. This should be compared with the 2-hr procedure now employed for irradiation. However, we are still not anywhere near the completion of the evolution of all of the practical details so important to the recommendation of a method for routine therapy.

Dr. Gordon: I fully agree with you on the question of the production of experimental lesions, and I hope to do some work along this line myself within the next couple of months, and I also agree with you in that I feel for the time being the conventional techniques are the best bet.

Dr. Ballantine: But I don't think this removes the stigma which you have attached to your neurosurgeons by not being imaginative enough to explore new areas and new methods. They can't be content with the old as we are in Boston. You've got to move forward as they do at the University of Illinois.

Dr. Dunn: Where does the ultrasonic method presently fall as compared to the other methods for treating humans?

Dr. W. J. Fry: If we include every patient that we have done, we have had complication in certainly 20% of the cases. If we consider only the last twenty or thirty patients with Parkinson-type complications, we experienced probably no more than 5%.

Dr. Dunn: How does that compare with alcohol or other methods?

Dr. Ballantine: You have just introduced another barrier. All I can say is that I would have a hunch that there are statistically significant differences that would lead me to employ the electrode or the freezing technique, whatever method you like, because I think that the results are probably in the 70 to 80% range. If you consider the possible complications and the percentage relief of tremor and rigidity, there would be a variation from neurosurgeon to neurosurgeon, as well as from technique to technique. Just as clinicians had difficulty 5 or 10 years ago in trying to find out what the results of cardiac surgery were, so we have the problem of trying to assess the validity of certain clinical reports of all procedures. However, I still feel that we would have to call ultrasonic neurosurgery a developmental and experimental method which should be restricted to one, two, or three centers at the present time.

Dr. Howry: Where was the lesion located in the patient shown in the film with the nonpatterned intention tremor?

Dr. W. J. Fry: This can best be shown by a diagram (Fig. 0–1) which includes the red nucleus and fibers called the tegmental field of Forel. We placed the center of the first site in the area designated "lesion"; the beam was coming in at an angle of approximately 45°. You noticed that the first site completely eliminated the abnormal movement, but nonetheless, we extended the irradiation in an anterior-posterior direction, 2 mm anterior and 2 mm posterior in the tegmental field of Forel.

Dr. F. J. Fry: I would like to indicate that we plan a histological study on the brains of those patients who succumbed to some ailment or other in the course of the 5 years, roughly, since the time we initiated these irradiations. The brains have been embedded in celloidin and special apparatus has been constructed so that we can determine how accurately we have placed the lesions with respect to the landmarks we used at the time of ventriculography.

We also want to check on the accuracy of the scaling methods applied in attempting to place the lesions within a given structure.

Dr. Ballantine: Can you tell us something about the differences in the irradiation parameters both stereotaxically and from the standpoint of the energy requirements when you irradiate through the scalp as opposed to when you irradiate transdurally?

Dr. W. J. Fry: We have effectively considered the skin and muscle to be much the same as brain.

Dr. F. J. Fry: We measured the muscle and skin thickness and averaged this over a number of precise craniectomies. The muscle is rather thin over the major part of the area, but we take an average value.

Dr. W. J. Fry: We found the absorption coefficient of this muscle layer to be essentially the same as that in the brain, and we compensate for the additional thickness, averaging out the fact that the muscle which comes up

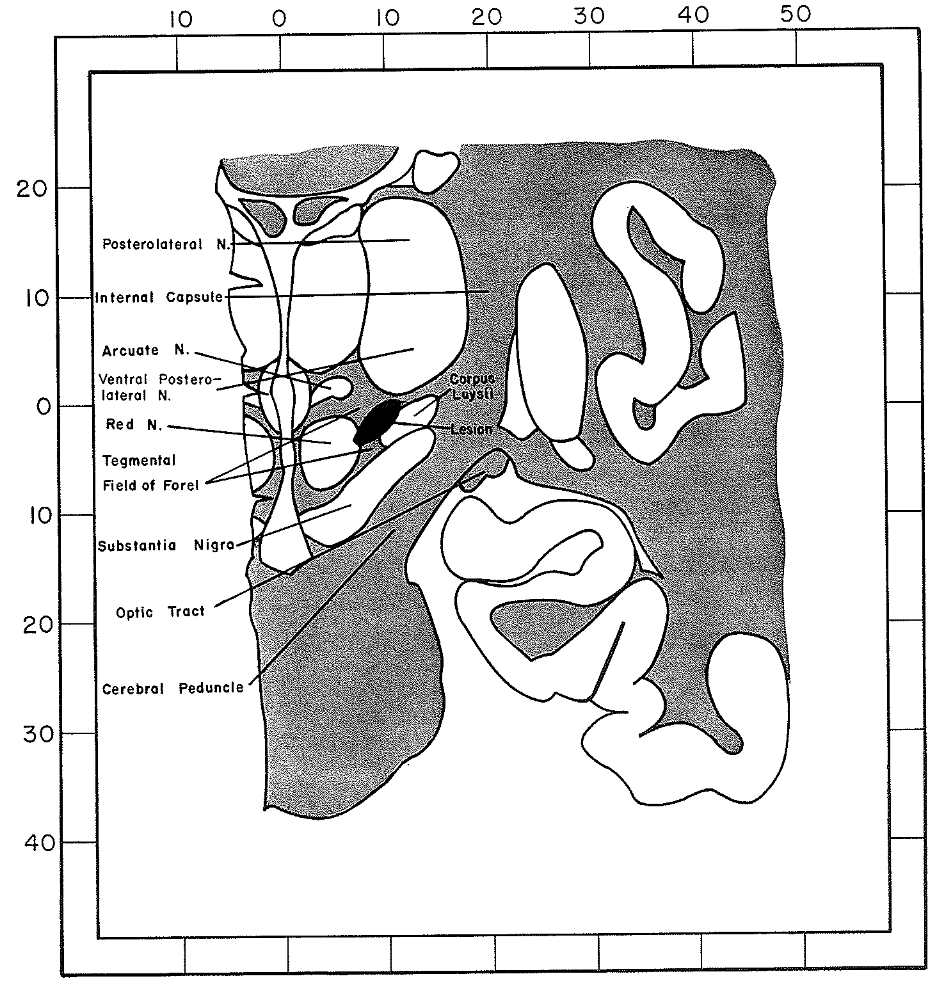

Figure 0–1. One of the sites in the tegmental field of Forel of the lesion array produced to relieve intention tremor.

over the temporal region is tapering off fairly quickly. We have seen no apparent difference between the effect in terms of localization, as we interpret it from the functional endpoint, in irradiating transdurally or transcutaneously.

Dr. Herrick: Do you still use a sort of hunting technique to detect the reversible effect?

Dr. F. J. Fry: On the human patients, of course, our apparatus is not set up to do any sort of reversible suppression, but one could use the reversible technique as an adjunct to localization with a ventriculography procedure. We used this technique on one patient. It is not generally true that irradiation at one site, for example, in the Parkinson-type patient, would necessarily produce the cessation of the tremor or modify it sufficiently to be able to tell by looking at the endpoint whether one were actually in an appropriate region. Therefore, the reversible technique with the apparatus available at that time was not really ideally suited for this problem. However, in the case of one patient, in order to demonstrate this as a possibility, we repeated the process at one site at a sublethal dose, so to speak, approximately ten times, with intervals of 5 to 10 min between each, to show that one could, in effect, first suppress and then have complete recovery with this many cycles for irradiation at one particular site. It just happened to turn out that this patient could be suppressed at that one site. This would not necessarily be true of all types of patients.

Dr. Herrick: That process is time-consuming.

Dr. F. J. Fry: Yes, it is quite time-consuming, but as I say, unless you are set up to cover more tissue or scan with the beam, so that you can suppress some function by irradiating a reasonable volume, you may not be able to utilize the method of reversible suppression very efficiently. But in this case we did demonstrate the reversible phenomena. The question of whether or not we produced a lesion can only be based on the finding that the patient had no apparent change in the tremor after approximately ten cycles of sublethal irradiation.

Dr. Herrick: I thought you did this to establish that there might be some analogous site in the brain for relief of these disfunctions and you said that this technique would insure accurate placement of your lesions.

Dr. W. J. Fry: No, this we never did on human patients, primarily from the point of view of apparatus insufficiency. We relied entirely on the ventricular pictures for our localization.

Dr. Mackay: I wonder if you would care to comment, for the sake of the record, on something we noted before lunch, namely the fact that in your transducer there is a $\lambda/4$ spacing between the piezoelement and lens whereas Dr. Yoshioka this morning showed a $\lambda/2$ spacing.

Dr. W. J. Fry: I can show here roughly how the output from a transducer varies as a function of this spacing dimension.

A half-wave spacing is, of course, the choice that one makes if he simply wants to achieve the effect of no spacing at all. In other words, if zero spacing is inconvenient, one can employ a half-wave. But a half-wave is not the best choice from the viewpoint of obtaining maximum power transfer for a given driving field strength across the crystal. One can obtain much more power from the transducer for a fixed driving voltage by choosing dimensions and characteristic impedances of the coupling media in other ways.

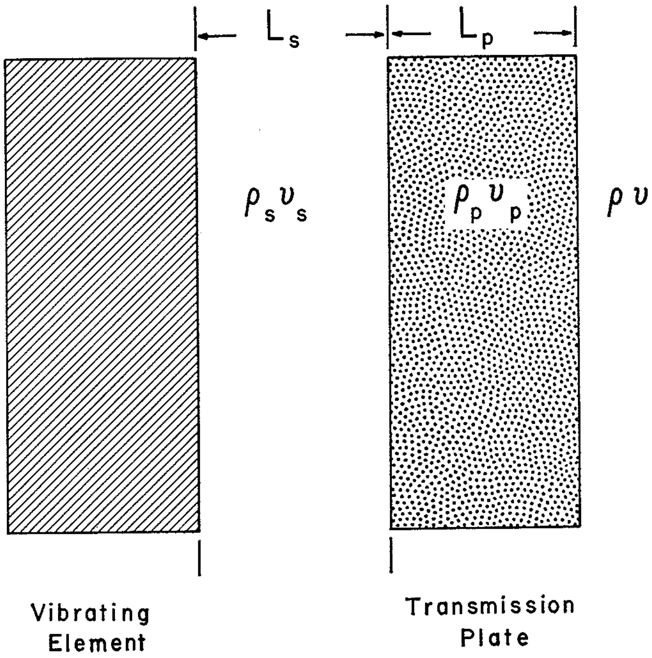

FIGURE 0–2. Schematic diagram illustrating system composed of vibrating element, spacing material with thickness L_s and characteristic impedance $\rho_s v_s$, transmission plate with thickness L_p and characteristic impedance $p_p v_p$, radiating into a medium of characteristic impedance ρv.

Consider the system shown in Figure 0–2 – a vibrating element coupled to a medium of characteristic acoustic impedance ρv by a two-layered assembly. The gain, G_p, is defined as the ratio – at equal driving voltages – of the power output of the indicated configuration divided by the power output of the vibrating element when radiating directly into the medium. Of course, the operating frequency is the same in each case. The gain obtained by this scheme arises as a result of the modification of the electrical input impedance at the terminals of the piezoelectric elements which allows the element to draw more current and more power for the same driving voltage from the electronic generator. The characteristic acoustic impedances of the transmission plate and spacing material are, respectively, $\rho_p v_p$ and $\rho_s v_s$, and the corresponding thicknesses of these two media are, respectively, L_p and L_s. For all values of the ratio $[\rho_p v_p / \rho v] > 1$ and for any fixed thickness of transmission plate, it is possible to realize values of the gain G_p greater than unity by choosing L_s equal to an odd multiple of a quarter wavelength. It is possible by appropriate choice of the acoustic parameters to realize rather high gains, for example, 10 to 100. For this case, the gain is given by

$$\overline{G}_p = (\rho v/\rho_s v_s)^2 \left[\frac{1+\tan^2\left(\dfrac{\omega L_p}{v_p}\right)}{1+\dfrac{1}{(\rho_p v_p/\rho v)^2}\tan^2\dfrac{\omega L_p}{v_p}} \right] \qquad (1)$$

where $L_s = (\lambda_s/4)\ (2m-1)$ and $m = 1, 2, 3, \ldots$. Large values of $\overline{G}_p$ are obtained by choosing materials such that the ratios $\rho v/\rho_s v_s$ and $\rho_p v_p/\rho v$ are large. The optimum thickness of the transmission plate, for high gain, is one-quarter wavelength. The graph of Figure 0–3 shows the bracketed factor of Equation (1) plotted as a function of L_p/λ_p (the thickness of the plate

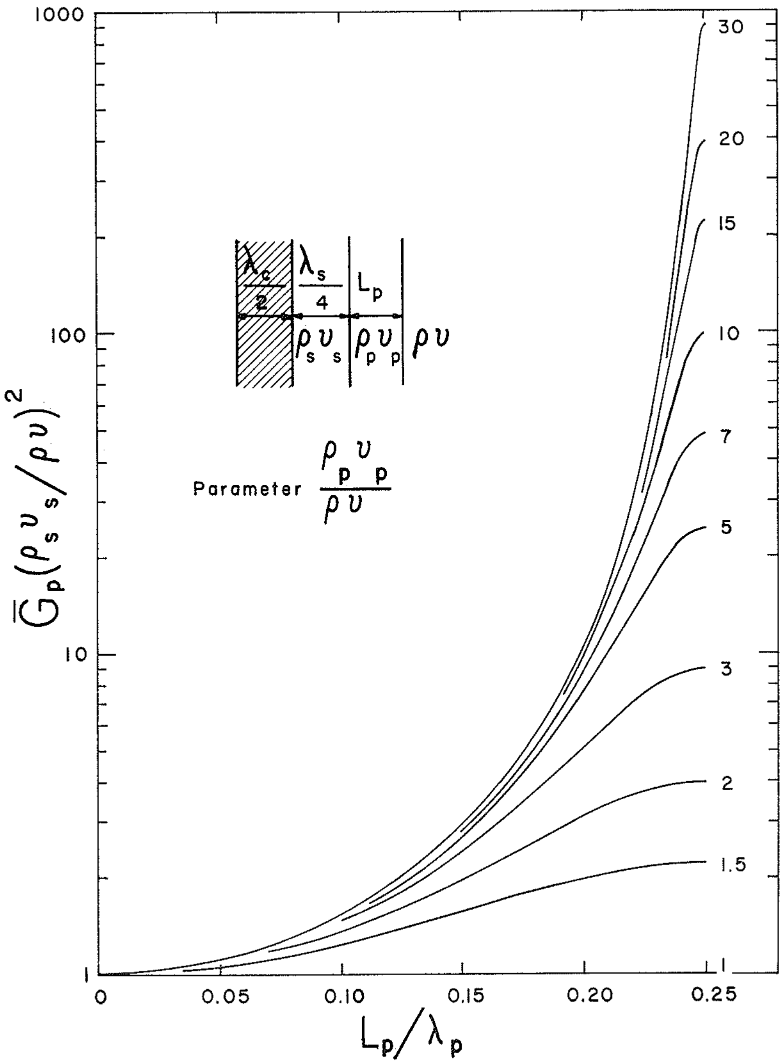

FIGURE 0–3. Gain of a composite system, for $\lambda/4$ thickness of spacing material, vs thickness of the transmission plate. Symmetrical about $L_p/\lambda_p = 0.25$ and repeats every $L_p/\lambda_p = 0.5$.

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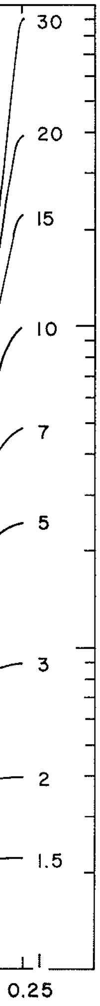

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divided by the wavelength of sound in the plate). The parameter from curve to curve is $\rho_p v_p/\rho v$.

The gain, $\underline{G}_p$, is equal to or less than unity if $[\rho_p v_p/\rho v] > 1$ and if the thickness of the spacing material is zero or any multiple of a half-wavelength for all thicknesses of the transmission plate. For this case, the gain is given by:

$$\underline{G}_p = \frac{1 + \tan^2\left(\frac{\omega L_p}{v_p}\right)}{1 + (\rho_p v_p/\rho v)^2 \tan^2 \frac{\omega L_p}{v_p}} \tag{2}$$

where $L_s = (\lambda_s/2)m$; $m = 0, 1, 2, \ldots$. Figure 0–4 shows $\underline{G}_p$ plotted as a function of L_p/λ_p.

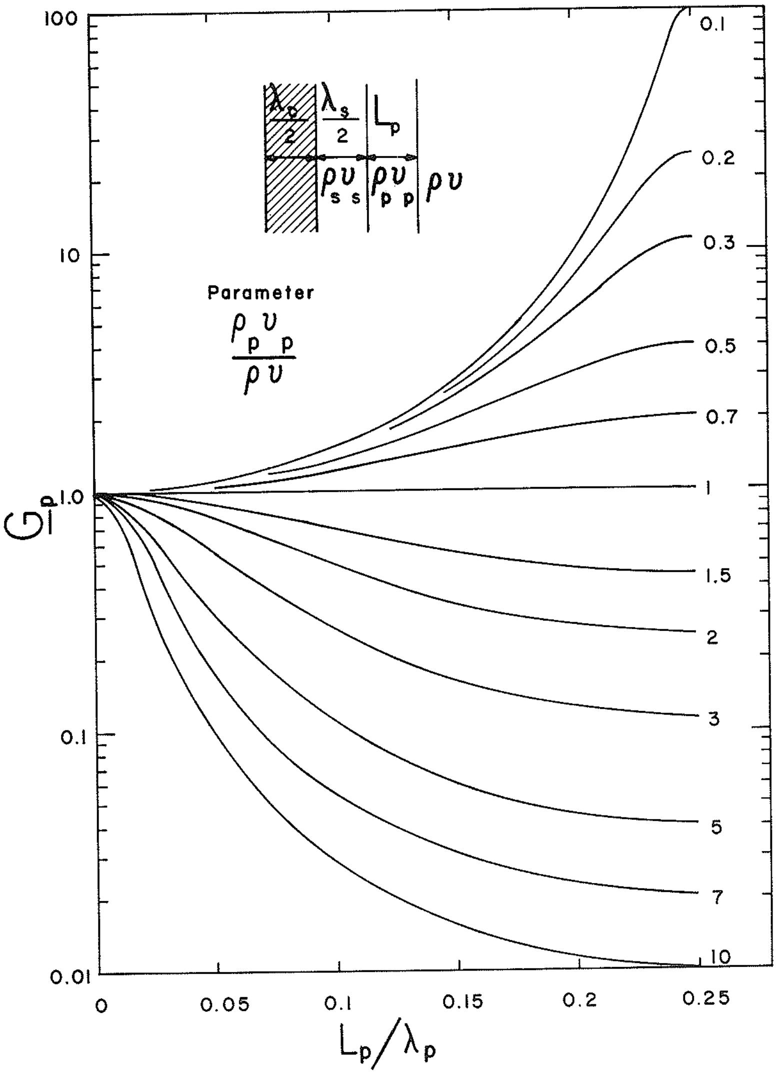

FIGURE 0–4. Gain of a composite system, for $\lambda/2$ thickness of spacing material, vs thickness of the transmission plate. Symmetrical about $L_p/\lambda_p = 0.25$ and repeats every $L_p/\lambda_p = 0.5$.

However, I should mention that the achievement of high gains by the procedure just described would result in a relatively sensitive transducer from the viewpoint of the variation of its characteristics with changing temperature.

DR. MACKAY: Would it be fair to say that this loading process changes the characteristic impedance of the transducer but doesn't help the impedance matching problem?

DR. W. J. FRY: It's probably better to say that it lowers the input impedance at the crystal face so that for a given electric field strength a higher power can be transferred.