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New Approaches to the Study and Modification of Biological Systems by Ultrasound

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As you all know, present methods of ultrasonic visualization of soft-tissue structure depend upon the existence of differences in the characteristic acoustic impedance at tissue interfaces – that is, differences in the product of the speed of sound and the density. Therefore, it is possible to detect only those structures, that is to say, interfaces between structures, that are characterized by different values for these parameters. This means that in the normal brain no structure is discernible except the ventricles, since only at the ventricular boundaries does the value of the impedance undergo sufficient change for successful visualization. The procedures that have been used up to the present time for the placement of electrodes in the brain or for irradiating specific nuclei with various types of energy have depended on various landmark systems. The most accurate of these systems employs the ventricles as references. Obviously, a method which would enable one to view brain structures directly would be extremely valuable in the field of applied neurology, including neurosurgery, and also in basic neuroanatomic and neurophysiologic research. I would like now to describe such a method which, in principle, will enable us to see all major brain structures directly.

Figure 1 illustrates diagrammatically the basic principle involved. Two beams of pulsed, focused sound are employed. Let us consider as an example the case of concentric beams – that is, an inner conical beam with an outer or enveloping beam surrounding it. The inner beam induces transient changes in the temperature of the medium of the order of a few degrees. If this is accomplished fast enough, let us say in a time interval of the order of 1 sec, then steep temperature gradients will be produced in the tissue at anatomic sites where the value of the absorption coefficient changes as a boundary is crossed.

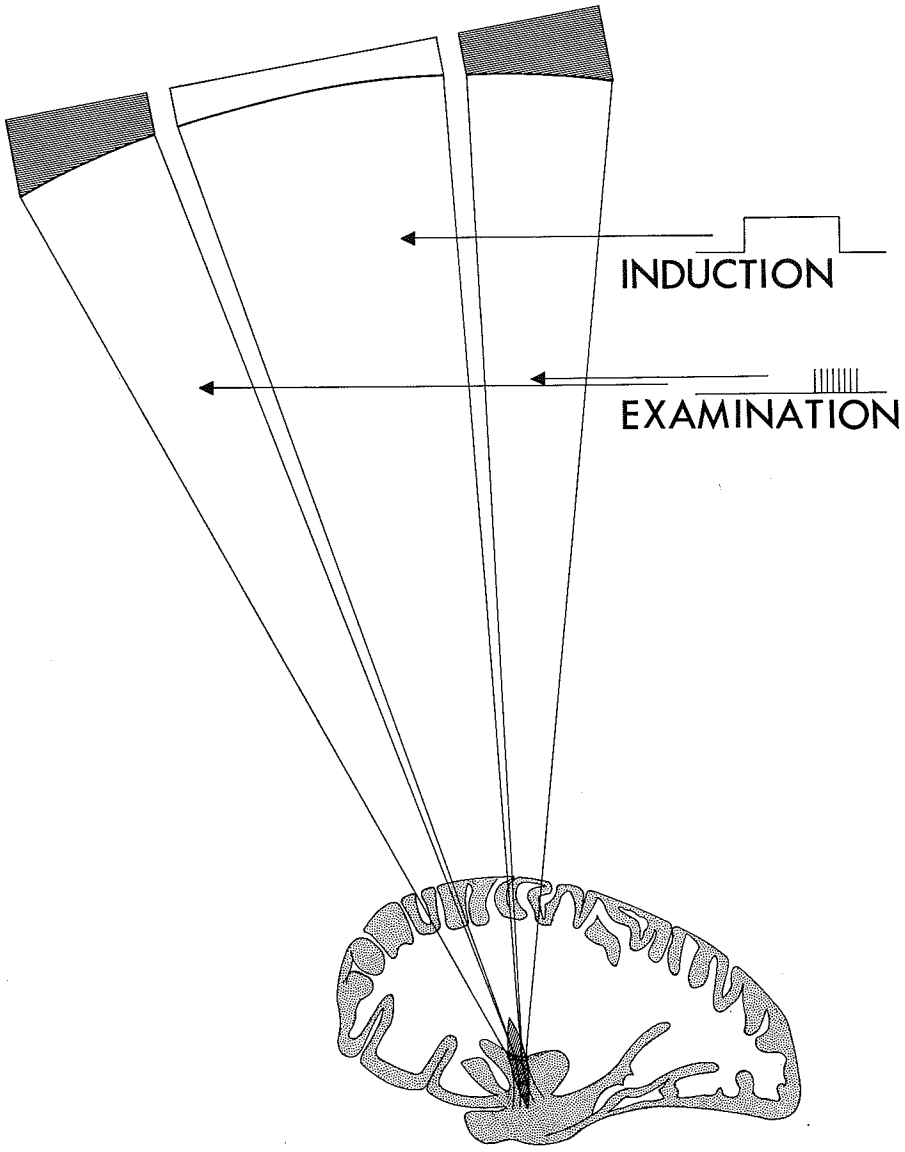


FIGURE 1. Schematic diagram illustrating the principle of detecting and locating interfaces between brain structures characterized by different values of the ultrasonic absorption coefficient. The relatively long duration pulse of the focused induction beam produces transient temperature gradients and therefore gradients in the speed of sound at interfaces between such structures. A second focused beam, consisting of a train of short duration pulses synchronized in appropriate time relation with the induction beam, locates the boundaries by echoing from the sites of the induced acoustic impedance gradients.

Measurements indicate that the value of the absorption coefficient for white matter is considerably higher than for gray matter – approximately 50% greater. Therefore, by this method one can produce at a white-gray matter boundary a transient thermal gradient with a temperature difference of at least 2°C without causing damage. Since the speed of sound is dependent upon the temperature, a corresponding gradient in its value would result. A gradient in sound speed implies a change in characteristic impedance, and since the sites of impedance differences are detected by present methods, the examining beam of Figure 1 is synchronized with the first so that a train of pulses of short duration is produced and echoes are detected as in the reflection methods used up to the present time. Thus, this new method provides the possibility of detecting any interface between two structures, if a sufficient change in the magnitude of the absorption coefficient exists. This happens to be the case for brain, since the white and gray matter exhibit such a difference in absorption coefficient. Other tissue interfaces should also be characterized by different values of the absorption coefficient, but we have not yet planned a measurements program. The indicated method would also be applicable in those cases where tissue structure is detected with difficulty by the older, presently employed method since one could expect to enhance the contrast by employing this new method.

In addition to directly visualizing major structures of the brain, the method described here will also make possible the viewing of lesions as they are produced and will thus provide a direct control of their position, shape, and size. Ultimately, present landmarking systems will probably be eliminated and lesion production would then be under the direct and automatic control provided by the visualization method itself.

Of course, one must use considerably higher acoustic energy levels for the temperature-inducing beam than those applied in present visualization methods, but the temperature gradients required to produce detectable changes in acoustic impedance would be of the order of only a few degrees.

At the present time, it is completely impossible to use the ultrasonic method in a controlled fashion for the modification of brain structure by transmitting sound through the intact skull. However, successful development of the method described here would provide the possibility of spreading the incoming ultrasonic energy over a major fraction of the area of the skull so that the ultimate objective for brain modification in the human – the complete elimination of all surgical procedures – might be achieved. The problems that will be encountered in reaching this objective are not simple, and the instrumentation that will be required will be extremely elaborate by comparison with present ultrasonic and other instrumentation used in brain-modification work.

Now, if anyone has any questions on this aspect of our proposed work I would be happy to answer them before going on to discuss other research plans.

Dr. Howry: I would simply like to comment that the concept you have

just outlined is very worthwhile and has tremendous possibilities. You are to be congratulated.

DR. GREENWOOD: I would like to ask if you have any data on the strength of the echo from the lesion after it has been produced and after the thermal transient has passed and whether this might be a way of controlling dosage.

DR. W. J. FRY: No, we do not have such data, but of course one would not necessarily have to observe the lesion after it is produced. That is, it could be observed during the period corresponding to the induced temperature change accompanying lesion production. In answer to your second question, I would expect that echo strength could be used to control the dosage.

DR. GREENWOOD: Echoes from a lesion would not necessarily be reflections from the thermal region per se but could be reflections from immediately surrounding tissue.

DR. W. J. FRY: Yes, this would certainly be a possibility. And in regard to this, when ultrasound is used to produce selective lesions, we have noted that histologically one does not see any general breakdown in the tissue structure for some time after irradiation, so it may not be possible to see the lesion immediately unless a thermal gradient is used. Of course, after a time, the breakdown of structure is very apparent.

DR. CURTIS: If I understand you correctly, you would use this new technique to visualize the tissue structure before you place the lesions. The usefulness of the method would then be very dependent upon knowing what sort of injury was associated with the associated very small temperature change.

DR. W. J. FRY: No injury would accompany the use of the method. In fact, one could employ previously obtained data to deduce limitations on the radiation conditions in order to restrict the effects to reversible changes. For example, at 100 w/cm^2 one can irradiate the lateral geniculate nucleus for about 30 sec at a frequency of 1 Mc/sec and still induce only reversible changes. I would expect the maximum dosage required for implementing the new visualization method (as applied to brain) to be about an order of magnitude below this.

DR. CURTIS: Do you know what sort of temperature changes you are producing at the reversible level?

DR. W. J. FRY: We have not measured these specifically for the reversible dose levels. However, for the irreversible levels we measured temperature changes of 10°C (gray matter) to 20°C (white matter) for exposures of 1 sec at an "intensity" of 800 w/cm^2. (I will use the parameter "intensity" to indicate approximate sound levels here even though we do not feel that it should be used in any precise description of the exposure conditions.) In the visualization method now proposed it should be possible to restrict the temperature to levels that might be associated with a high fever – but, of course, for a comparatively negligible period of time.

DR. CARLIN: Have you done any calculating of pulse lengths, repetition rates, etc.?

DR. W. J. FRY: Yes. The basic feasibility of the method depends upon

whether one can produce the requisite temperature change in the time available before conduction levels the thermal gradient. Computations indicate for intensities in the neighborhood of 100 w/cm^2 and time durations of the order of 1 sec, that thermal conduction would not destroy induced reflecting interfaces for practical values of range resolution.

DR. CARLIN: It seems to me you are talking about longitudinal waves almost entirely, but you may have had in mind more than this. Normally, in passing from a tissue with a low absorption coefficient value to one with a high absorption coefficient value there would be quite a temperature gradient because of the generation of heat. In addition, if one has reflection without this temperature gradient, then there is probably generation of shear waves at the boundary and an even stronger effect. That is, at a boundary that gives rise to reflection of longitudinal waves, there must be generation of shear waves which would give rise to a very localized heating effect. As you know, it is possible to see these reflections without the temperature gradient so we might consider your concept as a way of increasing contrast in tissue that you can already visualize.

DR. W. J. FRY: Yes, that is correct.

DR. VON GIERKE: What temperature gradient do you think is needed?

DR. W. J. FRY: I would say of the order of 3°C across the interface. This would probably produce a change in the magnitude of the impedance of the order of 1%.

DR. REID: In order to produce this at the interface, aren't you going to need a larger initial temperature difference?

DR. W. J. FRY: The induced temperature changes would be of the order of 6°C above the base temperature in white and 3°C in gray matter.

DR. CARLIN: If the time of travel of the ultrasound wave is of the order of, let's say, 20 to 30 μsec and the pulse length is 1 sec . . . , I wonder if you would explain your timing in greater detail?

DR. W. J. FRY: Both the temperature-inducing and the examining beams are focused into the same region. The inducing beam is pulsed on first, and the temperature increases. Then toward the end of the pulse – for example, 1-sec duration – the examining beam, which consists of a train of short pulses, is turned on and partially reflected from the region of induced impedance gradient if the focus of the induction beam is positioned in a tissue volume where the absorption coefficient is spatially nonuniform in value.

DR. REID: Perhaps I missed something in the train of logic with regard to tissue interfaces from which we now receive reflections, but it would seem to me that, since the change in impedance caused by the temperature rise is related to the attenuation coefficients, we might very easily destroy an existing impedance discontinuity – equally probable, we might enhance it. That is, I do not see that the probability is any greater than 50-50 that you would achieve an enhancement rather than a destruction of the impedance difference.

DR. W. J. FRY: I do not quite agree with your conclusion. The chances are that the tissue on both sides of an interface will have the same algebraic sign

for the temperature coefficient of velocity. So, one should have at the interface an impedance difference equal to that before temperature-gradient induction plus the difference caused by the transient induced gradient.

DR. DAWE: I would like to point out a couple of physiological facts here. The only person I know who has changed the temperature in deep areas of the brain is Hardy at Yale, and he finds some rather profound changes in the entire organism due to this temperature variation. One must remember, if he is going to affect the deep portion of the brain or to make a thermal scan of the brain, that every portion that is heated is going to require a little more oxygen because of the increased metabolic rate. From a physical standpoint your experimental approach looks very good, but you have to be careful that you do not make physiological changes in the animal.

DR. W. J. FRY: I agree. One must make the measurements in a short period of time. In the case under discussion, the peak of the temperature rise does not last more than a few tenths of a second. In our research on the production of lesions in brain by ultrasound and on the induction of reversible effects, we have produced greater temperature changes than those necessary in the new visualization method, so we do know what sort of temperature increases the tissue can experience without damage for the periods of time required.

If there are no further questions, I should like to amplify the statement I made previously regarding the possibility of ultimately irradiating directly through the intact skull. The possibility is remote at the moment, but I would like to indicate briefly the basic difficulties that prevent irradiation through the skull at the present time and also some possible means of circumventing these difficulties. First, refraction drastically limits the area of skull through which one can pass an ordinary converging ultrasound beam to produce a focus of small volume in the brain. The skull is so nonuniform in shape on the scale of importance here and the angles of entry of different portions of a large aperture converging beam are so different that the possibility is remote that the "rays" entering from various positions will superimpose accurately after transit. A second basic difficulty is the determination of dosage because of the variations in skull thickness as a function of position. In addition to evaluating the effect of absorption, the determination of dosage must take account of differences in the value of the deflection coefficient from position to position. A third difficulty arises from the fact that the amount of energy required in a transcranial irradiation procedure for focal lesion production in depth is such that the cortex would be damaged by heat unless the incident acoustic radiation is spread over a major fraction of the area of the cranial vault.

Now, let us consider how the proposed new visualization method would aid in the solution of these three difficulties. It is apparent that, in principle, the first difficulty could be handled because it would be possible to superimpose, by direct observation, individual incident beams of small cross-section. That is, the new method would show where each beam path is located in the tissue structures and would thus provide the information to permit them to be superimposed at a desired anatomic site by individual adjustment

of the positioning systems which support the separate transducers. Thus, one could in principle, solve the refraction problem. With respect to the problem of dosage, the new visualization method provides the possibility of direct determination of the dose at the common intersection by measuring the magnitude of the induced temperature gradients. The third difficulty—overheating of the tissue-neighboring bone at the port of entry of the sound—*is* a messy one, but since we have shown, in principle at least, how the first two difficulties might be handled, we can now consider spreading the incoming energy over a very large fraction of the skull. A computation shows that conceivably one might operate at a frequency as high as 1 Mc and still allow sufficient energy to penetrate the skull without overheating the cortex.

Therefore, in principle there exists the possibility of eliminating all three major difficulties which currently present a barrier to the direct ultrasonic irradiation of deep brain sites via the intact skull.

DR. BALLANTINE: Do you ultimately replace the bone flap in the work you are doing at Iowa?

DR. W. J. FRY: Ultimately a plastic replacement is inserted.

DR. BALLANTINE: Why don't you replace the bone flap with plastic immediately?

DR. W. J. FRY: This represents a difficulty. We hope that one of our next advances in method will be the development of a suitable replacement for the bone. Any ordinary piece of plastic cannot be used as a bone replacement since the same refraction difficulty would be present as with the original bone. We have been giving some thought to the design of a "sound transparent" replacement.

I would like now to present some other topics that are of interest to us. We reported a number of years ago on the reversible changes in function induced in the visual system of the cat by ultrasonically irradiating a lateral geniculate nucleus while flashing light in the animals' eyes. We showed at that time that one could obtain a three-dimensional "functional" mapping of this portion of the brain by using the sound focus as a probe to modify the relations between the stimulus or input and the output in the form of cortical-evoked potentials. Figure 2 shows the type of map that we published at that time. If one subjects the eye of an anesthetized cat to single flashes of light while maintaining the temperature and level of anesthesia fixed, a reproducible form of the evoked potential is elicited. Under the experimental conditions obtaining for the map and with the electrode placed at the cortical position indicated, the normal response was of the form appearing in the lower circle of the right side of the figure. Now, by focusing the sound into the lateral geniculate nucleus, we showed that one could produce drastic temporary modifications of the form of the potential, the extent of the change depending on where the focus is placed. For example, the response appearing in the upper circle of the right side of Figure 2 shows that all later components of the evoked potential can be suppressed without affecting the first. For some other electrode positions, one observes modifications of the form of

the initial response. Therefore, the ultrasound focus, when employed in the manner indicated, constitutes an analyzer for modifying the relations between stimulus and response.

To indicate the potential versatility of ultrasound from the viewpoint of determining maps of brain function, I would simply like to compare its use with that of electrodes alone to obtain comparable information. If one em-

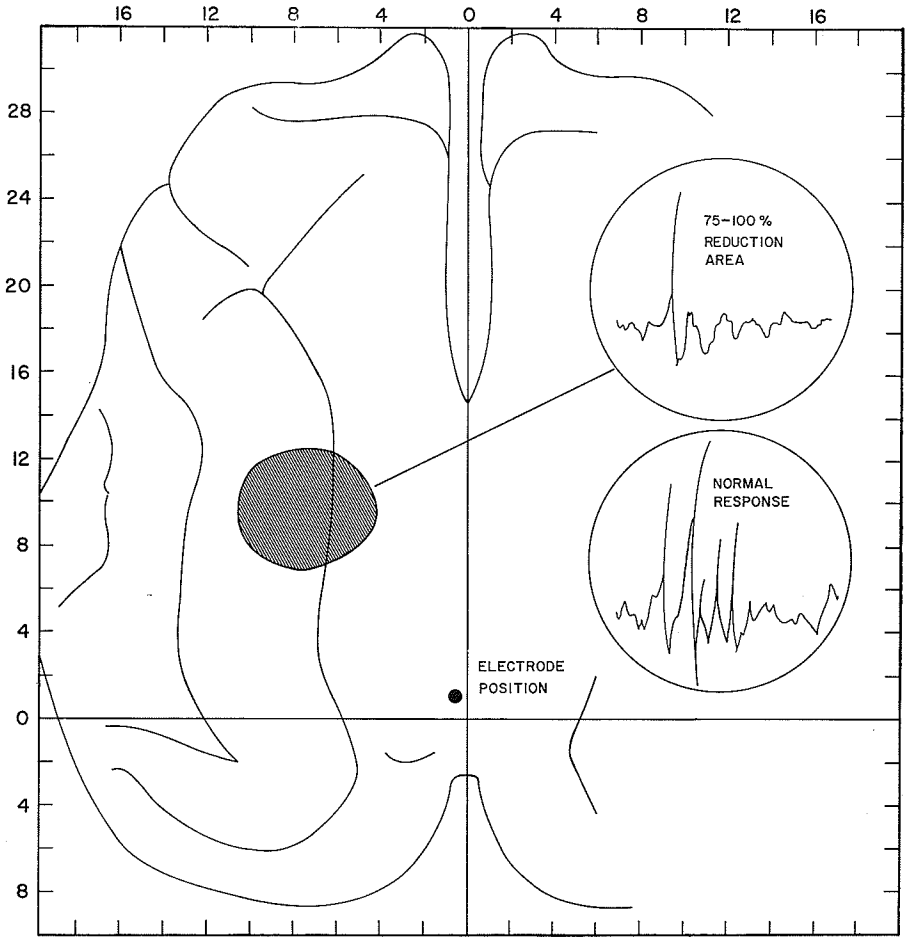


FIGURE 2. Induction of reversible changes by ultrasound in the cortical electrical response induced by subjecting the eye of an anesthetized cat to single flashes of light. The normal response for the level of anesthesia and brain temperature employed appears in the lower encircled area on the right. A number of readily distinguished components can be seen in the response pattern. When an ultrasound beam is focused into the region of the lateral geniculate nucleus and appropriate irradiation parameters are employed, the cortical evoked response pattern can be modified temporarily to assume the form illustrated in the upper circle of the diagram. The gray patch on the left side of the figure is the area, at the vertical level corresponding to the approximate middle of the lateral geniculate nucleus, in which the center of the focus can be placed to produce the result indicated. The cortical pattern of the cat brain is shown to indicate the position of the receiving electrode and also to indicate the approximate positions of the sites of irradiation in the longitudinal and lateral coordinate directions (scales are in millimeters).

ploys 4 Mc/sec ultrasound, as we do routinely for work on the cat brain, then the moving focus of the beam constitutes an analyzer of relatively small dimensions (the diameter, at a pressure amplitude $1/\sqrt{2}$ of the peak value, of the beam perpendicular to the axis of propagation is 0.6 mm). This focus can be moved anywhere in the brain consistent with the portion of the skull cap that is removed, and therefore one has an analyzer capable of modifying the mechanisms of operation in a very large number of positions. For example, it is not unreasonable to anticipate that 100,000 positions could be temporarily modified in a single brain. Obviously, it is completely impractical to consider placing anywhere near that number of electrodes in a brain. In fact, if a dozen electrodes are inserted into even a large structure, one worries whether the system has been disturbed to such an extent that observed function may not bear any resemblance to that of the normal structure. Of course, one can modify the function of neural circuits in various ways; for example, the relation between input and output events might be changed by inhibiting information transfer at specific locations or by potentiation. At the present time we are unable to specify the specific mechanism by which the sound acts on the lateral geniculate to disturb the "normal" mechanism relating the light stimuli and the evoked cortical responses. It may well be through suppression of some events, or it may be through enhancement of others. It should be noted in this regard that we do see enhancement of the amplitude of cortical evoked potentials under some experimental conditions of irradiation.

Considered in the manner described here, focused ultrasound might well provide a tool for the study of complex behavior which would permit some elucidation of the vast array of events which occur in the neural circuitry. Of course, one would require a considerable amount of instrumentation in order to initiate an effective program in this area and I will simply mention some of the types here. Data analysis for the simple experiments we have performed thus far—the measurement of latencies and amplitudes of electrical events—requires a week of one investigator's time to handle the information received at a single electrode by hand measurement and computation methods. In slightly more sophisticated experiments information would be recorded from a number of electrodes simultaneously so that data analyzers, programming equipment, and apparatus for presenting the results of the analysis would be required in order that the information could be processed and assimilated fast enough to determine the future course of the experiment. Some machine representation of the anatomy is necessary so that the investigators can "see" the present path and the history of the position of the focus in the brain. Obviously, automatic positioning and irradiation-control instruments are a prerequisite to such studies.

Some of the data pertinent to the irradiation procedure is now represented by diagrams of the type illustrated in Figure 3. The different shaded squares in the figure represent various sites in a number of nuclei on one side of the brain of a human. This particular diagram was constructed for use during the irradiation of a patient with Parkinson's disease. In this particular case,

FIGURE 3. Diagram of coordinate information employed in producing ultrasonic lesion arrays in the human brain. The diagram displays numerical values for the coordinates of reference sites in various brain structures of interest in the modification of hyperkinetic and hypertonic symptoms. The array of reference sites lies on one side of the midsagittal plane (right side). The legend at the side of the diagram lists information to be employed for the control of the dosage for each specific structure or part thereof. The voltage listed is proportional to the driving level applied across the transducer and the column labeled "sec" indicates the duration of each exposure in seconds.

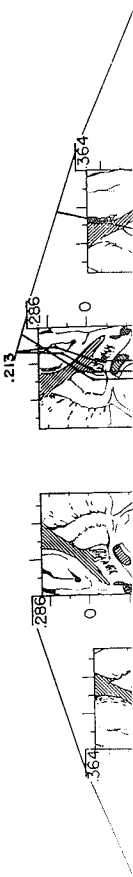
squares with cross hachure, +, represent sites in the tegmental field of Forel (FH); squares with diagonal box cross hatching designate positions in and at the base of the medial globus pallidus (GP); and squares with dotted stippling and with diagonal line cross hatching indicate positions at the base of the ventrolateral nucleus (VL) of the thalamus. Squares with horizontal line segment hachure indicate sites in the substantia nigra (SN). The specific sites indicated in the diagram constitute only a reference set and one does, in general, consider many other positions. Obviously, the representation of the diagram is a planar one, that is, only two of the three coordinate directions are designated by axes. The longitudinal direction or ordinate of the diagram corresponds to the anterior-posterior direction in the brain and the lateral direction of the diagram corresponds to a direction in the transverse plane at an angle of approximately 55° with respect to the vertical axis. The vertical[1] coordinate position is designated by a number in each of the shaded squares. It is readily apparent that it is rather difficult to "visualize" how the brain anatomy corresponds to this representation.

With further regard to information processing, we have found in work with awake human patients that the data obtained during the step-by-step production of changes in their neurologic state represent a quite complex array of information, and it has become apparent that machine aids for processing and presentation are necessary if this information is to serve its maximum utility in determining the lesion arrays to be made. The complexity of this information is illustrated by the diagram of Figure 4. This diagram shows the changing state, in a single ultrasonic irradiation procedure, of hypertonus[2] of different muscle groups all over the body in a Parkinsonian patient as a function of the positions of lesions placed in different anatomic sites. On such a diagram, one can note the changes in tone that occur in each particular muscle group by following the lines connecting lesion sites, indicated on the array of transverse sections in the diagram, with the position of the muscle group in the body. To conclude my comments on this topic, I would emphasize that one would like, during the course of an irradiation procedure on a patient with Parkinson's disease, to maintain an awareness of all of the data of the diagram and, in addition, of information pertinent to other symptoms. Clearly, data-processing and presentation instruments are necessary aids.

I would like now to mention briefly a major goal of our work on the pituitary gland. Basically, we are interested in seeing if the hypophysis can be redesigned by appropriate treatment with ultrasonic radiation – that is, we wish to determine if its hormonal output can be permanently changed to modify the endocrine state of the animal. This possibility is suggested by the histologically observed fact that the population ratios of the various glandular cell types can be affected to a marked extent by irradiation. For example, one can depopulate a region of glandular cells and the repopulation that follows need not duplicate that originally present.

[1]The vertical direction is perpendicular to the plane determined by the other two coordinate directions.

[2]The gradations in rigidity are represented by the hachures indicated in the legend of the diagram; the complete absence of stipple represents normal muscle tone.



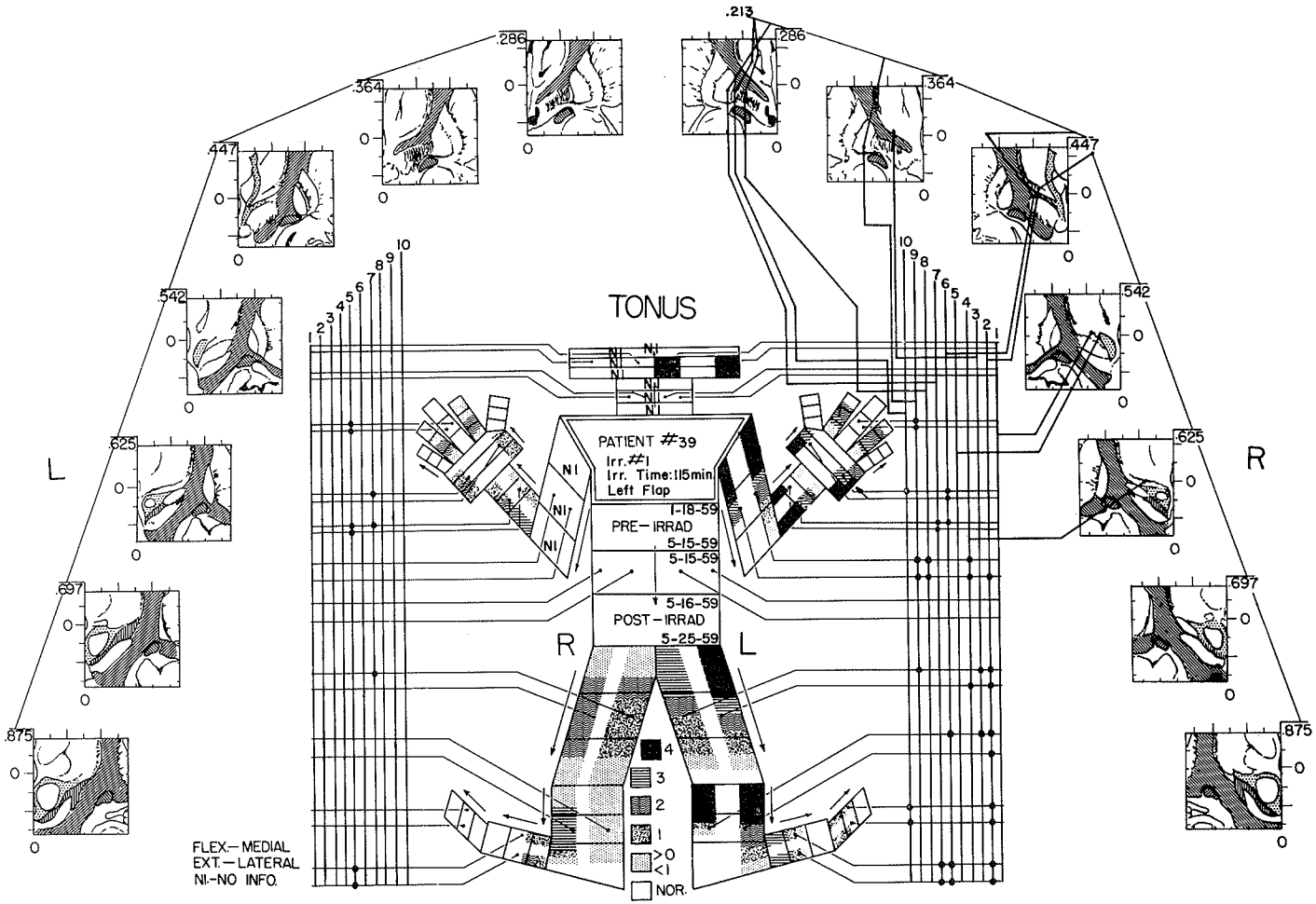


FIGURE 4. Diagram representing the sequence of changes in the tonus of the various muscle groups of a Parkinson patient undergoing brain modification for the relief of symptoms. The positions of the individual lesions, which result in changes in tone in each of the muscle groups, are designated by dots on the diagrams of the brain sections, and lines connect these sites with the vertical columns of lines on the right and left hand of the figure. The numbers at the top of each column refer to the lesions in the chronological sequence in which they were produced. The small black circles in the columns of lines indicate which lesions produce changes in specific muscle groups as shown by connection with the horizontal lines that terminate on the representation of the body.

It seems appropriate to comment here on our interest in ultrasonic absorption spectroscopy at very high frequencies (100 to 2000 Mc/sec). The work of Carstensen, Schwan, *et al.* on hemoglobin and other biologic materials demonstrates that absorption coefficient values for proteins depend upon the composition of the ionic environment, the degree of hydration, and other factors. It would be extremely interesting to extend such measurements to the high-frequency range indicated and thereby possibly determine the entire extent of the relaxation spectrum.

As you know, many soft tissues exhibit an almost linear relation between the frequency and the value of the absorption coefficient per unit path length. It is desirable to investigate this dependence at the higher frequencies to determine where marked deviations from the "linear" form occur. Up to the present time, although one can discuss analytically the observed absorption coefficient dependence on the frequency, it has not been possible to ascribe the absorption to specific dynamic events. That is, one can describe the data phenomenologically in terms of a distribution of relaxation frequencies. However, further work on the investigation of protein solutions might well show that different macromolecular configurations of biologic significance are distinguished by considerably different relaxation spectra. If this is the case, it might then be possible to derive information on the distribution of various macromolecular species within the cellular elements of tissues by employing ultrasonic microscope principles.

A number of years ago, I proposed a new form of ultrasonic microscope. In this regard, it should be noted that the development of an ultrasonic instrument of high resolution cannot be achieved by applying the design principles employed in light microscopy, for example, the use of lenses, because at the frequencies of operation necessary to obtain appropriate resolution (1000 Mc/sec and higher) the absorption coefficient values are too great to permit the use of the long transmission paths required. However, the type of design which I proposed would surmount this difficulty by: (1) employing plane waves that travel only a short distance to reach the specimen in which they are partially absorbed and (2) detecting the transmitted energy distribution by an array of thermocouple probes placed immediately adjacent to the specimen. The instrument would reveal structural features by localizing sites where the absorption coefficient experiences a gradient.

I will finish this outline of new approaches to the study and modification of biologic systems by ultrasound by noting that we are still pursuing the investigation of physical mechanisms. We feel that this aspect of our program is very important since results obtained will undoubtedly suggest new ways to employ acoustic energy to elucidate structure and function in such systems.

DISCUSSION

DR. GERSTEN: In the investigations of the reversible effects are the changes in excitability only at the focal point?

DR. W. J. FRY: We can discuss that on the basis of resolution, that is, how

much does one have to move the focus in order to see a change occur. This is a convenient way to localize the volume of tissue responsible for the observed change. The data that I showed was taken at 1 Mc where the resolution is not as high as one would like. The amount of movement of the focus that would result in a detectable difference in the responses would probably be of the order of half a millimeter or so. Now with 4-Mc frequency, we can increase this resolution to somewhere near a tenth of a millimeter.

DR. BALLANTINE: I would like to comment briefly on some of the results and publications of our laboratory at Massachusetts General Hospital because I think they bear on this question of the localization of the areas to be destroyed, or to be studied by the investigator. First, as I previously mentioned, there are the two publications by Lele [1] and Basauri.[2] Young and Henneman [3] and Shealy and Henneman,[4] who were working both in our laboratory and in the Department of Physiology at Harvard, have published in the Archives of Neurology. It seems to me that there are two methods which should be borne in mind for such a study. One is the anatomical method for visualization of tissue through ultrasound, and the other is the physiological method. Young and Henneman showed fairly conclusively that there was an immediate effect on peripheral nerve, which was differential and reversible. The differential part of this may be open to some question in regard to its reproducibility. We don't know yet but we are repeating some of the experiments. However, the reversibility of the effect on the compound action potential of peripheral nerve is, I think, fairly well established. Accompanying this effect was an initial enhancement of the compound action potential. Similarly, Shealy and Henneman, working with the cat's spinal cord, were able to demonstrate an effect on the monosynaptic and polysynaptic reflex response. With thirty pulses of ultrasound, one a second, there was a rather large enhancement of the potential of the monosynaptic reflex discharge, and then a falling off to almost zero and then after a period of 25 min, a recovery. In yet another experiment, in which both the monosynaptic and polysynaptic reflexes were investigated, there was, following an initial enhancement, a depression of polysynaptic reflexes and a slow recovery. It seems reasonable to deduce that if you can reversibly affect peripheral nerve and monosynaptic and polysynaptic reflexes in the spinal cord, that such reversibility should be feasible in the brain, and in addition, it may be possible that the ultrasound stimulation response could be used as a physiological indication of the location of the sound beam in the brain. I'd like to ask Dr. Fry if he has seen any such stimulation in the patients who were irradiated at the University of Iowa.

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[1] P. P. Lele. A simple method for production of trackless focal lesions with focused ultrasound: physical factors. J. Physiol. *160* (1962), 494–512.

[2] L. Basauri and P. P. Lele. A simple method for production of trackless focal lesions with focused ultrasound: statistical evaluation of the effects of irradiation on the central nervous system of the cat. J. Physiol. *160* (1962), 513–534.

[3] R. R. Young and E. Henneman. Reversible block of nerve conduction by ultrasound. Arch. Neurol. *4* (1961), 83–89; and R. R. Young and E. Henneman. Functional effects of focused ultrasound on mammalian nerves. Science *134* (1961), 1521–22.

[4] C. N. Shealy and E. Henneman. Reversible effects of ultrasound on spinal reflexes. Arch. Neurol. *6* (1962), 374–386.

DR. W. J. FRY: We did not see any motor stimulation during the irradiation of structures of interest to us from the viewpoint of relieving the symptoms of the hyperkinetic disorders, but we do have some evidence for stimulation in patients who were irradiated for the relief of intractable pain. The sensations experienced by these patients indicate stimulation, but, of course, at the time we were treating these patients we were concerned with making irreversible changes, so that we can't say in these cases that the stimulation was unaccompanied by irreversible change in the neural tissue. These patients, who were conscious during treatment, experienced various sensations over the surface of the body, for example, heat waves. Some of them would describe the sensations very vaguely because they hadn't experienced them before. Some were described as very desirable sensations and others as not so desirable. So there is no doubt that one does produce stimulation but I don't believe, in the present instance, that we could use these results to support the view that reversibility would also accomplish stimulation. However, we have other data that might support the view that one can produce stimulation with reversible change, namely, the enhancement of evoked cortical potentials. In our work on the production of reversible effects by ultrasound, we noted enhancement of these potentials, so that one might consider this as evidence for stimulation during the production of reversible changes.

DR. BALLANTINE: One other point which I believe needs reemphasizing is that probably a larger volume of tissue needs to be irradiated to produce a lesion, or to produce an effective lesion, than is encompassed in the single lesion produced by a single burst of sound. Wouldn't you say that was true? In the work that we have done, both with peripheral nerve, but more particularly in the spinal cord, so-called defocused ultrasound was used, that is, the focal region was slightly above the surface of the spinal cord in order to give a spraying effect to that segment of the cord to be irradiated. We have been working with various methods to focus and refocus ultrasound in order to get both a clean wave of high intensity and a narrow pencil of high intensity just near the focal region that we can use to irradiate a larger volume of tissue than we can with the ordinary focused beam.

DR. CURTIS: Would you comment on the reversible effect in the peripheral nerves, say in the C and E fibers?

DR. BALLANTINE: We found that if the right parameters of irradiation time and intensity were used with pulsed ultrasound, it was possible to abolish the compound potential, and after a certain interval, to have it return. Following an attempt to analyze the compound potential and to break it down into the A and C fibers, Young and Henneman found that the A fibers were more resistant to ultrasound than the C fibers.

DR. CURTIS: How reproducible did you find this and what frequency are you using?

DR. BALLANTINE: Young and Henneman felt that it was quite reproducible. We are repeating some of this work and initially found it as reproducible as they did. However, we are using slightly different parameters of irradiation, namely 1-, 1.8-, and 2.7-Mc frequency.

DR. CURTIS: I would like to ask Dr. Fry if he has tried any cortical work?

DR. W. J. FRY: Some years ago we did some work on the irradiation of the motor cortex of both the monkey and cat. Again, we were using dosages which produce irreversible effects, and we observed motor activity related to the position of the focus in the cortex. One could map the cortex in terms of ultrasonically induced muscle movement.

DR. CARSTENSEN: I would be very interested in your feeling regarding the mechanism involved in this stimulation. Is it purely thermal, do you suppose?

DR. W. J. FRY: It's probably a thermal effect; that would be my guess.

DR. CARSTENSEN: I believe that in the article by Young and Henneman, the authors indicated high-intensity ultrasound was used but they did not give precise data on the intensity values.

DR. BALLANTINE: Pulsed ultrasound was used of approximately 1300 w/cm^2. It was pulsed for very short durations. One of the problems inherent in that particular experiment, however, was that there was no adequate control of intensity, such as we have been able to achieve in later experiments; it is probable that the intensity was variable.

DR. CARSTENSEN: A scientific article which does not give ultrasound dosage is comparable to a pharmacology paper on a new drug in which no drug dosage data is presented. It is difficult to draw any conclusions from such a publication. The authors went to the trouble to give the voltage applied to the transducer, which is interesting, but fairly useless.

DR. BALLANTINE: Well, that brings me to a subject which has intrigued me for a number of years, namely, that investigators in their own laboratories use different characteristics for power measurement. Bill Fry uses acoustic amplitude and particle velocity. At our laboratory, we have used watts per square centimeter. When Lele joined our laboratory, he decided that this was a kind of arbitrary figure. Therefore, he multiplied the watts per square centimeter derived from the sonartestmeter, which I think is reasonably accurate, by the increase in gain due to the optics of the focusing system. One reads in his articles notations such as 42×15 or 42×20. I think that it is high time that we circulate a memorandum among the people working in the field and ask them for their ideas on the best measurement figure for ultrasonic power. In addition, I think it is wise to bear in mind that the choice of a unit of measurement which is familiar to the biologist and physician would be a great advantage.

DR. W. J. FRY: If one uses a radiation pressure detector for a focused beam, one has the problem of worrying about precisely what this is measuring in the focal region. The term intensity is directly applicable for plane waves or for small angle convergence lenses, but with a large angle of convergence the use of the intensity parameter alone introduces difficulties; that is, the specification of the intensity does not uniquely determine the values of the field parameters, and therefore we do not use the intensity in quantifying these wide angle converging fields. Of course, one can talk about a flow of energy, in which the pressure, particle velocity, and their relative time phase are

involved, but since we use the thermocouple probe[5] for calibration and it does not yield any measure of phase, we cannot determine values for the intensity. We calibrate in a plane wave field of known values for pressure and particle velocity amplitudes and then, by analyzing the form of the response in the focused field, obtain values for pressure and particle velocity amplitudes, but no phase measurement. It is true that with this technique we have not completely specified the field, but it is probably true that insofar as the biological effects are concerned, the relative phase of pressure and particle velocity is not important.

DR. KOSSOFF: What about describing a plane wave?

DR. W. J. FRY: Well, for plane waves the specification of intensity does determine the values of the other field parameters. If the form of the field distribution is not known, I don't see any way to obtain both it and values for the particle velocity and pressure amplitudes from intensity measurements alone. Do you have some particular scheme in mind?

DR. KOSSOFF: No.

DR. W. J. FRY: Even though measurements are made with a radiation-pressure device, it is very desirable for investigators to include in their publications a complete description of the specific method of measurement so that other investigators can, at least, make some computations to translate the presented data into values of parameters of interest to them. For example, everyone does not measure pressure and particle velocity amplitudes, so one can't expect them to list values for these parameters, but if one indicates the angle of convergence of the beam and also gives some information on the field distribution at the focus, then estimates of pressure and particle velocity amplitudes can be made.

DR. HERRICK: I believe Ralph DeForrest and Ted Hueter had a standards committee in the early days, when ultrasound was being introduced into physical medicine.

DR. W. J. FRY: The ultrasonic diathermic standards are certainly very desirable but when they were set up, the use of high-power focused ultrasound was not included because of the state of development of the field. It would be very desirable now to consider this problem so that some uniformity in the method of describing irradiation conditions would be employed.

DR. BALLANTINE: I would like to second what Bill Fry has said concerning the desirability of including in publications sufficient information so that other investigators can attempt to duplicate the results. Insofar as the work at our laboratory is concerned, I believe we have finally arrived, as I said, at a satisfactory description of our equipment, of our measurements of the various parameters of dosage, and of the results obtained. If any of you read Lele's

[5] W. J. Fry and R. B. Fry. Determination of absolute sound levels and acoustic absorption coefficients by thermocouple probes – theory. J. Acoust. Soc. Am. *26* (1954), 294–310; W. J. Fry and R. B. Fry. Determination of absolute sound levels and acoustic absorption coefficients by thermocouple probes – experiment. J. Acoust. Soc. Am. *26* (1954), 311–317; W. J. Fry. Intense ultrasound in investigations of the central nervous system *in* "Advances in Biological and Medical Physics," C. A. Tobias and J. H. Lawrence, eds. (Academic Press, New York, 1958), Vol VI, pp. 281–348.

paper [6] and are in doubt as to the precise details of the experiment or feel that you can't build the equipment from the information provided in the publication, then please tell us. We like to encourage other investigators to work with the same equipment, to see whether our results will stand up under such scrutiny.

DR. DUNN: Professor Fry and I published, several months ago, a chapter in the Academic Press series, "Physical Techniques in Biological Research," in which we attempted to record principles of measurement and desirable apparatus for high-intensity ultrasound research.[7] This chapter is about 135 pages in length and discusses in considerable detail many of the problems being considered here.

DR. GERSTEN: In connection with your previous comments regarding stimulation by ultrasonic energy, have you ever recorded any propagated action potential? We never recorded such potentials, but we have been using much smaller ultrasound intensities than you have.

DR. BALLANTINE: We have not measured a propagated potential as a result of stimulation, but we have seen from time to time, particularly during the irradiation of the spinal cord, a twitch in the hind leg of the experimental animal.

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[6] See n. 1, pp. 236, 255.

[7] W. J. Fry and F. Dunn. Ultrasound: analysis and experimental methods in biological research, in "Physical Techniques in Biological Research," W. L. Nastuk, ed. (Academic Press, New York, 1962), Vol. IV, Chap. 6, pp. 261–394.