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# Comments on a Recent Paper by Hueter *et al.* on Ultrasonic Lesions in the Central Nervous System

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The recent paper by Hueter *et al.* on ultrasonic lesions in the central nervous system, which appeared in a recent issue of this Journal (March, 1956), presents a rather limited view of this field and may lead to some misunderstandings.

This note is a critical analysis of the Hueter paper. Some of the more important points discussed are: (1) The unique advantages of producing ultrasonic lesions in the brain by using dosages appropriate for selective action combined with focusing of the beam in contrast to the use of focusing alone. (2) The choice of an irradiation procedure in experiments designed for the elucidation of physical mechanisms of the action of ultrasound on tissue. (3) The specification of the acoustic variables required for a dosage description. (4) The inapplicability of Eyring's theory of viscosity, plasticity, and diffusion to the elucidation of observed dosage relations. (5) The clarification of the usage of the terminology, nontemperature effects. (6) The applicability of the reciprocity method for the calibration of thermocouple probes.

THE recent paper[1] by Hueter, Ballantine, and Cotter entitled "Production of Lesions in the Central Nervous System with Focused Ultrasound: A Study of Dosage Factors," may leave a reader who is unfamiliar with the technical literature in this field with a rather unsophisticated view of its present state. The paper, for example, places major emphasis on the well-known and common effect produced by intense ultrasound, *viz.*, the nonselective destructive action. Such nonselective action on nerve tissue can be accomplished by a variety of older nonacoustic procedures. The *focused* ultrasound method for nonselective destruction, which receives major emphasis in Hueter's paper does, of course, have advantages over the nonacoustic procedures, for example, the intervening tissue can be left undamaged. However, the selective actions of ultrasound which imply really new possibilities in fundamental neurological research, in neurosurgery, and in the understanding of basic cellular mechanisms, are relegated in the paper of reference to a distinctly minor role.

It is extremely important that physical scientists be acquainted with the significance of this acoustic tool for fundamental investigations in the field of biology since such a realization will do much to encourage further research in this field. Many of the major publications on this subject have, of course, appeared in the biological journals. Unfortunately, many of the readers of this Journal, who enjoy the considerable advantage of understanding the basic physical techniques being employed may, therefore, not have had the opportunity of critically viewing the advances in this area of research. Since, in the opinion of the writer, the paper by Hueter *et al.* presents a somewhat restricted view and may even lead to some basic misunderstandings, the following detailed comments on this paper are presented here. For the convenience of the reader, the comments will follow the order dictated by the organization of the Hueter paper.

In their introduction, the authors state that "Some amount of reproducibility has been achieved ···for one frequency and for *one particular type of equipment*" (writer's italics). This statement, which emphasizes the use of a particular equipment,[2–4] appears to imply that precise ultrasonic dosage conditions (numerical values for the acoustic variables) are not as yet known which can be used to obtain a desired or predictable result. Such a situation is far from true as has been proved by extensive studies on the production of both subcortical and deep white matter lesions in cat brains. The results of these investigations have been reported in the technical literature.[2–6] However, it is true that dosage relations covering a wide range of values of the acoustic variables have not yet been determined. It should be emphasized here that a lack of understanding of the physical mechanism and a knowledge of the dosage conditions over wide ranges of values of the variables should not preclude the immediate application of the method which has already been fruitful in producing biologically significant results.

The authors also indicate in their introduction that spreading of damage induced by the ultrasound is dependent on the kind of nerve tissue irradiated. This statement, left unqualified in the paper, is misleading. Spreading of damage, induced by ultrasound, to adjacent regions is dependent on the ultrasonic dosage conditions. It is possible to produce lesions in nerve tissue, both gray and white matter, without any appreciable spreading.[2–6]

The authors conclude the introduction to their paper by suggesting that the method of controlling lesion size and shape by focal spot size alone, irrespective of selectivity, may be "···of more general validity" than the method which utilizes tissue selectivity. However, the nonselective approach is a special case of the selective method, and it is noted in this connection that any focal spot geometry developed for complete disruption of tissue within a given region can be used to deliver dosages at which selective changes are realized. The selectivity approach is considerably more powerful than the nonselectivity approach for the following reasons.[2–7] (1) White matter (fiber tracts) can be disrupted at lower dosages of ultrasound than gray matter. Therefore, in destroying fiber tracts, sharp lesion boundaries can be realized between the disrupted white matter and the neighboring or surrounding gray matter. This can be accomplished for any shaped boundary, however complex, between white and gray matter. (2) A fiber tract within the brain can be interrupted even though its position is not known accurately enough to place the focal spot of the beam within the tract. This can be accomplished since a

larger area can be irradiated at a dosage which does not disrupt the gray matter. The selectivity method is safer than the nonselective method since any inadvertent irradiation of gray matter, resulting from inaccuracy of positioning of the focal spot of the beam(s) relative to a particular brain structure does not result in undesirable damage. (3) The vascular system can be left intact and functioning in the lesion area thus preventing spreading of the lesion. (4) The functions of some of the individual components of the tissue can be isolated from others by studying tissue in which more susceptible components have been selectively eliminated by the sound.

If the use of the ultrasonic method in neurosurgery is restricted to the production of unselective lesions, then the outstanding advantages of the ultrasonic procedure would remain unrealized in human surgical practice.

Near the end of Sec. A, "Geometry of the Focal Region," the authors are concerned with the question of the choice of an "optimal frequency" (for a given depth). This discussion of the selection of an "optimal frequency" suffers from a lack of consideration of an important limitation imposed by the conditions for realizing some types of selective lesions. (Some selective lesions cannot be produced by purely thermal action.) The statement is made that heating effects due to frequency dependent absorption can be controlled by suitable pulsing. This statement is true, but there is no assurance that under the conditions required to control heating effects it is practical or indeed possible to produce a selective lesion of a desired type in a reasonable period of time. The individual acoustic pulses may be separated by such lengthy time intervals, that it would take an extremely long time to realize enough ultrasonic exposure to produce a lesion. In fact, it should be noted that since a decay process is operative[8] following a subliminal exposure it may occur that a spacing interval is used such that a lesion is never produced. Such considerations impose an upper limit to the frequencies which can be used to obtain selective lesions in bulk tissue. It should be noted that, at the present time, only sparse knowledge of this decay process is available and, therefore, it is not possible to specify "optimal frequencies."

In the first paragraph of Sec. B, "Determination of Focal Intensity," of their paper, the authors discuss the possibility of cavitation-type breakdown in the tissue at high amplitudes. In support of this possibility they refer to a paper by Hug and Pape which really does not constitute evidence for this view since the sound levels reported in the cited paper were very low (maximum 10 w/cm$^2$) compared to the levels (of the order of 1000 w/cm$^2$) used to produce the deep lesions illustrated in the Hueter paper. If the phenomenon observed by Hug and Pape occurred under the irradiation conditions used by the authors, such breakdown would probably be apparent along the transmission path in the tissue between the port of entry of the sound into the brain and the lesion area. Apparently, such changes were not observed by the authors since they refer only to "$\cdots$morphological changes$\cdots$in the tissue at, and adjacent to the focus$\cdots$." In fact, the work of Esche, also cited by the authors, indicates that cavitation does not occur in tissue at the sound levels used in the reported experiments.

Also under Sec. B, the authors compare the characteristics of the relatively recently developed thermocouple probes[9,10] with piezoelectric probes. Their tabulation (Table I) implies that the thermocouple probes cannot be calibrated by the reciprocity method. There is, however, no theoretical limitation which prevents such calibration. The free-field microphone response, $M$, of the probe is defined by

$$M = E_m/P^2,$$

where $E_m$ is the open circuit voltage across the probe after an arbitrary time interval beginning at the initiation of the acoustic pulse and $P$ is the magnitude of the acoustic pressure amplitude at the position of the junction (probe absent). The microphone response is then readily expressed in terms of measurable electrical quantities.

The authors discuss, for example, in Sec. C, "Relationship Between the Physical Irradiation Conditions and the Biological Effect," first paragraph, "$\cdots$the biological response to a given acoustic *intensity*$\cdots$" (writer's italics). Since this quantity alone does not describe a focused acoustic field, such as the authors use, and since all of the biologically significant effects are not expressible in terms of this single acoustic variable it is now recognized as desirable in the specification of dosage, for example, to state values for the pressure amplitude and the particle velocity amplitude. The dosage description is then independent of the particular focusing irradiator used to generate the field. Earlier publications[2,3,8,11] in this field, from this laboratory, specified the dosage in terms of intensity, which is satisfactory if a plane wave field is used and so stated.[8,11,12] The intensity alone was specified for nonplane wave fields,[2,3] in some of these publications. This is undesirable for the reason just given.

In order to obtain information regarding dosage conditions (over a wide range of values of the acoustic variables) required to produce a desired result, the authors report results (Sec. C of the paper) obtained on irradiated mice (spinal cords). The dual exposure procedure used (irradiation at two adjacent positions) complicates the interpretation of the results since the use of *multiple partially overlapping* exposures entails the uncertainty regarding the residual effect of previous exposures. Uniformity of dosage is extremely difficult to realize with such a procedure. The single exposure or multiple coincident exposure procedures are the procedures of choice for the elucidation of the physical mechanism of the action of the sound.[12]

It is to be noted that the large variation in the results indicated by the distribution curves reported by the authors is probably the result of the experimental procedure used rather than the variation in biological susceptibility. This is supported by results reported by the writer *et al.* in which young mice were used as test specimens.[12] The variation in results was much less than that reported in the paper under discussion.

In view of the variability of the results, the authors' suggestion of a relationship of the form $(A-A_0)^n t = \text{constant}$ and $n \geq 2$, is not very convincing. This is especially true since the most recent results reported from this laboratory,[12] as well as the early work on frogs,[8] show that $n$ does not deviate greatly from 1.0 at sound levels immediately above the region in which purely thermal effects appear to prevail. The authors also indicate in Sec. C that they achieve improved reproducibility of size and shape of lesions by using pulsed sound as compared with continuous wave (CW). They feel that the "$\cdots$more gradual temperature rise at the focus which can be achieved by pulsing as compared with CW irradiation brings about greatly improved control over the extent of tissue damage." For the focal spot size apparently used, some of the lesions (three of the four lesions illustrated are in white matter) illustrated in the Hueter paper are huge for a single position of irradiation in the tissue. Their large size suggests that the tissue damage is primarily the result of heat conducted from the focal region. A much more precise way of producing large shaped lesions is the use of the multiple spot irradiation procedure. This has been thoroughly demonstrated for white matter lesions and the results appear in the technical literature.[2,3,6] By utilizing the selectivity which can be attained, under suitably chosen dosage conditions, it is possible to produce a white matter lesion whose boundary follows any complex contour between white and gray matter. Thus gray matter regions neighboring a white matter lesion are left intact. It should also be noted that the blood vessels traversing such selective lesions are left intact and functioning.

The terminology "nontemperature effect" has been used in the literature to indicate a process by which ultrasound produces a change in the tissue which is not solely the result of heating.[8] In the first paragraph of Sec. D, "Mechanisms Involved in Tissue Destruction by Ultrasound," the authors state that "$\cdots$it seems unrealistic to attempt a clear-cut identification of nontemperature effects because most biological reactions are temperature dependent." This would imply that any process with a nonzero temperature coefficient must be classified as a heating process. This definition of terms appears to be at variance with general usage.

The authors state, in the second paragraph of Sec. D, that "The main argument for the existence of an interference of the ultrasound with the cell structure that is primarily mechanical rests with the finding that a subliminal dose of ultrasound, which by itself produces neither a substantial temperature rise, nor any histological or physiological effect, has a priming effect on the tissue; i.e., the tissue displays a "memory" for such a subliminal dose." This finding[8] is certainly important support for a "mechanical" process. However, the finding that changes (lesions) can be produced in the tissue in the absence of damaging temperature levels constitutes equally important support.[11,12]

The authors also state in their discussion of mechanisms (Sec. D) that "The mechanical hypothesis is corroborated by evidence shown by Peters, that the morphology of brain damage by ultrasound is similar to that following mechanical concussion." However, Peters does not give evidence in his paper that the morphology of brain damage by ultrasound is similar to that following mechanical *concussion*. The referenced paper indicates that ultrasound can produce effects similar to *contusion* (internal bruising and hemorrhaging). In fact, Peters clearly indicates that such ultrasonic injuries can be successfully compared with the classical contusion obtained by hitting the skull with a blunt instrument. Peters then proceeds to discuss one of the current theories of *concussion*—namely, the occurrence of reversible changes in the brain protoplasm. Since ultrasound can produce temporary clinical reversible symptoms, Peters then *postulates* that the action of ultrasound may also produce reversible changes of the protoplasm, and in that sense be similar to concussion. It is extremely important to distinguish between *contusion* and *concussion* since the mechanism of concussion is as yet unknown. A clear-cut experimental demonstration of "*concussion by ultrasound*" would constitute a very important finding and one which has not yet been demonstrated.

The authors feel (latter half of Sec. D) that some support for the applicability of Eyring's theory of viscosity, plasticity, and diffusion is furnished by extrapolations (on graph of $(It)^{\frac{1}{2}}$ *versus* $T$, where $I$ designates intensity, $t$ designates the total irradiation time, and $T$ designates the temperature in Centigrade degrees) of their data to zero values of $(It)^{\frac{1}{2}}$. The intercepts on the temperature axis are in the temperature range above 45°C, and this is stated as lending support to the applicability of this theory. This conclusion is based on the argument that the intercept temperatures are in the range at which heat alone is found to damage nerve tissue. However, much more precise results, obtained at this laboratory,[12] on young mice show that an extrapolation of the type given by the authors (graphing $I^{\frac{1}{2}}t^{n}$ against $T$ where $n$ is any arbitrary positive value) leads to intercept values of the temperature which fall in "normal" temperature ranges for the animals. In fact, using recently published data,[12] one obtains an intercept value which is less than 20°C. This is, for example, considerably less than 36°C at which these animals can live normally without experiencing tissue damage.

In concluding the paper, the authors state that "Because of the strong dependence of biological reaction equilibria on temperature, it would be difficult to separate effects that are primarily mechanical and effects that are primarily thermal." This statement is considerably different from that given in the main body of the paper, namely, that it is "···unrealistic to attempt a clear-cut identification of nontemperature effects···." It seems appropriate to indicate here that such a separation has already been quite conclusively demonstrated.[12,13]

The conclusion of the authors that "Tissue selectivity may only be expected in a narrow range above dosages that lead to only reversible damage and below dosages at which thermal effects prevail." is completely unwarranged at the present time. Data on the effects of ultrasound on tissue over a wide range of dosage conditions are not available at the present time, as the authors themselves point out. In the absence of such information it does not appear possible, at the present time, to conclude that tissue selectivity is probably restricted to a narrow range of values of the variables.

Ultrasonic lesions should not be produced in the central nervous system by a procedure which is based *entirely* on a choice of dosage conditions appropriate for selective action of the sound on particular tissue structures or components. This the authors also indicate. The high level sound should be localized as closely as possible to the region to be affected by focusing. It is, however, safer and the potential value of the ultrasonic method in human neurosurgery is increased enormously if an irradiation procedure is used which combines the choice of dosage conditions for selective action and the focusing technique[2–4,6] rather than the technique of focusing alone, irrespective of selectivity, as Hueter *et al.* appear to prefer.

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