EARLY EXPERIENCES WITH ULTRASONIC IRRADIATION OF THE PALLIDOFLUGAL AND NIGRAL COMPLEXES IN HYPERKINETIC AND HYERTONIC DISORDERS*

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I. THE PROBLEM AND EARLY APPROACHES

In 1939 a series of surgical investigations directed at the basal ganglia in an effort to alleviate the hyperkinetic and hypertonic features of parkinsonism, chorea, athetosis and dystonia was initiated by the senior author39,40 of the present paper. Taken singly and in combination, the structures interrupted or extirpated in the pre-World War II series of 16 patients subjected to such operations included the caudate head, the ansa lenticularis, the anterior limb of the internal capsule, the oral third of the globus pallidus and the oral third of the putamen.41,42

The most encouraging clinical results were noted among the parkinsonian patients, several of whom obtained complete relief of tremor and marked reduction (but never complete abolition) of rigidity. Evaluation of the pre-war and early post-war series up to 1949—comprising the first 54 cases—indicated that the most effective surgical measures inerred in (a) ansotomy ("pallidofugal section")43,44 and (b) section of the anterior limb of the internal capsule.6,7,34 Postoperative follow-up studies of these patients clearly established that it was possible to alleviate tremors without imposing paresis, dyspraxia, spasticity, hyperreflexia and other signs of so-called "pyramidal dysfunction" upon the patient. Such disabilities had been regularly encountered following the surgical procedures previously in use, namely, high cervical chordotomy31–53 and motor and/or premotor cortical extirpation8–10,36,62 and were also present to a variable degree following the later developed operation of lateral midbrain crusotomy.5,63,64

None of the operations at the level of the spinal cord, midbrain crus, cortex or basal ganglia was directed specifically at the pathologic changes (whatever they may be) responsible for the hyperkinetic and hypertonic disorders. (In point of fact, the pathological data at present available do not permit unequivocal conclusions concerning the relationship between lesions

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at various sites in the brain and the clinical manifestations of the disorders under inquiry.\textsuperscript{50,43,46} On the contrary, the aim of all such operations has been essentially that of interrupting, in some convenient region, a neural pathway (possibly forming a portion of a reverberating circuit), the integrity of which is conceived to be a necessary condition for the appearance of hyperkinesia and/or hypertonus.

Thus far, no procedure has been implemented for the relief of the so-called akinetic features of parkinsonism. Akinesia therefore constitutes a persisting problem that merits the serious attention of physiologists, pathologists, and surgeons.

The pallidofugal operations proved technically difficult to perform with the conventional surgical measures available at the time of their inception and, as in other "physiological operations" (e.g., anterolateral chordotomy for intractable pain), the surgeon sometimes failed to interrupt or interrupt sufficiently the intended pathways. The result in such instances was less than satisfactory. Moreover, in some cases postoperative hemorrhages spread into the hypothalamus and pretectal regions, producing damage beyond the structures intended for surgical interruption or extirpation. Such accidents led to serious neurological deficits and, in some instances, to death. The risks entailed in implementing these operations were reflected in the mortality of approximately 14 per cent in the first 35 cases. Further experience did not bring the operative mortality below approximately 11 per cent. These considerations obviously marked the basal ganglionic and anterior capsular operations as too formidable to permit their recommendation for therapeutic purposes.\textsuperscript{48} Hence, at this stage (1949) their usefulness seemed largely limited to pathophysiological inquiries into the neural mechanisms basic to hyperkinesia and hypertonus.

Finally, the effectiveness of such operations for the alleviation of tremor and rigidity, while seemingly established in one clinic, lacked confirmation from sources other than the original, chiefly because for a number of years the procedures were not undertaken by other workers.

\textbf{II. CONFIRMATORY DATA AND RELATED DEVELOPMENTS}

The development following World War II of human stereotactic instruments,\textsuperscript{1,35,38,47,59--61} comparable to the Horsley-Clarke apparatus used in animal experimentation during the second and third decades of the present century, and the parallel development of human brain coordinates\textsuperscript{48,50} which, however imperfect, made possible the first use of such stereotactic apparatus in clinical neurology, opened the way for a series of new neurosurgical experiments in America, Europe, and Asia.\textsuperscript{12,31--33,48--50,64--68,69} These endeavors soon confirmed the earlier contention as to the vulnerability of tremors and rigidity as attacked through the pallido-pallidofugal complex and reiterated the point previously made that, in effecting relief of hyperkinesia and hypertonus, it was clearly feasible to avert clinical dysfunction of the "pyramidal tract."\textsuperscript{41,43,44} No less welcome was the fact that the use of such stereotactic
apparatus reduced the operative mortality of basal ganglionic surgery to less than 3 per cent.\textsuperscript{12,13,49,50,57,60} The relative safety of these confirmatory procedures inhere mainly in their utilization of electrical, thermal or chemical coagulation by means of appropriately placed needles, cannulae and/or plastic tubes introduced through a simple burr or trephine opening in the cranial vault. Nevertheless, the lack of precise control in placement of these instruments, the lack of mechanical facilities for moving them about within the brain to effect lesions of desired shape and size, and, in the case of the chemocoagulants, the lack of predictability concerning diffusion in the brain tissues, all leave much to be desired. In addition, an obvious disadvantage inhere in the circumstance that electro-, thermo- and chemocoagulation, like the earlier used anal leucotome, produces indiscriminate damage to nerve tracts, neurocytes, glia, ground substance and blood vessels.

III. FUNDAMENTAL ANIMAL WORK WITH ULTRASOUND

Meanwhile, Fry and associates, studying the effects of intense ultrasound on the brain and spinal cord of the frog, mouse, rat, cat and monkey, demonstrated the differential susceptibility of central neural tissues to ultrasonic radiation and adduced conclusive histological evidence in adult mammals that irreversible lesions can be produced in white matter at dosages of ultrasound that do not irreversibly affect gray matter. In both gray and white matter, the vascular structures proved to be the most resistant to the action of ultrasound. As a consequence, it proved possible to disrupt all neural components in a given region of the brain without interrupting the flow of blood to the same and neighboring regions.\textsuperscript{2,3,17,23} In white matter, the myelin sheaths of the nerve fibers proved most susceptible to the action of the sound. Next in order of vulnerability came the axis cylinders, followed in turn by the glial elements. In gray matter, the myelin sheaths again proved the most susceptible and were followed in this regard by axis cylinders and neurocytes. The glial cells of the gray matter appeared to fall somewhere between the neural and the vascular components in their susceptibility to irreversible damage. Thus, a tool for selectively damaging neural tissue in situ was made available for the first time.\textsuperscript{2,14,17–29}

More recently, Fry, Ades and Fry\textsuperscript{15,16} showed that, by appropriate selection of ultrasonic irradiation parameters, reversible physiological dysfunctions without demonstrable histological damage can be produced in structures of the central nervous system. More specifically, the electrical potentials evoked in the visual projection cortex of the cat by single flashes of light at the retina were repeatedly reversibly suppressed by placing the focus of the ultrasonic beams at various positions in the region of the ipsilateral lateral geniculate body. With the ultrasonic parameters thus far employed, most of the functional recovery is accomplished within the first minute following discontinuance of ultrasonic irradiation and complete functional recovery, usually within 5 minutes. Manifestly, such reversible effects now make it possible to draw up functional three-dimensional maps
of the various central neural structures comparable to those already prepared for the region of the lateral geniculate nucleus.\textsuperscript{20}

The ultrasound is produced by x-cut quartz crystals which are excited electrically to vibrate mechanically in thickness mode (the piezoelectric effect) and is focussed by lenses or reflectors.\textsuperscript{19} Both single and multibeam focussing systems have been used, the choice depending upon the specific problem. The anatomic and physiologic changes are accomplished by focussing the ultrasonic radiation within the desired structure or region. A fixed fraction of the ultrasonic energy which enters a slab of tissue is absorbed within the slab. The fraction absorbed per given path length increases as a linear function of the frequency of the sound waves\textsuperscript{25} and at a frequency of 1 megacycle per second the average intensity absorption coefficient of brain tissue is 20 per cent per cm., i.e., one-fifth of the energy entering a slab of brain tissue 1 cm. thick is absorbed during transit.\textsuperscript{26} This absorption of sound by the tissue must be taken into account in calculating, for a specified depth of the focus in the brain, the required driving level for the transducer.

The minimum size focal region that can be produced decreases as the frequency increases. However, it is not possible to increase the ultrasonic frequency indefinitely in an endeavor to obtain smaller and smaller focal spots because the absorption per unit path length traversed increases and damage to intervening tissue would result because of the high incident sound level required to offset this loss. In fact, if damage to intervening tissue in the path of the converging beams is to be avoided, a frequency of 1 megacycle per second (1 mc./s.) is about as high a value as can be used for irradiating the structures in the human brain requiring the greatest penetration by the sound. At 1 mc./s. it is readily possible to produce lesions as small as 1 mm. in transverse diameter (i.e., perpendicular to the beam axis).\textsuperscript{19} Somewhat larger lesions can be produced by increasing the dosage, but, to retain selectivity, the acoustic dosage parameters must be limited.\textsuperscript{3} Selectivity in large lesions is realized by irradiating the tissue at a number of adjacent, overlapping exposure positions. This procedure also enjoys the considerable advantage of permitting shaping of the lesion.\textsuperscript{2,3}

Ultrasonic lesions produced by dosages that result in selective action possess sharp borders and exhibit minimal evidence of diapedesis. Except when very heavy doses of ultrasound are used, blood vessels coursing through the lesion remain histologically intact and capable of transmitting blood.

The principles of Horsley-Clarke stereotaxy, establishing certain cranial landmarks as "zero" planes and using craniocerebral coordinates fashioned therefrom, were employed by Fry and associates to place ultrasonic lesions of desired sizes, shapes and orientations at preselected sites within the brains of their experimental animals.\textsuperscript{19}

At the frequencies employed, the acoustic absorption coefficient of bone is very high.\textsuperscript{37} Hence, if irradiation is attempted through the intact skull, a large percentage of the incident ultrasonic energy is converted into heat and produces undesirable temperature changes in adjacent tissues. In addition,
the acoustic impedance (arithmetic product of the density and the velocity of sound in the medium) of bone is considerably higher than that of soft tissue, including the brain. This results in undesirable reflection and refraction of the ultrasound. These factors, complicated by the inevitable differences in thickness of bone met from part to part of the cranial vault, combine to prevent precision-irradiation of desired structures of the brain in the intact cranium. To circumvent such difficulties it is necessary to reflect a scalp flap and remove a bone flap over an area of brain sufficiently large to accommodate the converging sound beams.

The acoustic impedance of air is extremely small compared to that of brain tissue and therefore acoustic energy incident on the interface between these two media would be almost entirely reflected. Furthermore, air (gas) is not capable of withstanding the tension forces characterizing the high-level sound fields that are employed. Therefore, it is necessary to conduct the sound from the planoconcave lenses of the transducers to the target tissue through an appropriate liquid medium (physiological saline). This saline must be degassed (e.g., by boiling) in order to prevent cavitation (bubble formation) which seriously interferes with the passage of the acoustic energy.

With this objective in view, a bottomless hopper, provided with heat exchange coils for maintaining a temperature close to 99°F, is suitably snugged against the scalp adjacent to the incised margins of the skin. The exposed dura mater spans the lower rim of the hopper. The latter is filled with physiological saline, thus providing a sound-transmitting medium external to the dura mater. Within the dura mater, the sound-transmitting medium consists of all tissues lying along the path of the converging sound beams, viz., ground substance, neural parenchyme, glial, vascular and other connective tissues, and the blood and cerebrospinal fluid.

IV. NEUROSONIC SURGERY* FOR CONDITIONS CHARACTERIZED BY HYPERKINESIA AND HYPERTONUS

With a precision high-level ultrasonic instrument thus available for the selective production of accurately localizable lesions at pre-selected sites in the brain, it appeared logical to employ this tool to produce lesions in the pallido-pallidofugal complex of the human. This endeavor was implemented with two principal objectives in view: to enhance comprehension of the pathophysiological mechanisms underlying the hyperkinetic and hypertonic disorders (parkinsonism, chorea, athetosis, ballism, dystonia, etc.) and to improve the surgical therapy of these disorders.

The previous experience of the authors\(^46\) and that of others\(^59,60\) in using the conventional Horsley-Clarke stereotaxy made it obvious that the practice of employing cranial landmarks as reference positions for the placement of cerebral lesions is incompetent to provide the accuracy necessary to the

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\* The term, neurosonic surgery, was introduced by W. J. Fry\(^\text{18}\) in 1955 to designate the precision method of using high-level focussed ultrasound to produce selective changes in tissues of the central nervous system.
attainment of the optimal advantages of the ultrasonic method in neurosurgery. Hence, in undertaking to adapt the ultrasonic method to human use, the authors resorted to cerebral landmarks as reference positions, namely, the intercommissural line (connecting the posteromost limit of the anterior commissure to the anteromost limit of the posterior commissure) and the mid-sagittal plane of the third ventricle. In this connection, the data of the authors concerning variations in the size, shape and coordinate positions of various deep structures in the human brain were confirmed, supplemented and amplified by those of Blundell, Bailey and Amador.4

The exhibition of these landmarks manifestly required ventriculography relatively free of the artefacts inherent in pneumography. We therefore employed a radio-opaque medium in the form of a stabilized colloidal solution of thorium dioxide (25 per cent by volume). The dose used in all but two cases was 3 cc. and anteroposterior and lateral roentgenograms provided eminently satisfactory delineation of the cerebral landmarks. The roentgenograms were taken with the skull of the patient rigidly fixed with respect to the apparatus by four pinions arranged in polar opposite pairs (Fig. 1).

The head-holder frame which supports the pinions from four posts (each of which is provided with micrometers for resetting accuracy) also supports

![Fig. 1. Stage 1 of operation. Patient's head secured by four pinions “seated” in small superficial cranial burr holes at frontal and occipitoparietal sites. Adjustments on each post (P₁-P₄) supporting the pinions can be set by micrometer readings. This permits tridimensional spatial repositioning of each pinion for duplicating the position of the patient’s skull with respect to the head holder. Note pointer (Ph) carried by positioning system(s) mounted on head-holder stereotactic apparatus. A ventricular cannula, the tip of which rests in the anterior horn of the uppermost lateral ventricle, is visible.](image-url)
the roentgen-ray cassettes in fixed and duplicable positions. This head holder is also equipped with angular adjustments for attaining a desired orientation of the skull of the patient and, in addition, carries a positioning system supporting a metal pointer. The directions of motion of the positioning system (and hence those of the metal pointer tip) are parallel to the principal axes of the head holder. The shadow of the pointer appears on the anteroposterior and lateral ventriculograms along with the shadows of the cerebral landmarks as outlined by the radio-opaque material. The perpendicular projections of its tip (determined by the application of simple scaling-factor corrections to the coordinates of the tip positions as measured on the roentgenograms) can therefore be brought into coincidence with the perpendicular projections (similarly ascertained) of any desired cerebral landmark or other position determined by cerebral structures. Accordingly, it becomes possible, after removing the patient from the head holder, to place the tip of the pointer at that locus with respect to the head holder at which the target structure in the brain must be located when, later, the patient’s skull is replaced in the holder.

The ultrasonic transducer is also provided with a pointer, the tip of which, in its “lowered position,” coincides with the common focus of the four sound beams. With the patient’s head removed from the head holder, the tip of the pointer on the transducer is brought into coincidence with the tip of the pointer of the positioning system. The coordinates for positioning the transducer are thus precisely determined and can be duplicated with the irradiator pointer retracted for actual irradiation of the patient.

The target structures irradiated in the first 15 operations on 12 patients consisted of (a) the ansa lenticularis with and without portions of the medial segment of the globus pallidus and/or (b) portions of the substantia nigra and of structures bordering on its superior medial margin. As the lesion produced by the focussed beam in a single position is of considerably smaller dimensions than the target structures, production of the desired size and shape of the final lesion is accomplished by successive irradiations in an appropriately chosen array of positions for the multibeam focus.

The acoustic parameters for irradiation of the ansa lenticularis (white matter) were as follows: frequency, 980,000 cps.; duration of exposure, 2.30 sec.; acoustic particle velocity amplitude, 400 cm./sec. For irradiation of the medial segment of the globus pallidus and the substantia nigra the duration of exposure was 3.00 sec. at the same frequency and particle velocity amplitude.

From the standpoint of the clinician, the advantages of the ultrasonic technique over the anatal leucotome and electro-, thermo- and chemocoagulative procedures appear to inhere in the following circumstances. 1. Except for the ventricular cannula, no instrument needs to be introduced into the brain. 2. A precise placement and axial orientation of virtually any desired size and shape of lesion can be readily accomplished. (Simulation of
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such with coagulating needles or cannulae would manifestly require multiple penetrations and withdrawals of the instrument, with all the disadvantages inherent therein.) 3. A selectivity of ultrasonic effect upon white and gray matter and their respective neural, glial and vascular components can be realized, the order of vulnerability being that described above. 4. The problem of intracerebral hemorrhage is virtually eliminated, the only tendencies in this respect consisting of minimal diapedesis with the heaviest selective doses of sound. 5. Reversible physiological effects (currently in the stage of animal experimentation) are realizable.

On the other hand, the ultrasonic method entails the use of an expensive and elaborate instrument and a highly technically trained team. To consummate one operation requires that the patient be in the operating room for a total of 12 to 14 hours, divided in two unequal periods. Additional time is required pre- and postoperatively for calibration of the transducer, determination of the brain coordinates peculiar to the individual patient, etc. At present, bilateral operation requires two hospital admissions. However, it is not unreasonable to anticipate operating on both sides during one period.

V. SELECTION OF CASES

The present project is primarily investigative rather than therapeutic and has been arbitrarily limited to cases of parkinsonism (with and without tremor; and with and without rigidity) and nonpatterned hyperkineses (athetosis, chorea and ballismus). Candidates must appear capable of withstanding major surgery and be sufficiently cooperative to undergo two or more operations under local anesthesia. Inasmuch as the abnormal movements in the disorders under inquiry are characteristically held in abeyance during sleep and anesthesia, a state of wakefulness and sustained cooperation is at present* essential to determining the pathophysiological “end-points” of ultrasonic irradiation, namely, abolition of abnormal movements and hypertonus in the bodily members opposite the side of the brain being irradiated. It is necessary that patients, relatives and referring physicians be fully apprised of and express a willingness to accept the terms under which ultrasonic surgery can be implemented. Obviously, patients with mental deterioration, personality disorders and other psychologic aberrations that might interfere with the inquiry must for the present* be denied candidacy. Excluded from the present series are those who, because of advanced age (60 or more years) present a reduced statistical life expectancy which potentially compromises long-term follow-up studies. Preference has been given to those not yet 55 years of age who are geographically accessible for repeated first-hand check-up examinations by the investigators.

* In view of the reproducibility of physiological results from patient to patient (see below: IX. Results), it may safely be anticipated in the immediate future that operations for the relief of hyperkinesia and hypertonus can be performed under general anesthesia. This would make such operations accessible to many patients who, because of inability to cooperate, are at present excluded.
For equally obvious reasons, patients with coexisting independent disorders (cardiac, renal, pulmonary, metabolic, neoplastic, neural, arthritic, etc.) and those who have been subjected elsewhere to neurosurgical procedures aimed at the relief of their hyperkinetic and hypertonic disorders are also excluded from the present investigation on the grounds that follow-up studies might thereby be rendered equivocal.

In general, the duration of the disorder, the presence of advanced degrees of disability and the matter of unilateral or bilateral nature of affliction do not influence the selection of patients. Patients with minimal degrees of tremor and/or rigidity are, of course, excluded.

VI. CLINICAL WORK-UP

In addition to the usual history, physical and neurological examinations, urinalysis, blood counts, serologic tests, roentgenograms of the skull and chest and such special inquiries as appeared indicated for the individual case, a 14-lead electroencephalographic recording, motion pictures and a tape recording of spontaneous, responsive and reading speech were made preoperatively. Intelligent-quotient (Wechsler-Bellevue) tests were similarly administered, as were those of visual acuity and the visual fields. Finally, samples of handwriting were obtained and eupraxia, exemplified in the safety-pin test with each hand unaided, was documented in the form of motion pictures.

Postoperatively, the above-mentioned tests were performed repeatedly during the first 2 to 3 weeks after operation and, in any case, a complete set of tests was obtained within 3 to 4 months. The follow-up studies during the years to come will include repeated observations of similar character.

VII. PROCEDURE

Unilateral ultrasonic irradiation of the pallido-pallidofugal complex and/or portions of the substantia nigra and of structures bordering on its superior medial margin required the patient’s presence in the operating room on two separate occasions, 3 to 4 days apart. In all but one instance (Case 8, S.G.) Stage 1 was carried out under local anesthesia and in all instances Stage 2 was performed during local anesthesia.

Stage 1. With the patient in the sedentary posture, a template was applied over the depilated scalp to indicate positions for markings at four sites on the scalp: one pair over the frontal bosses and one over the parieto-occipital vault corresponding closely to the lambdoidal sutures. The scalp at these sites was infiltrated with procaine hydrochloride, 1 per cent, and incised to the bone. Small burr openings of approximately 5 mm. diameter were now made through the external table and partly into the diploë. Hemostasis was obtained and the patient was transferred to the ultrasonic operating table, where he rested on a well-padded air mattress in the lateral horizontal posture, the side of the head intended for operation being uppermost. The ear and eye bars of the stereotactic apparatus were then put in place and the tips of the four pinions were “seated” into their corresponding cranial burr
openings.* The pinion shafts were secured mechanically and their geometric positions were determined by micrometry. All pertinent data of position were duly recorded. The eye and ear bars were now removed.

The scalp was anesthetized locally at a region corresponding to the intersection of the coronal suture and an imaginary parasagittal line crossing it approximately 2.5 cm. from the midline. The scalp was now incised to permit the placing of a burr hole in the underlying bone. The dura mater was crucially incised, the pia-arachnoid was electrodesiccated and a small stab-blade was introduced through the leptomeninges and cortex. The scalpel was withdrawn and the tip of a ventricular cannula was introduced through the cortical opening for a distance of approximately 3 cm. in the direction of the anterior horn of the uppermost lateral ventricle. The cannula was then withdrawn and closure of the scalp was accomplished with two tiers of nylon thread.

The pointer carried by the head-holder positioning system was now placed lateral to the patient’s head with its tip in a position conveniently close (as determined by the usual stereotactic ear-bar coordinates) to the longitudinal and vertical coordinates of the target structure. A close approximation is not necessarily desirable at this time, since, if achieved, the shadow of the pointer might, for some configurations, obscure a critical portion of the shadows of the cerebral landmarks. At this time the anterior horn of the uppermost lateral ventricle was entered with a ventricular cannula, 7 to 10 cc. of cerebrospinal fluid were drawn up into a syringe containing 3 cc. of colloidal thorium dioxide and the entire mixture was re-injected into the ventricle.

A lateral roentgenogram was taken and the film was developed immediately. By appropriate use of coordinate measurements on the film and corresponding scaling factors, the perpendicular projections of the cerebral landmarks and pointer tip were determined and marked on the film. The intercommissural line was drawn and a reference position with respect to the line was marked on the film. (This reference position can be chosen for convenience; for example, its coordinates may be chosen to correspond to the coordinates of a site in the target structure.) The coordinate differences to bring the point of perpendicular projection of the pointer tip into coincidence with the reference point were determined and the pointer was moved to the new position. A second lateral roentgenogram was taken for check purposes. The position of the point of perpendicular projection of the pointer tip was now usually within $\frac{1}{2}$ mm. of the reference point (Fig. 2). The scale readings on the pointer positioning system were then recorded for use in the second stage of operation.

A somewhat similar procedure was carried out to determine the lateral coordinate scale reading on the pointer positioning system in order to place the pointer tip at the lateral coordinate corresponding to the midline of the third ventricle. Anteroposterior roentgenograms were taken for this purpose (Fig. 3).

The pinions were now removed, the scalp incisions were sutured and a dry dressing was applied. On the average, the first stage of the procedure consumed 3 to 3½ hours. Without exception, the patients exhibited diaphoresis and nausea, sometimes

* During this procedure, the patient was not required to aid in supporting his head to relieve the pressure which would otherwise be exerted on the lower ear canal by the ear bar. The necessary support was provided by a padded platform which surrounds the lower ear bar and which was adjusted in position so that the ear bar fitted snugly without producing pain.
Stage 1 of operation. First lateral radio-opaque ventriculogram showing coordinate lines relating roentgen-ray beam position to stereotactic apparatus and head position as projected on the film. The shadow of the pointer, carried by the head-holder positioning system, appears on the film. Its tip serves as an initial "bench mark" used for evaluating the longitudinal and vertical coordinates (with respect to the head holder) of the reference position in the patient's brain. The intercommissural line has been drawn between the positions of perpendicular projection of the anterior and posterior commissures. The longitudinal and vertical projections of the reference point (in this case, a "central" position in the anasal region) are computed. The position of perpendicular projection of the pointer tip's shadow is now revised to make it coincide with the reference point. The pointer is stereotactically moved to the new position and the roentgenogram is repeated.

also emesis, beginning 10 to 25 minutes after the injection of the thorium dioxide solution and lasting for a similar period. Otherwise, they withstood the procedure well and were usually able to eat their next scheduled meals.

Stage 2. This was carried out approximately 3 to 4 days following Stage 1. The purpose of the delay was to allow time for the absorption of any intracranial gas that might have been inadvertently introduced during ventriculography. Meanwhile, calibration of the instrument and determination of the irradiator coordinates for placing the focussed beam at an array of sites in the brain structure of interest in the particular patient were accomplished.

The patient was accurately re-positioned as in Stage 1, by using the cranial pinions without the necessity of employing the ear and eye bars. The pointer supported by the positioning system of the head holder was placed in the appropriate lateral and anteroposterior reference positions as determined in Stage 1. Roentgenograms (lateral and anteroposterior) were taken for each position of the pointer to
assure close duplication of the previous (Stage 1) relative positions of the patient’s skull and the pointer tip. Deviations up to approximately ½ mm. were accepted, but appropriate correction was made if the deviation was greater than about ½ mm.

A template placed relatively low over the frontal, temporal and parietal regions was next employed to indicate the site of the scalp and bone flaps. After reflexion of the scalp flap and removal of the bone flap, hemostasis of the dura mater, muscles and scalp edges was obtained. This always proved time-consuming. At its completion a specially designed support for the hopper was clamped into place and snugged up against the scalp by means of a pneumatic cuff. The hopper was then secured to it and filled with sterile, degassed physiological saline at a temperature of approximately 99° F.

The ultrasonic transducer was now swung into position and all gas bubbles were wiped away from the surfaces of the polystyrene focussing lenses. The patient was now ready for ultrasonic irradiation (Fig. 4).

Preliminary recordings of motor power, tremor rate and amplitude, degree of rigidity, cog-wheel phenomena, posture, eupraxia and other facilities of movement, deep and superficial reflexes, and cutaneous and vibratory sensibility were made as they referred to the patient’s upper and lower limbs. Irradiation was then instituted.

![Fig. 3. Stage 1 of operation. First anteroposterior radio-opaque ventriculogram, showing coordinate line relating roentgen-ray beam position to stereotactic apparatus and head position as projected on the film. The shadow of the pointer, carried by the head-holder positioning system, appears on the film. Its tip serves as an initial “bench mark” used for evaluating the lateral coordinate (with respect to the head holder) of the reference position (midline of the third ventricle) in the patient’s brain. Computations are similar to those indicated for Fig. 2 and after the pointer is moved to the new position a second roentgenogram is taken.](image)
With few exceptions, the patients reported a subjective vertigo beginning some 5 to 10 seconds after the termination of each exposure and lasting on the average for some 15 to 35 seconds.

After each irradiation, an interval of at least one and frequently several minutes was allowed to elapse before the next succeeding exposure. During this time observations were made on any modifications of tremor, rigidity, posture, cupraxis, reflexes, etc., that might have ensued. Irradiation was continued in this manner until maximal benefit with respect to hyperkinesia and hypertonia was obtained. At the end of each experiment, closure was carried out with interrupted steel wire sutures in the bone and 3–0 nylon in the muscles, fascia, galea and scalp. A dry dressing was applied.

VIII. CLINICAL MATERIAL

The salient features of the 12 patients of the current series subjected to 15 ultrasonic neurosurgical procedures are synopsized in Table I. All pa-
tients exhibited bilateral involvement. It was usually planned to operate first so as to relieve the more severely afflicted limbs.

IX. RESULTS

Acting on the basis of the previous surgical experience of one of the present authors (R.M.), and that of others, which had indicated that favorable results in the alleviation of hyperkinesia and hypertonus could be obtained by pallido-pallidofugal section, it was decided to attempt to place ultrasonic lesions in the ansa lenticularis in the early parkinsonian patients of the current series. In the first patient (Case 1, R.H.), rigidity was abol-

<table>
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<th>Case #</th>
<th>Initials</th>
<th>Age</th>
<th>Sex</th>
<th>Duration of Disease (years)</th>
<th>Classification</th>
<th>Pertinent Symptoms</th>
<th>Diagnosis</th>
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<th>Disparity</th>
<th>Etiology</th>
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<td>45</td>
<td>M</td>
<td>5</td>
<td>P</td>
<td>Tremor and rigidity</td>
<td>Minimal</td>
<td>R&gt;L</td>
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<td>49</td>
<td>M</td>
<td>33</td>
<td>P</td>
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<td>Severe</td>
<td>R&gt;L</td>
<td>Postencephalitic</td>
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<tr>
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<td>P.I.</td>
<td>50</td>
<td>M</td>
<td>30</td>
<td>P</td>
<td>Tremor and rigidity</td>
<td>Moderate</td>
<td>L&gt;R</td>
<td>Postencephalitic</td>
<td></td>
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<td>M</td>
<td>4-6</td>
<td>P</td>
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<td>Moderate</td>
<td>R&gt;L</td>
<td>Arteriosclerosis (?)</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>E.B.</td>
<td>51</td>
<td>M</td>
<td>4-9</td>
<td>P</td>
<td>Tremor and rigidity</td>
<td>Moderate</td>
<td>R&gt;L</td>
<td>Undetermined</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>M.G.</td>
<td>15</td>
<td>F</td>
<td>15</td>
<td>A</td>
<td>Abnormal movement and rigidity</td>
<td>Severe</td>
<td>R&gt;L</td>
<td>Birth trauma</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>K.F.</td>
<td>49</td>
<td>M</td>
<td>15</td>
<td>P</td>
<td>Tremor and rigidity</td>
<td>Moderate</td>
<td>L&gt;R</td>
<td>Undetermined</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>S.G.</td>
<td>50</td>
<td>M</td>
<td>5-15</td>
<td>P</td>
<td>Tremor and rigidity</td>
<td>Severe</td>
<td>R&gt;L</td>
<td>Undetermined</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>R.M.</td>
<td>38</td>
<td>F</td>
<td>3-6</td>
<td>P</td>
<td>Rigidity, minimal tremor</td>
<td>Severe</td>
<td>R&gt;L</td>
<td>Undetermined</td>
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</tr>
<tr>
<td>10</td>
<td>A.G.</td>
<td>44</td>
<td>F</td>
<td>3-4</td>
<td>P</td>
<td>Rigidity, minimal tremor</td>
<td>Severe</td>
<td>R&gt;L</td>
<td>Postencephalitic</td>
<td></td>
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<tr>
<td>11</td>
<td>M.S.</td>
<td>52</td>
<td>F</td>
<td>7-10</td>
<td>P</td>
<td>Tremor and rigidity</td>
<td>Severe</td>
<td>L&gt;R</td>
<td>Undetermined</td>
<td></td>
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<tr>
<td>12</td>
<td>A.N.</td>
<td>50</td>
<td>M</td>
<td>2-15</td>
<td>P</td>
<td>Tremor and rigidity</td>
<td>Severe</td>
<td>L&gt;R</td>
<td>Undetermined</td>
<td></td>
</tr>
</tbody>
</table>

A = Athetoid (tension and abnormal movement)
P = Parkinson’s disease
L = Left
R = Right
> = Greater than
* = Time required for progressive involvement of all limbs.

In the next 2 patients (Case 2, R.R., and Case 3, F.L.), ultrasonic irradiation of the ansa lenticularis resulted in prompt abolition of both rigidity and tremor. But again, in the fourth patient (Case 4, C.M.) irradiation of the ansa lenticularis resulted (very like that of Case 1) in abolition of contralateral rigidity without reduction in tremor. It was therefore decided in this instance to irradiate 5 to 6 mm. posteriorly to the "central" region of the ansa lenticularis where it emerges from the globus pallidus, the purpose being to explore here the possibility of alleviating the tremor. The first lesion placed in the new site resulted in prompt reduction of tremor without neurologic deficit and further irradiation at neighboring apposite sites led
to complete abolition of contralateral tremor—again without neurologic deficit. In the next 2 patients (Case 5, E.B., and Case 7, E.F.) irradiation of the ansa alone resulted in abolition of both tremor and rigidity.

Post-irradiation observations on these patients revealed in one instance a perceptible return of tremor by the end of a week, although in no sense equivalent to that noted preoperatively. In 3 other patients (Cases 2, 3 and 5) a minimal tremor was detectable between the first and second weeks postoperatively. Accordingly, it was decided to irradiate the next 3 patients (Case 8, S.G., Case 9, R.M., and Case 10, A.G.) at the new site posterior to the ansa, at the ansa itself and at the medial segment of the globus pallidus. This plan was first implemented in Case 8 and, in addition, several lesions were placed medial to the ansa at anteroposterior and vertical coordinates corresponding to those of the ansal irradiation. In Cases 8, 9 and 10, alternating tremor was completely abolished in the contralateral limbs. In Case 9, rigidity also was completely relieved. However, in Cases 8 and 10 a negligible rigidity persisted in one synergic muscle group of each patient, namely, the forearm flexors in Case 8 and the quadriceps femoris muscles in Case 10.

An analysis of the clinical results of irradiation obtained up to this point—especially of those following irradiation of the novel site posterior to the ansa—and a comparison of atlas coordinates with the coordinates of irradiated positions at the posterior site suggested that irradiation of the substantia nigra complex alone, or a portion thereof, carried considerable promise of eliminating both tremor and rigidity. Accordingly, in Case 11, M.S., Case 12, A.N., Case 1, R.H. (in whom operation on the left side was repeated), and Case 7, E.F. (in whom an operation on the right side, opposite that of the first procedure, was performed) a portion of the caudal half of the substantia nigra and its superior medial neighborhood (Forel's field H2) was irradiated. Contralateral tremor was promptly and completely abolished in all 4 cases. Rigidity was likewise completely abolished in Case 11 but in Case 12 a minor degree of rigidity persisted in the flexor and extensor muscle groups of the forearm and in Case 7 a similarly small degree of rigidity persisted in the hamstring muscles. In Case 1, no rigidity had been present since the first operation on the same side, performed 5 months earlier.

Unanticipated complications developed in 3 of the parkinsonian series. In Case 8, apathy developed on the second day following operation and has persisted up to the present. This state appears imputable to the circumstance that irradiation was intentionally carried out closer to the midline in this case than in any other cases of the series. The hypothalamus may have been inadvertently involved. In Case 7, a left hemiplegia with mutism appeared toward the end of the day following operation. The mutism cleared after 3 weeks and the hemiplegia was gradually replaced by a hypotonic, hyper-reflexic hemiparesis, permitting ambulation. In Case 9 a right hemiplegia and aphasia developed 2 days following operation. The paralysis began to recede during the third week and ambulation was accomplished after 2 months. Highly useful speech, in which dysphasic features are discernible
chiefly when the patient is fatigued, has been regained. A spastic, apraxic and hyperreflexic hemiparesis persists.

In addition to the 11 parkinsonian patients, 1 cerebral palsy patient (Case 6, M.G.) suffering from severe tension athetosis and so-called quadriplegia was subjected to ultrasonic irradiation. At her first operation, the left ansa lenticularis alone was irradiated. Abnormal movements and hypertonic tension of the right upper limb were completely abolished. Tension was likewise abolished in the right lower limb, but athetoid movements of greatly reduced amplitude as compared with those observed preoperatively persisted. Mechanical shortening of the hamstring muscles, caused by chronic preoperative flexion contracture, limited full passive extension of the right leg and thigh.

Postoperative observations on this patient during the ensuing 3½ months revealed an absence of hyperkinesia in the right upper limb and but weak athetoid movements in the lower limb in conditions of repose. The reduction of abnormal movements and hypertonus permitted her to sit in a wheel chair without strap supports, such as had formerly been required, and she was able to assume a more natural sitting posture with the lower limbs in the dependent position. During habilitative training at the Hospital School of the State University of Iowa, the patient gained some voluntary movements of the right arm, forearm, hand and fingers. This made possible the performance of purposive acts of which she had formerly been wholly incapable, e.g., bringing the right hand to her mouth. Although crudely adaptive, such movements were characterized by intention ataxia. Under conditions of noxious stimulation and other situational stresses, the patient exhibited weak athetoid movements of the right-sided limbs. A highly gratifying improvement recorded postoperatively bore reference to the patient's ability to eat. Prior to operation, the bringing of food to the lips almost regularly evoked an athetotic outward thrusting of tongue and lips, causing forceful ejection of food and rendering the act of feeding a long, drawn-out process. Following operation, she accepted and swallowed food with nearly normal facility.

This patient's second operation was performed on the opposite (right) side, 3½ months following the first procedure. Irradiation of a major portion of the caudal half of the right substantia nigra and its superior medial neighborhood resulted in complete elimination of athetotic movements in the hand, fingers, foot and toes of the left side and almost complete abolition of hyperkinesia in the more proximal members of the corresponding limbs. Although tension hypertonus was greatly reduced in the entire left upper limb, passive movements during and subsequent to operation revealed some persisting resistance (preoperative contracture?) at the biceps and triceps muscle groups. In the left lower limb, hypertonus was likewise notably reduced and such passive resistance as remained seemed imputable to persisting mechanical shortening of calf and thigh muscles because of chronic preoperative contractures.
One untoward operative sequel in this case consisted of a right conjugate ocular deviation which gradually regressed after 7 weeks.

X. DISCUSSION

As the maximal period of postoperative observation of patients in the ultrasonic series is but 5 months, the present report, concerned as it primarily is with pathophysiological rather than therapeutic considerations, should be regarded as comparable to a report bearing on acute and subacute animal experiments. The data here submitted are likely to have significance chiefly for the student of speculative neurology and theory.

A comparison of the results of irradiating the geometric region considered to correspond to (a) the ansa lenticularis alone (6 operations), (b) a portion of the substantia nigra and of its immediate superior medial neighborhood (5 operations), (c) the ansa lenticularis plus sites posterior to it as described above (1 operation) and (d) the ansa lenticularis plus the posterior sites plus portions of the medial segment of the globus pallidus (3 operations) indicates that the most economical manner thus far employed for simultaneously alleviating hyperkinesia and hypertonus, as judged in terms of numbers of positions irradiated, duration of relief obtained and smoothness of postoperative course, consists in irradiating a portion of the caudal half of the substantia nigra and its superior medial neighborhood.

The studies also show that, with respect to relief of rigidity, there exists in the geometric region corresponding to the ansa lenticularis a somatotropic differentiation in at least some patients between representations of the upper and lower limbs, namely, a rostro superior region corresponding to the contralateral upper and, continuous with it, a caudo-inferior region corresponding to the lower limb. In the present series of 9 patients irradiated in this region, more exhibited this phenomenon than otherwise. (The phenomenon was not suspected at the outset but was gradually revealed as experience grew.) The extent of overlapping and the variation of the representation from one patient to another requires further investigation.

A topographic differentiation between neural representations of the flexor and the extensor muscles of the limbs has also been observed in some individuals. Whether this is characteristic of all individuals with different neural counterparts of the upper and lower limbs in the region of the "ansa" cannot be decided with our present limited data. Again, further observations directed specifically at elucidating this problem are required.

In Cases 1 and 4 ultrasonic irradiation of the "ansa region" abolished rigidity but did not appreciably reduce tremor in the contralateral limbs. In Case 8 rigidity was nearly completely eliminated, but again the tremor persisted. While this circumstance of preservation of tremor after effectual elimination of rigidity did not obtain in the other 4 patients so irradiated, the fact that it did so in 3 instances indicates that the neural mechanism mediating tremor is not always identical or even very closely concurrent
with that mediating rigidity. On the other hand, in all 4 parkinsonian patients and 1 tension athetoid in whom a portion of the “nigral region” was irradiated alone, tremor was abolished in the contralateral limbs and rigidity was simultaneously reduced to a minimum. In the tension athetoid patient (Case 6), ultrasonic irradiation of a portion of the “nigral region” was followed promptly by complete abolition of hyperkinesia in the contralateral limbs and by all but complete elimination of tension hypertonus. As there was no exception to this observation, it appears that the neural mechanisms subserving tremor and rigidity course in close proximity to or perhaps intertwine with one another through, within or in the immediate superior medial neighborhood of the substantia nigra, including Forel’s field H2. It is not beyond the theoretical possibility that, at least in respect to this region, the two mechanisms share neural components in common.

It is apparent that the therapeutic value of ultrasonic irradiation of the structures attacked in Cases 1 to 12 cannot be decided until rigorous examinations have been periodically implemented over the course of several years. In point of fact, nothing short of a life-time follow-up study of these patients will furnish reliable data on the basis of which dependable predictions may be formulated. In future patients, especially those presenting moderate hyperkinesia and hypertonus, it may prove desirable to induce prophylactic lesions at sites beyond those required for immediate therapeutic purposes.

The clinical observations following ultrasonic surgical procedures must eventually be supplemented by data derived from postmortem examination of the brains of all patients subjected to irradiation. Only intensive histological studies of such material can make possible a complete spatial reconstruction of the sonically induced lesions. Meanwhile, pending the acquisition of palpable evidence of this sort, an indication of the accuracy of placement of the ultrasonic lesions at the desired sites can be inferred from the fact that in all 5 “nigral” cases the first lesion, having a diameter of the order of 1½–2 mm., a length of 4–5 mm., and being geometrically aimed at the same target, namely, the region common to the dorsal and lateral thirds of the substantia nigra and structures neighboring upon its superior medial margin at the coronal level 7 mm. anterior to the anterior tip of the posterior commissure, produced marked reduction or complete elimination of hyperkinesia and hypertonus (Fig. 5). Several neighboring lesions were subsequently added in each case to abolish any hyperkinetic residues and/or to assure sustained clinical benefit.

Finally, on the basis of experiences obtained thus far, it appears that any favorable modification of hyperkinesia and hypertonus that can be obtained by the use of leucotome or electro-, thermo- and chemocoagulation can be duplicated by ultrasonic lesions. The greater accuracy of placement and tissue selectivity of ultrasonic lesions and hence the potential for greater safety appear to offer certain advantages over therapeutic procedures that entail penetration of the brain by a material instrument.
1. In the effort to alleviate hyperkinesia and hypertonus without imposing clinically perceptible neurologic and psychologic deficits on patients suffering from parkinsonism, chorea, athetosis, ballism and dystonia, interruption of the pallido-pallidofugal complex was found effective in 1940. However, the technical difficulty of executing the operation by the conventional surgical techniques then available limited its implementation. This prompted efforts to make the procedure more safe, in consequence of which

Fig. 5. Approximate site (illustrated by black spindle) in the superior medial neighborhood of the substantia nigra at which the first ultrasonic exposure in each of the five “nigral” irradiations was made. Irradiation here was promptly followed by reduction (or in some cases abolition) of tremor and by decreased rigidity. Additional exposures were placed in neighboring sites in coronal planes 1½ to 2 mm. anterior and posterior to the first site and in some cases more than one exposure was placed in the same coronal plane. Other sites, at which lesions were placed in the border zone and within the substantia nigra, are illustrated semidiagrammatically by the white spindles of the figure. However, the configuration illustrated does not correspond to the array of exposures produced in any patient since the brain section of the figure does not lie in a coronal plane and so consequently the long axes of neighboring sites of exposure could not lie in the plane of this section. It should not be assumed that a complete set of four lesions, in the form of the array schematically illustrated here, was produced in all coronal planes in which lesions were placed.

electro-, thermo- and chemocoagulation under stereotactic control emerged following World War II.

2. The development of a focussed multibeam ultrasonic instrument by means of which tissue components of the central nervous system can be selectively affected for the production of lesions of predetermined size, shape and position in the brains of experimental animals offers a safer and more precisely controllable tool for neuroanatomic, -physiologic, -pathologic and surgical investigation than any heretofore employed. The neural parenchyme is most, and the vascular tissue least vulnerable to the action of the ultrasound. With certain modifications, this instrument has been redesigned and adapted to human use.
3. Eleven patients with severe bilateral parkinsonism and 1 patient with severe bilateral athetosis have now been subjected to 15 operations. Two of the patients have had bilateral ultrasonic irradiation and 1 has had re-operation on the same side as that initially implemented. The procedures were performed during local anesthesia.

4. All 9 parkinsonian patients irradiated at the ansa lenticularis alone were promptly relieved of rigidity. In 4 of these, tremor was simultaneously abolished and in 2 others, was a negligible feature of the initially presenting clinical picture and was imperceptible at the operating table. However, tremor persisted in 3 patients thus irradiated. In the latter cases, the tremor was subsequently eliminated by irradiation at more caudally situated sites.

Within 3 weeks of operation 5 patients exhibited clinical manifestations which were interpreted as representing some decrements in the gains realized during operation and for the ensuing several days. Follow-up data on these patients obtained during the next several months revealed that the decrements were transient in 3 patients and enduring in the remaining 2.

In view of the early postoperative decrements just mentioned and the primarily experimental objectives of the program, irradiation was performed in the 5 most recent operations at the geometric site (alone) corresponding to portions of the substantia nigra and its immediate superior medial neighborhood. In all cases the first exposure promptly reduced the tremor in at least one and, more often, in both contralateral limbs. Rigidity was simultaneously reduced following this first exposure. (One patient who had been relieved of rigidity by irradiation of the “ansal region” alone 5 months previously, but whose tremor had not been alleviated, was completely relieved of tremor in both contralateral limbs on the first exposure.) Further exposures of the “nigral region” resulted in complete relief of tremor and complete or nearly complete alleviation of rigidity.

5. With regard to relief of rigidity in parkinsonian patients, a somatotopic differentiation in the “ansal region” is recognizable in at least some patients: a rostrosuperior region corresponds to the contralateral upper; and a caudo-inferior region to the lower limb. This differentiation was observed more often than not. In addition, a topographic differentiation in the “ansal region” between neural representations of the flexor and extensor muscles of the contralateral limbs has been noted in some patients.

6. In some parkinsonian subjects, irradiation fully encompassing the “ansal region” was not followed by reduction of tremor, even though rigidity was abolished in the contralateral limbs. This observation indicates that in such individuals tremor is mediated by a different neural mechanism than that subserving rigidity.

On the other hand, irradiation of the “nigral region” was always followed by prompt abolition of tremor and simultaneous reduction of rigidity. Since this was true in all cases, it may be deduced that the portion of the neural mechanisms subserving tremor and rigidity in the “nigral region” are here closely associated, perhaps even share neural components.
7. In the single case of quadriplegic tension athetosis the patient was irradiated at the "ansal region" on the left side and, 4 months later, at the "nigral region" on the right. The hypertonus (ebbing and flowing tension) was reduced in the contralateral limbs, possibly to the degree representing the muscle shortening of pre-existing contractures. As to the hyperkinesia in this case, involuntary thrusting movements of the tongue and lips subsided following the left "ansal" irradiation, permitting facile feeding for the first time in years. The athetotic movements in the limbs of the right side were generally reduced in vigor, amplitude and frequency and, during repose, were in abeyance. Crude purposive acts could now be executed with the right upper limb. The athetosis of the left-sided limbs was completely abolished following "nigral" irradiation on the right. Purposive movements were not noted on the limbs of this side during the first 3 postoperative weeks.

REFERENCES


5. Broager, B. Cerebral pedunculotomy in four cases of hyperkinesia. (Three cases of choreoathetosis and one of rhythmic tremor.) Acta psychiat., Kbh., 1955, 30: 107-114.


EXPERIENCES WITH ULTRASONIC IRRADIATION


45. Meyes, R. Discussion of Carpenter.11


