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TOPICAL DIFFERENTIA OF PATHOGENETIC
MECHANISMS UNDERLYING PARKINSONIAN TREMOR
AND RIGIDITY AS INDICATED BY ULTRASONIC
IRRADIATION OF THE HUMAN BRAIN

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We have carried out a series of ultrasonic irradiation procedures on 18 cases of parkinsonism and two of cerebral palsy of the tension athetotic type. All procedures were performed during local anesthesia, thus enlisting the active cooperation of the patients. There was no operative mortality.

The ultrasonic method of producing lesions in the central nervous system enjoys a number of advantages over other procedures. The focus of the ultrasonic beam or beams can be placed at a series of sites in the brain without entailing multiple penetrations of any instrument. Lesions of virtually any desired size and shape can be accomplished and determined by results noted during the procedure. All neural components can be destroyed without disruption of the vascular system within the lesion site. By appropriate control of dosage it is possible to interrupt the fibre tracts of white matter without disrupting adjacent or neighboring gray matter which receives the same dosage of ultrasonic radiation.

The instrument employed for humans represents an adaptation of that previously developed for fundamental animal studies. It uses brain landmarks demonstrated by radio-opaque ventriculography, rather than the bony landmarks utilized in the studies on the cat and monkey. The patient's head is supported by four stainless steel pins the rounded tips of which fit into burr holes of equal diameter in the outer table of the skull. A pointer mounted on the positioning system, the directions of motion of which coincide with the principal axes of the head holder, is utilized for determining the coordinates of appropriate brain landmarks with respect to the head holder. The brain landmarks currently in use, namely, the posterior tip of the anterior commissure and the anterior tip of the posterior commissure, are clearly delineated. The pointer tip necessarily appears on the ventriculogram. From measurements made with respect to coordinate lines scribed on the ventriculogram, longitudinal and vertical coordinates of appropriate landmarks or reference points in the brain can be determined. Comparable measurements from an A-P ventriculogram provide values for the lateral coordinates.

On the day of irradiation a low, lateral bone flap is removed. The dura mater is left intact. A bottomless hopper is placed over the opening and made water-tight against

the scalp. The hopper is filled with degassed sterile saline at body temperature, as shown in the slide. The four-beam ultrasonic irradiator, here shown in position over the top of the hopper, is then lowered into the saline and set so that its focus lies at the first target site intended for irradiation.

The frequency of the ultrasound used in the current series is 980,000 cps. In all but one of the 25 procedures carried out to date, the particle velocity amplitude was 350 cm/sec. at the site of the lesion. The exposure time ranged from 1.80 to 3.00 seconds, depending on the structure to be affected. In one procedure, acoustic parameters were employed which repeatedly produced reversible physiologic effects, namely, abolition and reappearance of tremors. This observation was then followed by irradiation with dosage parameters which resulted in enduring abolition of tremors.

To date, the ultrasound has been aimed at the following sites: the ansa lenticularis as it leaves the globus pallidus; the medial segment of the globus pallidus; the superior medial neighborhood of the substantia nigra; the caudal half of the substantia nigra; the medial part of the corpus Luysi; and portions of the tegmental field of Forel. A series of lesions were produced in each case and changes were observed regarding the following phenomena after each exposure: deep and superficial reflexes—especially as to whether signs of “pyramidal system” dysfunction appeared; vibratory and cotton wool perception; motor power (dynamometrically determined); nonequilibratory coordination; postural set of the limbs in repose; rigidity, including the cog-wheel phenomenon; eupraxia; abnormal movements; speech articulation; vital signs; and state of responsiveness (“consciousness”).

Only a brief summary of our results is presented here. It is necessary to divide the procedures into several categories and to comment on each separately.

In the “ansal” region it was possible to reduce contralateral rigidity and in some patients to eliminate contralateral tremor by irradiation of the sites indicated in the slide. This illustrates three frontal sections at 1 mm., 3 mm., and 4.5 mm. posterior to the posterior tip of the anterior commissure. Irradiation at these and at corresponding sites in intervening tissues resulted in the reduction of rigidity and, in some instances, in abolition of tremor. Three patients exhibiting severe rigidity, two of whom had minimal and one, severe tremors, were irradiated along the medial border of the medial segment of the globus pallidus. Contralateral rigidity and tremors were abolished in all three.

In a somewhat larger series of 10 cases, irradiation in the superior medial neighborhood of the substantia nigra invariably resulted in abolition of contralateral tremor. Contralateral rigidity was simultaneously reduced and the residue eliminated by irradiation within the substantia nigra.

In the majority of our cases signs of “pyramidal system” dysfunction were not elicitable during repeated testing at the operating table when tremors and/or rigidity were clearly in abeyance. Our findings thus fail to support Bucy’s contention that abolition of tremor requires damage to the pyramidal tract—at least, if the conventional clinical signs be taken as indicative of such damage.

Dysarthric, monotonous and low-volume speech and masked facies are apparently uninfluenced. However, bradykinesia and certain deranged auto-

matic associated movements have been favorably affected and in some cases virtually eliminated.

Both in the "ansal" region and the superior medial neighborhood of the substantia nigra evidence of a somatotopic representation of the contralateral upper and lower limbs with regard to the alleviation of hypertonus and hyperkinesia was demonstrated. Thus, in some cases the tremor was eliminated only in the upper limb by irradiation at one or several sites that were consistent from one patient to another. Elimination of tremor from the lower limb, however, required irradiation at other similarly consistent sites. A comparable somatotopic representation with respect to the relief of rigidity was also observed and, in addition, a discernible central topology of flexor and extensor synergic muscle groups was observed.

Our last three parkinsonian patients were irradiated bilaterally through a single craniotomy opening at one operation. On the side ipsilateral to the bone flap, the superior medial neighborhood of the substantia nigra was irradiated in all three. In two of the three the ipsilateral ansal region was also irradiated at a few sites. The result was elimination of contralateral tremor and rigidity. Homotopic lesions were similarly placed on the side contralateral to the bone flap. However, because of the orientation of the beam axis, portions of the medial part of the corpus Luysi, the tegmental field of Forel and the fasciculus lenticularis as it travels in field H2 were also irradiated on the second side. Here again, tremor and rigidity were completely eliminated from the contralateral limbs.

The dimensions of a lesion following a single exposure vary with the dosage and the tissue of the target site, but for the dosages quoted here a diameter of 1 to 1.5 mm. and a length of 3 to 4 mm. would be reasonably typical. Some indication of the total number of exposures required for elimination of tremor and rigidity in all four limbs inheres in the fact that the first patient so treated received 27 irradiations at different sites, the second, 10 and the third, 13.

With respect to the cerebral palsied patients, it is apparently possible to eliminate or greatly reduce athetotic movements and fluctuating muscle tension without impairing "voluntary" movement. However, since only two such patients have been irradiated thus far, this statement should be viewed as tentative and subject to modification as more patients are treated.

Further investigation by this method promises elucidation of the mechanisms of the hyperkinetic and hypertonic disorders. From the therapeutic viewpoint we incline to believe that in most cases tremor and rigidity can be relieved bilaterally at one procedure. Moreover, it seems highly likely that as experience grows successful operations can be performed during general anesthesia on patients incapable of sufficient cooperation.

We have planned to attack other problems, including those related to intractable pain and before concluding wish to indicate that we have recently initiated this phase of our study. A middle aged male with severe

phantom limb pain was irradiated in the ventral posterolateral nucleus of the thalamus. He was completely relieved of his phantom. This result was accomplished without loss of motor power, but entailed some loss of vibratory, tactile, thermal, position and pain senses on the side opposite the irradiation. The patient retains good coordination of the corresponding limbs (e.g., the heel-to-shin act).

We plan to attack other intractable pain problems, such as post-herpetic and thalamic pain, tic douloureux, atypical facial neuralgia, etc., in the immediate future.

E. M. HOUSEPIAN: Dr. Fry and his associates are to be congratulated for this development of ultrasound stereotaxy as a clinico-investigative tool. The success of this group clearly shows that there are still rich rewards for idealists who strive for perfection. There is no doubt that the creation of a circumscribed lesion of predetermined configuration, localized by precise stereotaxic methods, and checked by subliminal impulses with reversible effects is an achievement which previously was believed to be an unattainable goal.

As Dr. Fry has suggested it seems naive to believe that we can unravel the enigma of the pathophysiology of dyskinesias by an elementalistic surgical approach; and yet, we are not yet able to discuss general theories. Nevertheless, I would like to present briefly some of our own findings which substantiate Dr. Fry's present report by providing histological confirmation of some of the lesion sites in question.

In the last 17 pallido-ansectomies at the Neurological Institute of New York, Dr. Pool and I have used a leukotome which cores out a 1 cm. sphere of tissue, and with which we are able to obtain biopsy confirmation of our lesions. During these procedures we have observed that lesions made in the medial segment of the globus pallidus reduce tremor but do not alter rigidity significantly, and that when the leukotome is advanced as little as 2-3 mm., presumably placing it within the ansa lenticularis, there is instantaneous melting away of rigidity in the contralateral extremities. We agree, therefore, that the ansa is implicated in the maintenance of rigidity and can report moderate to marked alleviation of rigidity without paresis in 87% of our last 15 Parkinson patients undergoing pallido-ansectomy.

Lesions of the medial segment of the globus pallidus have alleviated but not abolished tremor in 70% of this group; but, whereas the relief of rigidity has been lasting, we have observed some return of tremor within 7 to 12 days in over one-half of these patients.

Although we have already agreed that it is still too early to propose general theories, it is tempting to suggest a skeleton hypothesis which seems to tie together pretty well the physiological and clinical studies to date: The principal projections of the substantia nigra are to the striatum and (via the ansa lenticularis) to the globus pallidus and thalamus. Though there is a convergence of pallidal afferents from various sites, the principal outflow of the globus pallidus appears to project largely to the antero-ventral and ventro-lateral nuclei of the thalamus. The reticular formation, via the reticulo-spinal tract, has been implicated in tremorgenesis, yet there is no demonstrable *direct* connection between the pallidum and the reticular formation. Dr. Carpenter has recently suggested that perhaps this relay occurs via thalamic projections to the cortex, thence by corticoreticular fibers to the mesencephalic pantine and medullary reticular formations.

I would like to comment on the akinesia which Dr. Fry discussed, and emphasize one outstanding observation from our studies. We have been impressed with the finding in 35 patients undergoing pallidal surgery, that general improvement has not always

accompanied marked objective improvement in tremor and rigidity. This surgical dissociation of rigidity and tremor from the remainder of the Parkinsonian symptom complex has clearly suggested that hypokinesia (or bradykinesia), when present, must be considered as a distinct and separate incapacitating symptom; that it is unrelated to rigidity and therefore not affected by pallido-ansal surgery. In Parkinsonism, it seems appropriate to consider the wide variation of clinical manifestations as a direct reflection of diffuse and varied cerebral pathology.

I would like to ask whether ultrasound is feasible for palliative hypophysectomy. I wonder too, if the authors have investigated the selective susceptibility of tumor cells to sound destruction.

WILLIAM H. SWEET: Dr. Meyers and his associates have made an outstanding contribution to our knowledge of involuntary movement disorders in their demonstration that lesions in the region of the substantia nigra will relieve tremor and rigidity. Dr. Meyers was the first to demonstrate that lesions in the neighborhood of the medial globus pallidus were likewise potentially successful in this disorder.

I would go along with Dr. Guiot, of Paris, in describing that first contribution, when he said of Russell Meyers, "*Voilà l'homme de génie.*"

I am amazed that the ultrasonic lesion in the substantia nigra seems to have the effect described. In our own considerations of this problem, the fact that the pathological material in patients with parkinsonism more consistently reveals lesions in the substantia nigra than elsewhere, made this a site to be avoided in the making of additional lesions, rather than one to be sought. Although we know that in parkinsonians there are lesions throughout the pallidum as well, these are less consistent. I had assumed we were achieving success by making lesions here because of the possibility that the lesions in the globus pallidus caused by the initial disease were not causing the tremor and rigidity. I think this hypothesis now becomes much less tenable in view of the demonstration of the results following lesions in the substantia nigra. I find it impossible personally to understand the pathophysiological mechanisms when consistent major lesions in the substantia nigra are apparently correlated with the appearance of tremor and rigidity. Why we can hope to relieve these manifestations strikingly by increasing the lesion here is, obscure to me. I should like to know the reasoning which led Dr. Meyers to go ahead and make such lesions.

The essayists have referred to the complexity of the problem and I should like to cite a single case that illustrates that. A patient who, following a lesion of the globus, had had satisfactory relief of contralateral tremor and rigidity, suddenly went into an unresponsive state on his second postoperative day with a hemiplegia in those limbs. He gradually recovered in a gratifying way in the course of about a month, excellent strength, without evidence of tremor or rigidity recurring in those limbs. But at the same time rather abruptly he developed a severe rigidity with the sort of fixation of the ipsilateral upper limb one sees in parkinsonians of many years' standing. This limb had prior to these episodes been only mildly afflicted. This sequence of events indicated that while a large lesion released an earlier contralateral tremor and rigidity, it was perhaps capable of pushing such signs to an even greater degree ipsilaterally.

I am at a loss to understand whether or not the complex maneuvers involved in making a four-beamed focussed lesion with ultrasound are really worth the trouble in many patients. By far simpler means, a lesion can be placed in a predetermined site within the brain in man and the only advantage that I can see to this system, would be that it may be possible differentially to destroy certain portions of the tissue within a given area, white matter say, as opposed to gray matter. Otherwise, it seems to me that the submission of a patient to this extensive, protracted procedure has less to commend it than a variety of other methods some of us are using.

I would like also to ask about other possible results, sequellae, or ancillary features

in the behavior of these patients. Have any of them had any awkwardness of the limbs upon which you have been seeking to influence movement? Have there been any patients who had a tendency not to use the limb, even though it appeared to have no obvious neurological deficit, the syndrome of Browder and associates? Have there been any other side effects, disturbances in mentation or abilities on any other scores than those related to motor symptoms?

PAUL C. BUCY: This is an important presentation—primarily because we see further evidence of the fact that studies are being made in the only way that they can be made to understand the neurological mechanism which controls muscular activity, whether it be normal or abnormal, and that is the study in man. Obviously, in this preliminary report—we do not have the answers. The answers will come only with prolonged study and with detailed controls. In this instance in particular we are lacking in anatomical controls. We know where Dr. Fry and Dr. Meyers wish to make these lesions. We shall wait to learn where they have made them.

This study illustrates the great complexities of the neurological control of movement. That these investigators have been able to influence tremor and rigidity by lesions in a variety of locations only serves further to emphasize that complexity.

Dr. Fry has stated that their observation tends to disprove the hypothesis which I advanced many years ago that the existence tremor requires that the corticospinal fibers from the precentral gyrus be intact. I still do not know whether that is true. It was advanced as a hypothesis. It remains a hypothesis, not a proven fact; but it is still a possibility. Until these investigators have accurate anatomical controls of the lesions they have made correlated with long term clinical and physiological observation they will not have proved or disproved anything. The fact that they do not find clinical evidence of damage to the "pyramidal tract" is meaningless, and I am sure that Dr. Meyers will agree.

RUSSELL MEYERS: Those engaged in studies of the hyperkinetic and hypertonic disorders welcome the kind of evidence that Dr. Housepian and his associates are bringing to us in consequence of making discrete lesions during pallido-ansal surgery. Biopsy confirmation of the tissues removed during such surgery must be recognized as an important advance. There remains, of course, the important question as to the locus and quantum of the damaged tissue which remains in the brain following the use of the leukotome. For, aside from the tissue removed, we are bound to recognize that some tissue remaining in the brain has been devitalized. It is safe to suppose that some tissue in the immediate neighborhood of that removed is devitalized in consequence of direct mechanical trauma and that some is devitalized in consequence of thrombotic interruption of arterial blood supply and/or venous drainage or of extravasation of blood into the ground substance. We need not doubt that the clinical result, for good or ill, is quite as much imputable to such inadvertent damage as to the deliberately ablated tissue. But apart from such reservations, it can be said that our own experience concerning the readiness of obtaining relief of tremor by surgical measures as compared with that of rigidity corresponds closely to that described by Dr. Housepian.

A few words are in order regarding what is done *in principle* when a surgical attack is mounted against the hyperkinetic and hypertonic disorders. In the first place, no procedure thus far developed is deliberately directed against the lesions in the brain responsible for these disorders. In point of fact, we do not know the pathogenesis of any of these disorders. Hence, it follows that until such knowledge is arrived at it would not be feasible to plan the attack along such lines, even if this seemed promising. All the surgical procedures that have been devised up to now, namely, those employed prior to World War II and the more recent modifications of them, in which the adjunct of stereotaxy is generally employed, aim to interrupt at some convenient place a portion of a complicated neural circuit, the integrity of which is conceived to be an

essential condition for the appearance of the abnormal movements and/or abnormal muscle tonus. It now appears that such can be accomplished at a number of places in the nervous system: at the cortical level, at the capsule, in the pallido-pallidofugal complex, the ventrolateral thalamic region, the substantia nigra and Forel's field H₂, the midbrain peduncle and the spinal cord. It remains for us to determine the site or sites at which such procedures can be carried out most expeditiously and with the least threat to life and function. The ultimate hope of all of us is that we may witness the development of a useful drug or biological agent which will completely obviate the necessity of surgical attacks. Meantime, we must fully exploit the information that is acquired in consequence of surgical efforts. Another important comment in this connection is that the most salutary effects of surgery are on the signs of tremor and rigidity. Inasmuch as parkinsonism encompasses many other abnormal signs and symptoms than tremor and rigidity, it is inaccurate to speak of the "surgery of parkinsonism" or of the "extrapyramidal diseases" in general. We are at liberty at present to speak only of the surgery of tremor, non-patterned hyperkinesias and rigidity. If we adhere to this sort of terminology we will avoid many unfruitful discussions.

The statement has been made that the "akinetie" symptoms of parkinsonism are not influenced by the surgical procedures directed against parkinsonism. This is not quite correct, in my experience. "Akinesia" has generally been used to encompass all symptoms other than tremor and rigidity, e.g., poverty of movement, bradykinesia, masked facies, low, monotonous and dysarthric speech, defects in automatic associated movements and so on. I have never seen the speech of the parkinsonian patient improved by any surgical measures. However, I have not infrequently seen bradykinesia appreciably improved, micrographia disappear and automatic associated movements, such as those seen in walking, return to a normal or near-normal level following surgery. This to me suggests that we need to revise the signs and symptoms that have conventionally been subsumed under the name, akinesia. Let us recognize that the term, akinesia, is a high-order abstraction and that we are not forced to conclude that this man-made category necessarily means that the phenomena we have arbitrarily included under it all fit neatly into place. I would like to be able to discuss this at greater length, but the limits of time preclude.

As to the use of ultrasonic irradiation for hypophysectomy, we have not yet undertaken to do this. We have been urged by some of our colleagues to attempt the experiment and have already begun to make some plans for it.

Concerning the question of selective damage of tumor cells by ultrasonic irradiation, there is no question but that this can be accomplished. Dr. Janes of the Department of Orthopedics at the Mayo Clinic, working in conjunction with Professor William Fry, has succeeded in disrupting osteosarcoma of the rabbit.

We share with Dr. Sweet the suspicion that certain of the conventional hypotheses concerning the neuropathology of parkinsonism seem less tenable now than formerly. He expressed some amazement that the deliberate production of a lesion in the substantia nigra should have a salutary effect on tremor and rigidity, especially since lesions in the substantia nigra have been regarded, at least in some circles, as "the essential" lesions of parkinsonism. I would comment that one is "amazed" under such circumstances only if he brings to his observations a preconceived attitudinal set regarding the pathology of parkinsonism. One of these attitudinal sets, which is more teachable than defensible, holds that the substantia nigra is *the seat* of pathology of parkinsonism. This notion was proposed by Benda and Cobb and by other writers. If it were true, it would certainly be difficult to reconcile with alleviation of tremor and rigidity by the production of a lesion in the substantia nigra. However, in my opinion, it cannot be accepted as true because too many exceptions obtain in both the positive

and negative directions to allow placing faith in the doctrine. Lesions have been found in the substantia nigra at autopsy in individuals who, during life, exhibited no manifestations of parkinsonism. Conversely, individuals who, during life, have exhibited full-blown pictures of parkinsonism have not infrequently come to autopsy without evidence of damages in the substantia nigra. What has been said here applies with equal validity to all other claims concerning "the locus" of lesions responsible for the hyperkinetic and hypertonic disorders. We simply do not have at present a clear-cut notion regarding the pathogenesis of the disorders under inquiry. Much less do we have evidence of the existence of a one-to-one correspondence between structure and what our feeble minds choose to designate as a "function" or "dysfunction." The time has come to abandon searches for one-to-one correspondences and look for exponential interrelationships among neural structures that may be variously involved from case to case. Such relationships cannot be discovered by scrutinizing the individual structure or structures, regardless of how earnestly one does so. The point to be made here is that if we are "amazed" at some of our findings, we are obliged to seek the genesis of this amazement in the attitudinal sets we bring to our observations, rather than in the phenomena themselves.

To answer the question raised by Dr. Sweet concerning the line of reasoning that led us to produce lesions in the substantia nigra would require a devious explanation at this point. I beg to be allowed to defer this account until Dr. Sweet and I can get together. But as to his inquiry whether the procedure we are now using is "worth the trouble," the answer is to be found in one's own orientation. Clinicians and others primarily concerned with *therapy* and similar "practical" matters would certainly conclude that the procedure is not worth the trouble. And in this frame of reference they would be right. On the other hand, those primarily oriented toward *investigation of the neural mechanisms* subtending the hyperkinetic and hypertonic disorders and concerned with the ultimate formulation of a *sound theory* relative to these disorders would probably agree that if we are to make progress it is indispensable that we make use of instruments of precision capable of producing small lesions of predetermined size, shape and axial orientation which can be verified at later postmortem examination. It cannot be denied that investigations of this sort entail a great deal of "trouble." Unfortunately, there does not appear to be any other way to wrest secrets from Nature. And, except for the ultrasonic tool, we possess no agent in experimental and clinical neurology by means of which the size, shape and orientation of lesions can be determined and the gray matter, the white matter and blood vessels of the central nervous system differentiated.

To answer Dr. Sweet's final question, we have encountered several untoward results in the series here reported upon. Interestingly, these developed one to three days after operation. The athetotic girl experienced a transient diplopia consequent upon a paresis of the right third nerve. This cleared completely within five weeks. One of our parkinsonian patients developed a persistent state of apathy. Although relieved of tremor and rigidity in the limbs contralateral to the side of operation, the patient exhibits this apathy now three and one-half months after operation. Three cases developed hemipareses postoperatively. Two of these have largely cleared and one persists to a severe degree although evidences of recession have recently been observed.

Dr. Bucy has properly indicated that, for convincing study, detailed study of autopsy material is indispensable. We heartily concur. Thus far, we have had no operative deaths. Last week we acquired the brain of one of the early cases in the ultrasonic parkinsonian series. This patient had been free of tremor and rigidity in the limbs contralateral to the side irradiated in December, 1957. Operation on the opposite side was contemplated for October, 1958. The patient drove his car home

from work and several hours later was found asphyxiated in his garage, presumably a suicide. The brain will be subjected to thorough histologic study.

Finally, as to the controversy over the question whether damage to the pyramidal system is a necessary condition of alleviation of alternating tremor, I should recall that we did not state that our evidence has disproved the hypotheses advanced by Dr. Bucy; we merely observed that our evidence failed to lend support to it. Here again, it is clear that, until histological material is available, the *possibility* must be retained that the pyramidal tract (whatever may be meant by the term) has been inadvertently damaged. We can say with some confidence, however, that *if* damaged, no clinical evidences thereof have appeared in most of our cases.