SENSORY, MOTOR AND AUTONOMIC EFFECTS OF MESIAL TEMPORAL STIMULATION IN MAN

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In the past decade the mesial structures of the temporal lobe have received particular consideration. Their importance in temporal lobe epilepsy has emerged in clinical studies and their curiously rich functional and sensory representations have intrigued neurophysiologists. Studies of the effects of both surface and depth stimulation in man have been made in the course of operations with local anesthesia, and the literature in this field already is extensive.

The graphic registration of the autonomic effects of depth stimulation in the human temporal lobe, however, has received scant consideration, and the anatomical placement of the points of stimulation has been poorly controlled or largely a matter of speculation. In the present observations depth electrodes were implanted in the mesial temporal region for diagnostic purposes. This permitted the unhurried observation of the effects of depth stimulation. Of perhaps greater importance was the fact that this approach allowed, in most cases, the observation of a relaxed and comfortable subject not distracted by the stress of a concomitant craniotomy. Furthermore, advantage could be taken of the opportunity to restimulate the same areas on several consecutive days. The relationship of the shaft of the depth electrode to the tip of the temporal horn was determined in all cases by pneumography with the electrodes in place. In this manner the regions of stimulation could be controlled anatomically. In evaluating the accuracy of this method the individual variations in the mesial temporal region were studied in a series of specially prepared brains sectioned in the sagittal plane.

METHOD

The patient material consisted of 11 individuals (Table 1). In 10, bilateral depth electrodes were implanted in the temporal region and in 1 a unilateral depth electrode was implanted. One patient (C.T.) with bitemporal electrodes partially destroyed the right electrode during a seizure so that the total number of deep temporal electrodes numbered 20 (60 depth stimulation points) in all. The first 10 patients presented evidence of bitemporal epilepsy, and it was impossible by routine electroencephalographic means to determine the side of maximal activity. In the last instance, the epileptogenic activity appeared rather diffusely over the frontal and temporal regions and the single temporal depth electrode was inserted to compare the activity in this region with the epileptiform abnormality recorded from subdural electrodes in the frontal region.

The depth electrodes were made of .006 inch stainless-steel wire insulated with Kel-F plastic apart from the tip. These wires were mounted serially on a central 30 gauge stainless-steel core 4 cm. long so that the bare tips of the wires lay at the tip of the core and at 1.0, 2.0 and 3.0 cm. from the tip. For patients C.T. and G.L., 0.5 cm. intervals from the tip were used. The electrodes were inserted freehand from a burr hole over the lateral aspect of the second temporal convolution, and in most cases were directed toward the region of the amygdaloid nucleus. Since the brain at this particular level averages about 5.5-6.0 cm. from the midline to the periphery, the tips of the needles came to lie approximately 15-20 mm. from the midline which includes the greatest sagittal area of the amygdaloid nucleus. Pneumograms were carried out with the needles in place and particular care was taken to fill the temporal horns. The position of each of the needles was plotted on a sagittal plan of the brain taken 20 mm. from the midline after suitable corrections for roentgen-ray magnification. The anterior inferior extremity of the air-filled temporal horn formed the zero point for the vertical and sagittal planes. The details of insertion of electrodes and roentgen-ray evaluation are given.
TABLE 1*

Clinical and electrographic summary of patients in present material

<table>
<thead>
<tr>
<th>Name</th>
<th>Age (Years)</th>
<th>Sex</th>
<th>Duration &amp; Possibly Cause of Seizures</th>
<th>Aura</th>
<th>Seizure</th>
<th>Abnormal Neurological Signs</th>
<th>X-ray†</th>
<th>EEG Type of Examination§</th>
<th>Final Localization of Epileptiform Activity</th>
<th>Depth Electrode Position</th>
</tr>
</thead>
<tbody>
<tr>
<td>M.B.</td>
<td>19 M</td>
<td></td>
<td>8 yrs. Head injury</td>
<td>Chest sensation, auditory hallucination, visual illusion changed interpretation of self and surroundings</td>
<td>Automatism or major fit†</td>
<td>None</td>
<td>Enhanced left lateral ventricle (A)</td>
<td>R0 S2 M3</td>
<td>Bitemporal, maximal right</td>
<td>4P; 8S; 0; 15S</td>
</tr>
<tr>
<td>J.C.</td>
<td>41 M</td>
<td></td>
<td>39 yrs. Traumatic at birth</td>
<td>None</td>
<td>Automatism with staring, posturing</td>
<td>Left hemihyphenesis to pin and touch</td>
<td>M3</td>
<td>Bitemporal and diffuse left hemisphere</td>
<td>9A; 0; 15A; 3I</td>
<td></td>
</tr>
<tr>
<td>C.D.</td>
<td>21 M</td>
<td></td>
<td>12 yrs. Prolonged labor with forceps</td>
<td>Epigastric sinking sensation</td>
<td>Early automatism, lately only major fits</td>
<td>Weakness and wanting left leg (old poliomyelitis)</td>
<td>Negative (A)</td>
<td>Diffuse right frontotemporal</td>
<td>4P; 108</td>
<td></td>
</tr>
<tr>
<td>R.G.</td>
<td>43 M</td>
<td></td>
<td>13 yrs. Minor head injury</td>
<td>Head turning to right, automatism or major fit</td>
<td>None</td>
<td>Normal</td>
<td>R8 S1 M1</td>
<td>Bitemporal, maximal left</td>
<td>5A; 5S; 0; 38</td>
<td></td>
</tr>
<tr>
<td>P.K.</td>
<td>46 M</td>
<td></td>
<td>26 yrs. Biopsy: infarction and gliosis</td>
<td>None</td>
<td>Automatiaisms, rare major fits</td>
<td>None</td>
<td>Negative R5 S2 M2</td>
<td>Bitemporal, maximal left</td>
<td>10A; 7S 5A; 88</td>
<td></td>
</tr>
<tr>
<td>G.L.</td>
<td>19 F</td>
<td></td>
<td>11 yrs. Rising epigastric sensation</td>
<td>Salivation, choking, pulling left hand, automatisms</td>
<td>None</td>
<td>Normal</td>
<td>R3 S3 M4</td>
<td>Bitemporal, maximal left</td>
<td>7P; 35 10A; 5S</td>
<td></td>
</tr>
<tr>
<td>I.M.</td>
<td>42 F</td>
<td></td>
<td>14 yrs.</td>
<td>None</td>
<td>Automatism, grimacing, incontinence, major fits</td>
<td>None</td>
<td>Postop. dilated left temporal horn</td>
<td>R10 S15 M4</td>
<td>Bitemporal</td>
<td>5A; 7S 0; 5S</td>
</tr>
<tr>
<td>M.R.</td>
<td>31 F</td>
<td></td>
<td>19 yrs. Head injury</td>
<td>Epigastric sensation, retching</td>
<td>Preocordial pounding, sweating, pallor, automatism or major fits</td>
<td>None</td>
<td>Normal R19 S4 M5</td>
<td>Bitemporal, maximal left, subcortical</td>
<td>10A; 38 0; 41</td>
<td></td>
</tr>
<tr>
<td>E.S.</td>
<td>46 M</td>
<td></td>
<td>4 yrs. Head injury</td>
<td>Ringing sound then auditory hallucination</td>
<td>Automatism with chewing</td>
<td>None</td>
<td>Dilated right temporal horn</td>
<td>R6 S2 M3</td>
<td>Diffuse left hemisphere and istemporal</td>
<td>See Fig. 4 10A; 4l</td>
</tr>
<tr>
<td>C.T.</td>
<td>54 M</td>
<td></td>
<td>15 yrs.</td>
<td>Objects look big, illusion in head, neck, chest</td>
<td>Automatism, rare major fits</td>
<td>None</td>
<td>Left frontal calcification</td>
<td>R4 S5 M4</td>
<td>Bitemporal, maximal right</td>
<td>— 3P; 7S</td>
</tr>
<tr>
<td>G.T.</td>
<td>23 M</td>
<td></td>
<td>2 yrs. Biopsy: mild gliosis</td>
<td>None</td>
<td>Automatism with hemiatasia or major fit</td>
<td>None</td>
<td>Nonfilling right temporal horn (A)</td>
<td>R14 S6 M3</td>
<td>Bitemporal, maximal right</td>
<td>6P; 0 31P; 38</td>
</tr>
</tbody>
</table>

* In the columns of electrode localization, the figures are distances in millimeters of shaft of electrode, A (anterior), P (posterior), S (superior) or I (inferior) to the anterior-inferior extremity of temporal horn after correction for roentgen-ray magnification. See Methods for preparation and insertion of electrodes.

† Patient experienced postictal metallic taste.

‡ Patient experienced postictal metallic taste.

§ A (A) indicates that bilateral carotid arteriography was done in addition to plain roentgenograms of the skull and pneumography.

∥ R indicates a resting EEG examination. S and M indicate examinations carried out with sleep and Metrazol (pentamethrion) activation respectively.

elsewhere.1,22

Variations of the surrounding structures, particularly the amygdaloid nucleus, were evaluated by the following method.

The temporal lobe was cut in the sagittal plane in 13 normal adult brains and measurements of the distance between the anterior inferior extremity of the temporal horn and the anterior extremity of the amygdaloid complex were made. Since the maximum sagittal diameter of the amygdala frequently did not lie in the same sagittal plane as the maximal anterior excursion of the temporal horn, a second method was used for more careful study. Twenty-one cerebral hemispheres from 12 adults dying of causes unrelated to the nervous system (Table 2) were embedded in agar after accurate separation along the midline sagittal plane. The brains were sliced in the sagittal plane at regular intervals (in the vicinity of 2.5 mm.) on a commercial rotary meat slicer. After each slice the remaining block was photographed beneath a millimeter grid engraved on plexiglass so that correction could be made for inadvertent changes in photographic magni-
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TABLE 2

Variations in distance between anterior aspect of amygdaloid complex and maximum anterior excursion of anterior inferior aspect of temporal horn in 12 brains

<table>
<thead>
<tr>
<th>Number</th>
<th>Sex</th>
<th>Age (yrs.)</th>
<th>Body Length (cm.)</th>
<th>Brain Weight (gm.)</th>
<th>Distance (mm.) of Anterior Extremity of Amygdala from Anterior Extremity of Temporal Horn</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Right</td>
<td>Left</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A58-158</td>
<td>F</td>
<td>73</td>
<td>154</td>
<td>1160</td>
<td>6.0</td>
</tr>
<tr>
<td>A58-282</td>
<td>F</td>
<td>40</td>
<td>153</td>
<td>1160</td>
<td>7.0</td>
</tr>
<tr>
<td>A58-107</td>
<td>F</td>
<td>55</td>
<td>156</td>
<td>1200</td>
<td>6.0</td>
</tr>
<tr>
<td>A58-184</td>
<td>M</td>
<td>78</td>
<td>160</td>
<td>1210</td>
<td>3.0</td>
</tr>
<tr>
<td>A58-276</td>
<td>F</td>
<td>54</td>
<td>162</td>
<td>1250</td>
<td>7.0</td>
</tr>
<tr>
<td>A59-85</td>
<td>M</td>
<td>57</td>
<td>163</td>
<td>1300</td>
<td>5.5</td>
</tr>
<tr>
<td>A59-165</td>
<td>F</td>
<td>50</td>
<td>168</td>
<td>1355</td>
<td>3.0</td>
</tr>
<tr>
<td>A58-281</td>
<td>M</td>
<td>50</td>
<td>178</td>
<td>1360</td>
<td>6.0</td>
</tr>
<tr>
<td>A58-182</td>
<td>F</td>
<td>50</td>
<td>180</td>
<td>1365</td>
<td>7.5</td>
</tr>
<tr>
<td>A58-188</td>
<td>M</td>
<td>41</td>
<td>189</td>
<td>1390</td>
<td>4.5</td>
</tr>
<tr>
<td>A58-145</td>
<td>M</td>
<td>15</td>
<td>164</td>
<td>1540</td>
<td>5.0</td>
</tr>
<tr>
<td></td>
<td>M</td>
<td>56</td>
<td>-</td>
<td>1635</td>
<td>3.0</td>
</tr>
</tbody>
</table>

* The inferior aspect of the amygdala was not observed to lie inferior to the inferior margin of the tip of the temporal horn.

fication. The grid was positioned according to colored needle tracts in the brain placed so that the lateral projection of the anterior commissure at the midline and the anterior-posterior commissure line could be visualized in all sections.

Stimulation in the initial cases was carried out by means of a Grass Model S-4 stimulator, either between two adjacent points on the depth electrode or between a point on the depth electrode and an indifferent electrode applied to the patient’s back. Square-wave unidirectional pulses were used usually at a frequency of 60 per sec. with a duration of 2.5 msec. Current in these cases was monitored with a direct current milli-ammeter. This was calibrated against an oscilloscope and the voltage was directly proportional to the milliamperage providing the frequency and duration of the impulses remained constant. With the above parameters, this relationship was about 1:7. Using this rather rough method of current estimation, it was found that considerable swings in current occurred despite the fact that the electrodes were fixed firmly in place. In most cases, there was a surge of current in the initial 1 to 2 sec. of stimulation followed by a considerable fall off, often to 75 per cent or even 50 per cent of the initial current.

In subsequent work, a stimulator designed by Dr. J. C. Lilly was used. The initial stimulus was supplied by the above Grass stimulator but was modified into two decremental waves of reversing polarity which appeared at the beginning and end of each square-wave pulse. The time constant of these pulses was adjusted to 60 μsec. By the interposition of an oscilloscope on the output circuit, it was possible to visually monitor the current and wave form of the stimulating current during the actual stimulation. With this type of stimulus, the polarizing effect appeared to be considerably less. It may be noted that because of the short duration of the stimuli the actual output of power was relatively low. For square waves 2.5 msec. in duration the energy per pulse amounted to 2.5 × 10⁻⁶ coulombs per ma. of peak current, whereas for the modified pulses there were about 0.10 × 10⁻⁶ coulombs per peak ma. Thus, the energy ratio approximated 25:1. When the current of the stimulus is mentioned in the text peak current is implied. It may be noted in passing that the results of stimulation did not appear to be closely proportional to the energy used in that the modified reversing pulse pairs had a greater ability to produce both clinical and autonomic effects than the unidirectional square waves when the stimuli were compared on the basis of equal energy.

During stimulation the patients were questioned to determine their level of response or, when it appeared desirable not to upset the autonomic tracing, were told to remain quiet and then were questioned later as to their sensations during stimulation. Considerable effort was made to use minimal currents so that the patient remained comfortable and at ease during the examination. In most instances, this resulted in a cooperative and interested patient who seemed in a condition to report accurately his thoughts and sensations. Since the periods of examination were unhurried, attempt was made to check all positive results by subsequent restimulation. Al-
though it was not practical to isolate the patient so that he was unaware that he was being stimulated, points of stimulation were rotated without the patient's knowledge for purposes of checking. Throughout the stimulation, the patient was always aware that any movement or sign of discomfort on his part would cause the stimulation to be shut off immediately.

In addition to routine observation, records were made in all cases with an apparatus to record a number of simultaneous autonomic functions which has been described in detail in a previous communication. In brief, blood pressure was recorded by a combined auscultatory-impulse method at 1-min. intervals and not by an arterial puncture. The temperature of the surface was recorded from the pad of the great toe, and the electrocardiogram between the right arm and left leg. In most cases, the plethysmographic record of the finger usually was made from the fourth finger of the left hand. Since it seemed desirable not to restrict the limbs in view of the possibility of producing an ictal automatism, the plethysmogram was recorded from a simple glass capsule into which the finger was thrust. The space between the capsule and the finger was occluded by a rubber sleeve fitting closely about the mouth of the capsule and the finger. Records of esophageal and gastric motility were made with condom balloons 4 to 6 cm. in length. The esophageal balloon was inserted in the lower third of the esophagus and the gastric balloon in an undetermined portion of the stomach. Recording pressures of the balloons were respectively 1-4 cm. of H2O and 10 cm. of H2O. The recording balloons were attached to polyethylene tubes of 1.5 mm. diameter which had been passed through the nose. Respiratory artefact was seen on both gastric and esophageal records, and in the latter, a superimposed cardiac artefact usually was seen as well. Respiration was recorded by an ordinary laboratory rubber accordion-type of pneumograph placed over the epigastrium. In this position it served to monitor not only respiratory movements but also adventitious movements of the abdominal wall which might have interfered with the interpretation of changes in intragastric pressure. Photographs on 35 mm. Kodachrome film were made of all visible phenomena.

In the last 3 cases attempts were made to record simultaneously with a 16-channel Grass electroencephalograph, Model IVA. Satisfactory records without excessive electrical interference were achieved only in C.T. and M.B.

RESULTS

I. Electrode Positions and General Observations. Since the accuracy of our anatomical determinations of placement of electrodes depended upon the constancy of the relationship of the anterior inferior extremity of the temporal horn to surrounding structures, this was evaluated in autopsy material. An initial study of 15 normal formalin-fixed brains indicated that the amygdaloid nucleus never lay below the inferior extremity of the temporal horn and its anterior surface might lie roughly 2 to 8 mm. anterior to the tip of the temporal horn. Furthermore, it became apparent that the most anterior excursion of the temporal horn frequently lay somewhat medial to the maximum sagittal diameter of the amygdaloid nucleus. In order to evaluate this relationship better, a second series of 21 hemispheres was prepared by embedding in agar and accurate gross slicing in the sagittal plane. Since the lateral projection of the anterior commissure and the orientation of the anterior-posterior commissure line was marked in each hemisphere by needle punctures through the anterior and posterior commissures perpendicular to the sagittal plane, the maximal anterior excursions both of the temporal horn and the amygdaloid nucleus could be evaluated with greater accuracy (Table 2). In both of these anatomical studies, the average distance between the anterior surface of the amygdaloid nucleus and the anterior inferior extremity of the temporal horn amounted to approximately 5 mm. and this has been used in our standard sagittal anatomical plot 20 mm. from the midline. Anatomical variations that would effect the visualization of the tip of the temporal horn consist in narrowing of the distance between the anterior surface of the pes hippocampus and the extremity of the temporal horn which may amount to virtual occlusion of the tip of the horn, and the occasional bridge of tissue between the hippocampus and the surrounding ventricular wall. Although none of these anatomical variations was recognized in the present study, errors in interpretation because of these changes would result in an apparent shortening of the temporal horn on the pneumogram and an erroneously anterior placement of the depth electrode on our plot.

Figs. 2, 3 and 4 show that the majority of
Fro. 1. Stimulation anterior to amygdala (10 mm. anterior and 5 mm. above antero-inferior extremity of temporal horn) with 4 ma. with Lilly apparatus. She was questioned as soon as expiratory apnea was seen and her reply is noted. She swallowed once in the sample before stimulation and a wave of esophageal peristalsis is shown. Note regularity of esophageal peristalsis before and during the automatism. Size of pupils in photographs a and b is 4 mm.; in c and d, 3 mm. Skin resistance is in ohms. Note sudden warming of pad of the toe late in the automatism.

Electrodes were placed just anterior to the anterior inferior extremity of the temporal horn. The majority of positive responses arose from this area and responses from electrodes placed elsewhere appeared more prone to be negative. It should be pointed out, however, that electrodes lying in the periphery were considerably fewer so that a strict comparison is not warranted. The vast majority of the responses were obtained from stimulation of the first 2 electrodes, i.e. stimulation of electrodes lying approximately 15–20 mm. and 25–30 mm. from the midline whereas electrodes lying 35–40 and 45–50 mm. from the midline never produced original responses on stimulation. If responses appeared with stimulation in these lateral electrodes, the same result could also be obtained by stimulation of the more medially situated pair. It may be noted that the lateral border of the amygdaloid complex lies 28–30 mm. from the midline.

Isolated motor responses were conspicuous only by their absence. Unilateral clonic facial movements were noted in 2 patients, G.L. (Fig. 1) and C.T. (Fig. 6A), after stimulation during an ictal automatism. In G.L. the movements were contralateral to stimulation, in C.T., ipsilateral. No facial movements were noted during any period of stimulation. No tonic or clonic movement of the limbs or contraversive movement of the head appeared. Although typical automatisms were induced by depth stimulation, stimulation was never followed by a generalized tonic-clonic convulsion.

II. Autonomic Responses. Although a wide variety of autonomic responses were seen to accompany the induction of an ictal automatism by stimulation, surprisingly few autonomic responses appeared without such evidence of central spread of epileptiform activity. In most of those that did appear, the patient also reported a visceral or somatic sensation from the same area. Brief periods of expiratory apnea were seen to be coincident with stimulation in 2 individuals (P.K. and E.S.). In P.K. the expiratory apnea was associated regularly with a narrowing of the amplitude of the plethysmographic oscillations and usually a small fall in skin resistance (10,000 to 20,000 ohms). In this in-
stance, the stimulated point lay 10 mm. anterior and 7 mm. above the anterior inferior extremity of the temporal horn and presumably outside the amygdaloid complex. With some of the stimulations producing these autonomic changes, he reported an abdominal sensation described as "a hollow feeling in the pit of my stomach almost bordering on the hungry feeling." In some instances, however, the autonomic changes were associated with no apparent subjective sensation. With E.S. (10 mm. anterior, 2 mm. inferior) expiratory apnea frequently was associated with stimulation of all the electrodes implanted on the left side 20 to 50 mm. from the midline. In each case, the patient reported an unpleasant odor. With some stimulations, there were small falls of skin resistance (2,000 to 8,000 ohms) and mild hypertension (rise of 10 mm. systolic and 2 to 8 mm. diastolic pressure). In 1 instance the response was associated with mild tachycardia (84 to 90/min.) but this could not be reproduced. Bradycardia was seen with stimulation in only 1 patient (G.L., Fig. 1) but proved to be reproducible. Although rapid changes in arterial pressure might well have been missed (since the pressures were recorded at only 1 min. intervals), remarkably few changes occurred in the pulse rate which was recorded continuously.

Gastric peristalsis appeared during the period of stimulation in 3 subjects. In patient C.D. the peristalsis followed a half hour's period of observation during which subdural electrodes located over the precentral gyrus were stimulated. The results of this stimulation were quite reproducible and consisted in movements of the contralateral face, thumb, and wrist according to the electrode stimulated. In the other 2 instances (G.L. and E.S.) the peristalsis first appeared during stimulation of various ports within the temporal lobe. In C.D. and G.L. repeated stimulation in the medial temporal region of both sides failed to give any evidence that the peristaltic activity could be altered by this means. (In C.D. the tip of the electrode lay in the inferior portion of the globus pallidus 2 mm. posterior and 20 mm. superior; in G.L. the left electrode lay 10 mm. anterior to and 5 mm. above the anterior inferior extremity of the temporal horn while the right electrode lay 7 mm. posteriorly and 3 mm. above and presumably in the hippocampus.) In E.S. loss of active gastric peristalsis followed stimulation in the vicinity of the pes hippocampus, then an hour later it restarted and continued for a short period after restimulation of the same point (cf. Fig. 11, Van Buren). It may be noted that both E.S. and C.D. were exceedingly ill at ease during the examination and mention will be made below of the sensations of fright that accompanied the stimuli. In view of this, the appearance of gastric peristalsis, which usually is abolished by apprehension, was somewhat surprising. Abdominal sensations induced by stimulation never were accompanied by increased motor activity of the stomach or certain change of the peristaltic pattern when peristalsis was present during the period of observation.

Pupillary changes were sought in the many Kodachromes taken of the face during stimulation but no gross dilation was noted in these or by bedside observation. The only exception to this was G.L. (Fig. 1) in whom a mild pupillary dilatation was noted early during an automatism induced by stimulation (enlargement of pupillary diameter to 4 mm. from a 3 mm. resting pupillary diameter). Nothing comparable to the wide pupillary dilatation seen so frequently with major tonic-clonic seizures was noted in the present material or in spontaneous or Metrazol-induced automatisms studied elsewhere.

III. Subjective Sensations. The plot of points (Fig. 2) indicates the general distribution of the areas stimulated and those producing abdominal, cephalic, chest and olfactory sensations. It appeared that one point might produce differing sensations on repeated stimulation. Thus, G.T. with stimulation in the same region of the hippocampus (6 mm. posterior to and on the level with the anterior inferior extremity of the temporal horn) reported at different times "feel cold in the forehead." "Now my stomach feels funny." "I feel lightheaded." On question he
said, "I feel it in my stomach. It felt like it was getting big. Just before that I felt real lightheaded." Likewise, M.B. reported, "Sick to my stomach, I might have one anytime" (meaning a seizure). On repetition of the stimulus he said, "I feel like a seizure anytime—feeling in my stomach—some odor in the air I can taste." On question as to its nature, he replied, "It's not a bad odor." (This point lay 2 mm. posterior and 8.5 mm. above the anterior inferior extremity of the temporal horn, and probably lay within the amygdaloid nucleus.) On the opposite (left) side from a point 15 mm. directly above the anterior inferior extremity of the temporal horn M.B. reported, "a feeling in my stomach and chest" which he later defined as a "nauseated" feeling. On restimulation of this point he reported a hallucination which will be mentioned below. Another instance of combined sensations appearing at different times from stimulation of the same point was noted with R.G. (5 mm. anterior and 5 mm. superior). He reported a sensation described variously as a "vibration in my nose," "a sick feeling like before an attack," "a sick feeling in my nose." Later on with stimulation of the electrode pair 40 and 50 mm. from the midline he reported, "a new sick feeling through my stomach." Stimulation on the opposite (left) side in this patient at a point 3 mm. directly above the anterior inferior extremity of the temporal horn caused him to say that he had a sensation "like water in my face." This sensation was reported again just prior to a brief loss of responsiveness following stimulation of this point later in the period of examination. I.M. reported a "slight odd sensation in my head and chest" and expiratory apnea was seen during the stimulation. This point lay 5 mm. anterior and 7 mm. above the anterior inferior extremity of the temporal horn. Restimulation of this point later produced one of the patient's typical automatisms.

An unusual response was seen in P.K., who reported "chills all over" from stimulation 10 mm. anterior and 7 mm. above the anterior inferior extremity of the temporal horn. This was reproduced 3 times and was accompanied by easily observable piloerection on the forearms and chest on both sides. He also complained spontaneously of a strong desire to void on all 3 occasions. It may be noted, however, that at an observation period 6 days later this response could not be elicited. E.S. and I.M. voided during automatisms induced by depth stimulation.

Sensations localized in the extremities were unusual but were reported in 3 instances. E.S. reported a "feeling in both my legs" which on one occasion was associated with a bad odor, expiratory apnea, fall of skin resistance and slight elevation of both pulse rate and blood pressure. It may be noted that on repeated stimulation the somatic sensation was not reproducible, although the other responses were. The localization of this point was 10 mm. anterior and 2 mm. below the anterior inferior extremity of the temporal horn. P.K. reported a sensation of "movement of my right elbow" from stimulation 2 mm. anterior and 8 mm. above the tip of the temporal horn. This sensation was associated with expiratory apnea and narrowing of the plethysmogram and was reproducible on one subsequent stimulation but not thereafter,
although the autonomic effects remained. Close observation of the limb failed to demonstrate any movement. From a point 5 mm. anterior and 5 mm. superior to the right temporal horn R.G. reported a “quivering in my right side” which could not be reproduced.

Olfactory responses were obtained in M.B. and E.S. The far anterior and inferior placement of the electrode in E.S. was somewhat surprising in this respect, but the response was reproducible on many stimulations not only from the most medial but also from the laterally lying pairs of electrodes.

Sensations of hallucinatory nature were reported by 2 individuals. Stimulation both of the medial and laterally lying electrodes in M.R. (10 mm. anterior and 3 mm. superior to the anterior inferior extremity of the temporal horn) produced “a funny feeling—like passing out” (she was unable to define it), “I feel like I dreamed it,” later “like something I had seen—like I am floating.” With further question and restimulation she still was unable to define the sensation saying, “I can’t remember it.” In M.B. stimulation of the point 15 mm. above the anterior inferior extremity of the temporal horn was associated with his report of a variety of sensations. These were seen not only with stimulation of the medial but the lateral electrodes. With repeated stimulations, the general nature of his responses was as follows: “I saw something, a dream, a nightmare I had a couple of years ago”; “a dream of an object lying on a table”; “a feeling in the stomach and chest—nauseated. I might have a spell” (after discharge seen in the temporal region on a concomitant electroencephalographic record). Later, “that brings back the nightmare-like picture of the ‘Wizard of Oz’—‘Little Men from Mars’.” Restimulation with the same parameters caused him to make the same remark. Later with stimulation he remarked that he had had a “different dream but I have forgotten.” On restimulation he said, “In a dream I have had before—a monkey doing something impossible.” It may be noted that under ward circumstances this boy was garrulous and had many minor systemic complaints but was maintaining average high-school marks and had a Wechsler Adult Intelligence Scale score of 116. On several occasions, he reported that “people look smaller and weaker” just prior to a spontaneous attack.

It may be re-emphasized that unless specifically mentioned above, all responses were obtained from the medial pair of electrodes (20 mm. and 30 mm. from the midline). The responses to stimulation of a single electrode and the indifferent electrode on the back appeared more poorly localized, apparently because of greater spread of current, so that the latter method never was used alone. The report of different sensations at different times from restimulation of the same points and the general failure to reproduce subjective sensations regularly should be noted. Since in the later observations of the present series the output of the stimulator could be monitored closely, these variations did not seem to be caused by differences in the electrical form of the stimuli. The use of implanted electrodes would seem to preclude a significant shift in the area of stimulation.

IV. The Production of Ictal Automatism. Stimulation in the vicinity of, but apparently not necessarily within, the amygdaloid complex (Figs. 3 and 4) produced loss of response and apparently a typical automatism in 7 of the 11 patients. The autonomic tracings of 3 patients (I.S., G.T., and I.M.) have been illustrated previously. The position of the electrodes in patient E.S. has been omitted from Fig. 3 since marked dilatation of the terminal portion of the right temporal horn rendered the anatomical correlates doubtful. In any case, it is given in Fig. 4 and the stimulating electrode lay within the horn (pes hippocampus).

In comparison with the rather meager autonomic changes associated with stimulation of points not eliciting automatism, the automatisms themselves were associated with a marked variety of autonomic changes. The automatism elicited by stimulation in patient G.L. (Fig. 1) was unusually favorable for observation. The patient, although unresponsive, remained absolutely still through-
out the attack. Although pupillary changes were noted in this attack, their mild degree may be pointed out. Stimulation was accompanied by expiratory apnea which was seen at the start of automatism in 4 of the 7 patients. The association of expiratory apnea or the lack of profound respiratory change with automatism appeared to be a characteristic either of the patient or of the placement of the electrode since on repeated stimulation the effects were usually the same. Auras usually were not reported but may have been obliterated by a retrograde amnesia following the attack. Some evidence in support of this consists of typical auras reported both by G.T. and G.L. with stimulation of the same area which at other times produced an automatism. The autonomic effects, although varying in their time sequence, nearly invariably resulted in autonomic changes moving in a similar direction. Thus hypertension, tachycardia, narrowing of the plethysmogram, swallowing and inhibition of respiration occurred if any change appeared in these respective functions. Patient G.L. was an exception in that very distinct bradycardia occurred during stimulation. This apparently was characteristic of the stimulation point in this individual and proved to be reproducible.

It may be noted that, although the patient’s ability to respond might be extinguished during the stimulation, this was by no means invariably the case. Thus, patients I.M., G.L., G.T., and C.T. were able to respond verbally and appropriately to question following stimulation and indeed patients I.M. and G.L. responded during expiratory apnea. None of the patients who responded after such a stimulation was able to recall doing so after recovery from the automatism. The duration between stimulation and loss of response was considerable in some instances (45 sec. in G.T., about 20 sec. in G.L.). P.K. (Fig. 5) demonstrated that a monotonous movement might be carried on even beyond the point where the patient would respond verbally. In this instance, the patient was instructed to press a key (response bar) at 1 sec. intervals and was able to continue this following stimulation and continued even after he ceased to respond to the investigator’s commands.

Fig. 6C illustrates the electroencephalographic correlate of such an automatism. Initially following stimulation and during the
period of increasing epileptiform activity in the left temporal lobe the patient was able to respond. The sudden depression of voltage in the left superficial temporal electrodes corresponded closely with loss of responsiveness. Thereafter, the spread of epileptiform activity in the left temporal lobe and spread to the right side occurred.

Responses of emotional character were elicited in 3 patients. Patient C.D. remained fearful throughout all stimulations whether directed at the cortical surface (subdural electrodes were placed in the posterior frontal and precentral areas) or in the deep temporal region. This diminished as the stimulation was repeated on subsequent days and is of doubtful significance. In E.S. stimulation of the area inducing an automatism was accompanied by severe fright and because of this the examination was curtailed after 2 automatisms had been induced. Although the patient was somewhat apprehensive, during stimulation of other areas, it was not entirely clear why such a disturbing emotional response should have resulted from the stimulation. It may be noted that there was evidence of spread of the current to the 3rd nerve (the ipsilateral eye was opened and the eye deviated medially) but the patient, on considerable questioning, was unable to explain satisfactorily the reason for his fright. Quite specifically, he denied pain nor was he able to describe the nature of his unpleasant sensation.

P.K. laughed heartily at the time of stimulation (Fig. 7). This laughter was reproducible on repeated stimulations on separate days (May 12, 1959 and May 18, 1959) but had not been apparent during stimulation that led to an automatism from the same area on May 11, 1959. In this instance, the point causing automatisms was stimulated 9 times during the latter 2 periods of observation. In no instance did the patient recall what amused him and indeed had no recall of laughing. Repetition of this stimulation was carried out only when the patient gave evidence of having fully recovered from the previous stimulation (intervals between 10 min. and ½ hour) but at these intervals fatigue of the point appeared evident. Thus, on May 12, 1959 (Fig. 7) the point was stimulated initially at 2:35 p.m. Subsequent stimulation at 2:46 p.m. produced only a
single laugh and a reduction of both the autonomic effects and periods of loss of consciousness. The third stimulation with identical parameters shown at 2:54 p.m. (Fig. 7) resulted in only a brief period of confusion. A similar sequence of apparent fatigue of the stimulation point was noted on May 18, 1959 with the degree of laughter, autonomic change, and the duration of unresponsiveness diminishing progressively as the point was
restimulated. On the latter day, eventually no response could be elicited from the point even with doubling the intensity of the current. It may be noted that in this instance the stimulator permitting oscilloscopic visualization of the output of current was used so that there seemed little chance that variations in the intensity of the stimulation could have resulted in the variations in the response. The reproducibility of the same pattern of fatigue from stimulation of the same point on 2 separate days suggested that the loss of response was not caused simply by destruction of tissue from stimulation.

DISCUSSION

In the present study it appeared quite certain that the majority of the positive responses to stimulation arose from within or very close to the amygdala. The fact that no responses appeared with stimulation of the electrodes 40 mm. and 50 mm. from the midline (except in those few instances when similar responses were obtained by stimulation of the more medial electrodes), likewise would appear to implicate the central gray substance in the temporal lobe. Positive responses also appeared to arise from the stimulation of the white substance anterior to the amygdaloid complex or from the adjacent transitional cortex. This is not without precedent as the anatomical plots of Kaada et al.\textsuperscript{21} also suggest that somatic and visceral responses may arise from stimulation anterior to the gray substance of the amygdaloid complex in the cat.

The production of visceral and somatic sensation from the region of the area olfactoria or substantia innominata and lower pallidum was unexpected. This, however, may be of some importance in indicating that the inferior thalamic peduncle and other mesially directed pathways, which stream through this region from the anterior mesial temporal lobe, may carry clinically important impulses from the temporal region. Prominent degeneration in this area has been found in a recent serial-section study of degeneration following temporal lobectomy in man,\textsuperscript{34} earlier studies of vascular lesions,\textsuperscript{8} and in experimental lesions in monkey.\textsuperscript{22,23,26}

Stimulation of 2 of 3 electrodes situated in the region of the pes hippocampus resulted in sensation and automatisms quite similar to those resulting from more anteriorly placed electrodes. Similar results have been reported
by Pampiglione and Falconer,\textsuperscript{27} and Jasper and Rasmussen.\textsuperscript{19} The failure of Penfield and Jasper\textsuperscript{28} (p. 530) to elicit ictal phenomena from stimulation of the middle and posterior hippocampus, following resection of the anterior temporal region, is interesting and may underline the importance of the inferior thalamic peduncle and tracts in its vicinity as important pathways for mesial propagation of temporal epileptiform activity.

Motor responses to amygdaloid stimulation have been noted in man and animals.\textsuperscript{2,5,10,12,13,19-21} Our failure to reproduce motor phenomena apart from those related to ictal automatism may rest upon two factors. It was our custom to increase the stimulus until a response was obtained (though not over 4 ma. for square-wave pulses and 30 ma. for the short decremental pulses—see Methods) but once a response appeared we usually did not exceed this threshold. It is possible that somatic movements may simply require greater strength of stimulus than we cared to employ. The specificity of the response under these conditions might be open to question. Kaada et al.\textsuperscript{22} apparently did use higher currents since stimulation resulted occasionally in generalized seizures. Secondly, movements in cats, appearing quite similar to those that we observed following the stimuli that induced automatisms in our patients, might well have been construed as primary somatomotor responses since the responsive state of the animal could not be determined readily. Since all somatic movement in our material occurred when the patient was unresponsive, its relationship to the general ictal nature of the discharge seemed quite obvious.

Responses of emotional nature have appeared in reports of depth stimulation in man from time to time. Fear has been the most common response and has been reported from stimulation in the amygdaloid region,\textsuperscript{5,18,27,29} from the fornix\textsuperscript{30} and from pallidum.\textsuperscript{17} It must be noted, however, that well defined emotional responses to stimulation are infrequent and are relatively infrequent as a part of the seizure patterns in epileptics.\textsuperscript{28} Laughter as a part of an ictal pattern is most unusual although such has been cited by Clark \textit{et al.}\textsuperscript{3} (pp. 179–181) and Druckman and Chao.\textsuperscript{9} Foerster and Gagel’s\textsuperscript{11} report of laughter and joking from mechanical stimulation of the walls of the 3rd ventricle appears unique and we have seen no report of laughter comparable to that produced by stimulation of the amygdala in patient P.K. In this case, it may be significant that laughter was absent during the automatisms induced during the first session of stimulation and that laughter during subsequent sessions was seen only as a part of the ictal automatisms induced by stimulation. On the other hand, our own experience and that cited in the literature suggest that fear appears on stimulation without gross evidence of concomitant epileptic discharge. We have had difficulty being certain whether fear actually was the result of stimulation or whether it was not simply the result of an unusual sensation experienced under conditions that were alarming to the patient. In 1 instance (C.D.) fearfulness had appeared from stimulation of electrodes in the depth and on the cortical surface and practically disappeared as the patient became accustomed to the procedure of stimulation.

The curious variability of the responses elicited from stimulation of the mesial temporal region\textsuperscript{18,27} had attracted our interest early in the study. Since depth electrodes were used that maintained a constant area of contact with tissue and the stimuli were monitored carefully, it led us to the conclusion that the instability must lie primarily in the neuronal system that was subject to the stimuli. The intervals between stimulation and the onset of unresponsiveness (which might be prolonged) suggested that this period was required before the local epileptiform activity had increased sufficiently to surge into central structures of the brain in sufficient quantity to obliterate the patient’s ability to respond. Differing sensory responses from stimulation of the same region might result from variation, from time to time, in the accessibility of more centrally placed sensory mechanisms to the widely directed barrage of epileptiform impulses.
sent out by the amygdaloid area. Our results thus would lead us to agree with Gloor who found evidence that the relationship of the amygdala to central structures is "a somewhat loose and variable type of connection."

Experimental evidence has been available for some time (see references cited by Gloor, 1960) that the amygdaloid area is the recipient of a wide variety of sensory afferents in addition to olfaction. Human anatomical studies show a direct connection between the mesial temporal region and the lower brain stem which would afford ready communication between the amygdaloid region and the primary visceral afferent receptor centers. We thus would find support for the hypothesis that the amygdaloid area serves not primarily as a region for discrete sensory-motor representation, but rather as an area by means of which the sensitivity of response of the central nervous system may be adjusted by afferent impulses from both somatic and visceral sources. Such an interpretation would be in accord with the apparent anatomical overlapping of the sensory representation in the amygdala and the profound effect that stimulation of this region exerts upon the electrical activity of the cerebrum and upon the conscious response of the individual.

SUMMARY

In a series of 11 patients subject to epilepsy of the temporal lobe, depth electrodes were implanted in the mesial temporal regions. In each instance the relationship of the electrode to the tip of the temporal horn was visualized pneumographically so that anatomical plots of the position of the electrodes could be made. The electrodes were left in place 1–2 weeks and the effects of depth stimulation were observed clinically, photographically and with a special apparatus recording autonomic function. The latter apparatus recorded blood pressure, skin temperature, electrocardiogram, skin resistance, plethysmogram, esophageal and gastric motility, and respiration.

The areas in which stimulation resulted in a clinical automatism were clustered close to or within the amygdaloid nucleus and the pes hippocampus. Autonomic effects with the automatisms were invariable and included hypertension, tachycardia (rare bradycardia), fall of skin resistance, reduction in the amplitude of plethysmographic oscillations, swallowing with repeated esophageal peristaltic waves (rarely inhibition of gastric motility), and inhibition of respiration or inspiratory apnea. In several cases, patients responded appropriately during and after a stimulation leading to an automatism yet later became unresponsive. Emotional responses were few. Fear was noted in apprehensive subjects but not in those who were previously at ease. In 1 patient laughter appeared with stimulation and was reproducible as a part of an automatism.

Autonomic changes, apart from those seen with stimulations inducing an automatism, were relatively few (fall of skin resistance and respiratory inhibition were most frequent) and usually were accompanied by a subjective sensation of visceral or poorly localized somatic nature. Epigastric sensations were most frequent, and sensory responses appeared from electrodes placed well outside the amygdaloid complex, including the region of the substantia innominata and the pallidum. The proximity of these regions to the inferior thalamic peduncle and other systems running medially from the anterior temporal region may be noted.

The responses proved variable and often were not reproducible despite close monitoring of the stimulation current. In 1 case progressive fatigue of the response of the region from which automatism could be elicited was observed during two separate periods of stimulation.

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