The hypothalamus, anterior thalamic nuclei, gyrus cinguli, hippocampus, and their connections were believed by Papez to constitute a harmonious mechanism which may elaborate the functions of central emotion as well as participate in emotional expression. A broader concept of the function of the limbic system was expressed by Herrick, who considered the limbic system an activator of all neocortical functions facilitating or inhibiting not only affective behavior, but memory and learning as well.

The hippocampus itself is regarded by many authors as the "hub" of the limbic system. Papez speaks of the "central emotive process of cortical origin" being "built up" in the hippocampal formation before being relayed to the mammillary bodies and the anterior nuclei of the thalamus. Grunthal suggests that the hippocampus acts as a "catalytic activator" essential for the central affective and neocortical activity.

To gain a greater insight into the function of the hippocampus, a technique for subtotal hippocampectomy was developed in the cat and monkey. Following hippocampectomy, a marked taming effect was observed, similar to that described by Klüver and Bucy and Schreiner and Kling. During these studies it was noted that following hippocampectomy the animals showed less response to painful stimuli. Whether this was due to diminished perception or reactivity remained undetermined.

The laboratory findings provided an encouraging basis for further exploration of the effects of hippocampectomy on a clinical level. It appeared that the procedure might prove useful in psychosurgery and pain control. The transfer of a laboratory procedure to the clinical level is fraught with many unexpected pitfalls, and it was decided, therefore, to use the procedure only for intractable pain due to widespread carcinomatosis, or pain states which had not responded to routine neurosurgical pain-relieving procedures. Over a period of 2 years this careful selection produced seven cases. Thus the evaluation of hippocampectomy, on the clinical level, can only be considered to be in a preliminary stage, and the observations are presented more as a study of results than a proposal of a new technique with definite therapeutic indications.

**Technique of Hippocampectomy**

The technique of the procedure for clinical trial was adapted from the methods previously developed in the laboratory. Initially, a series of twinbladed retractors were made (Fig. 1); these were inserted into the middle part of the temporal lobe between the superior and middle gyri, just in front of the vein of Labbe. Through this transventricular approach, the hippocampus was removed by suction, with suction tips of varying shapes. The attached photographs will illustrate the extent of the lesion. The transventricular approach in the human subject proved to be far less satisfactory than in the animal, and was characterized by incomplete resection and fairly marked damage to the overlying neocortex of the temporal lobe.

Hippocampectomy was next attempted by means of lesions produced by coagulation, with stereotaxic approaches made through the posterior parietal lobe and the trigone of the ventricle, and with the electrode running along the medial wall of the temporal horn in the hippocampus to the tip of the temporal horn. Multiple small coagulation lesions were made at 1 cm intervals.

**Case Reports**

**Case 1.** This 27-year-old man was admitted to the V.A. Hospital, Houston, Texas, on December 6, 1962, with a diagnosis of Hodgkin's disease, based on a biopsy in 1954. In 1962, bony lesions were found in the right ilium, lumbar spine, and left femur. The lesions were treated with irradiation and Vincristine. One week before admission he
developed increasingly severe lumbar pains, a marked paraparesis, dysuria, and difficulty in defecation.

On examination he was found to have widespread adenopathy, marked tenderness of the spine from T-11 to the sacrum, severe flaccid paraparesis, and a sensory level at T-11, with hypesthesia below this level. X-rays demonstrated multiple bony lesions of the lower thoracic, all lumbar and sacral vertebrae, and the pelvis. Myelographic blocks were present at T-10 and L-2. A decompressive laminectomy was performed at these sites without any significant improvement. Following decompression, morphine at ½ gr every 2 hours was required to control the pain of the spinal and pelvic lesions. No psychological testing was possible in this very ill, emaciated and drowsy patient, who only woke up sufficiently to ask for more medication. Grossly he appeared to be fairly well oriented though semi-illiterate and dull.

First operation. On December 11, 1962, a right hippocampectomy was performed through a 1-inch incision between the upper and middle temporal gyri, just in front of the vein of Labbe, and an estimated 80 to 90% of the right hippocampus was removed.

Postoperatively, all narcotics were discontinued. A temporary mild disorientation was noted in the first postoperative week, but this cleared completely. During this period the patient never complained of pain and showed a remarkable lack of concern for painful stimuli. By December 24, the patient had some return of pain, but this was controlled by Darvon every 4 hours and he was able to get up in a wheelchair. Psychological testing on December 27 showed an I.Q. of 72, no disorientation, a slight memory impairment, and signs of indifference.

The patient was discharged home in a wheelchair where he remained for approximately 2 months. By then the pain had once again become too severe to be controlled by Darvon.

Second operation. February 21, 1963, a left hippocampectomy was performed in the same fashion and extent as before. Again, all analgesic medication was withdrawn. Psychological evaluation 3 weeks later showed a Wechsler and Verbal I.Q. of 66 and a comparable rating on Performance subtests. The patient was fairly well oriented in time and space. He knew where his home was but could not remember the house number. He knew the year but not the date, and he could not name the president. After 3 weeks he was discharged home in a wheelchair with a supply of Darvon tablets which seemed to control the residual discomfort in his spine until his death at home on June 9, 1963. No autopsy was obtained.

Case 2. This 73-year-old man was admitted to the V.A. Hospital on December 31, 1963. The diagnosis of carcinoma of the prostate with metastases to the spine and pelvis had been made in April, 1963. In July, 1963, a decompressive laminectomy at T-5 had been performed and was followed by a right mid-thigh amputation for gangrene of the foot due to vascular insufficiency. After the last operation, the patient had severe pains in the stump.

On examination the patient was found to have metastases in his right femur, pelvis, lumbar and thoracic spine, and one scapula. In the week prior to hippocampectomy, he required Morphine ½ gr four to six times a day.

Operation. On January 20, 1964, a series of lesions were made stereotaxically (Fig. 2) throughout the length of the left hippocampus by means of a leucotome, and this was followed by a series of coagulative lesions at 1 cm intervals in the same area (Fig. 3).

Following the operation the patient became markedly dysphasic and would only talk in his Spanish mother tongue, although before the hippocampectomy he had been fairly fluent in English. He did not complain of pain, and all narcotics were stopped. By
January 28, he was up in a wheelchair responding to simple commands, talking a mixture of Spanish and English. By February 10, he was alert, active, and still did not complain of pain. He died suddenly on February 15, 1964. Although there had been a preoperative psychological evaluation, the patient died before a postoperative performance plateau had been attained. Psychological data are therefore incomplete.

Autopsy showed no definite immediate cause of death, only widespread carcinomatous deposits in an old, emaciated individual. The brain showed marked cerebral atrophy. Serial sections showed disruption and degeneration in the left hippocampus, and the loss of bulk was clearly evident when the left and right hippocampus were compared. Approximately 50 to 60% of the left hippocampus had been destroyed.

Although there was some extension of the lesion beyond the hippocampus, the volume of extra-hippocampal tissue affected was quite small.

Case 3. This 46-year-old man had had a nephrectomy and radiation for renal carcinoma. Nine months before admission he had a sudden onset of severe pain which was followed by paraparesis with inability to micturate and control his bowels. X-rays showed metastatic lesions in the mediastinum, the first four lumbar vertebrae, and the pelvis. He required Pantopon, ½ gr every 4 hours.

Operation. On October 31, 1963, a bilateral hippocampectomy was performed by direct approach. An estimated 70% of the hippocampi was removed bilaterally. Immediately after the operation all narcotics were stopped. The patient was confused and restless but did not ask for medication to relieve pain. He gradually improved, talking freely with a tendency to ramble, yet partially oriented. No spontaneous complaint of pain was uttered in the recumbent position but sitting up did cause some pain; the patient would ask to lie down but did not ask for medication. On November 7, the steady improvement was reversed as the patient gradually became confused and developed signs of an intracerebral abscess in the left temporal lobe. This abscess was evacuated and the patient recovered. By December 12, his speech was only moderately dysphasic and he appeared to be fully oriented in space and partly in time, commenting on the hospital but showing a marked memory defect; he was not able to give his age. On January 2, 1964, he started to deteriorate physically and mentally with increasing anemia due to bone marrow metastases. The patient died on March 1, 1964; at no time following hippocampectomy had he asked for medication to relieve pain.

Fig. 4 shows the brain sections demonstrat-
ing subtotal removal of the right hippocampus with relatively good preservation of the rest of the temporal lobe.

Case 4. This 43-year-old man noted a gradual onset of pain and tenderness in the right shoulder in January, 1963. In April 1963, a tumor opacity was noted in the right apical region on x-rays. A supraclavicular node biopsy showed metastatic carcinoma of the bronchus and a course of radiation therapy was given with minimal change in signs and symptoms. Because of constantly increasing pain, the patient had a cervical cordotomy at the C-2 level with rhizotomies of C2-5 on the right. Good relief of pain was obtained.

Gradually over the course of the next 3 months, pain recurred in the original site and started to radiate upward to the base of the skull. Increasing doses of narcotics were required until he was taking $\frac{1}{2}$ gr codeine, 50 mg Demerol, 2 mg Levodromoran, and 50 mg Thorazine, simultaneously at 2- to 3-hour intervals. An excellent cordotomy level was present extending to the midcervical region on the right side. In spite of the analgesia, the patient complained of severe pain.

Operation. On December 24, 1963, a subtotal left hippocampectomy was performed through a direct approach. In addition, a stainless steel coagulation electrode was introduced stereotaxically throughout the length of the right hippocampus.

Following the operation, all medications for pain were discontinued. He was given Thorazine, 300 mg daily, for severe restlessness. Immediately following the operation, the patient showed a dysphasia. He did not complain of pain. Over the course of the next 9 days, his speech improved rapidly so that at times no dysphasia would be noted. He appeared to be fully oriented and jovial. Eight days after the procedure he again started to complain of pain although with a cheerful countenance and without insistence on medication.

On the morning of the tenth day after the left hippocampectomy, he suddenly developed a pyrexia of 104°, became critically ill and feeble. A small amount of drainage was noted at this time around the electrode in the right hippocampus and, therefore, the electrode was removed. On removal, a few drops of cloudy fluid emerged from the electrode site. A presumptive diagnosis of meningitis was made. In spite of all measures, the patient rapidly deteriorated and died the same day.

Autopsy showed a sero-purulent meningitis. Fig. 5 demonstrates an 80 to 90% removal of the left hippocampus with adjacent temporal lobe damage.

Case 5. This 55-year-old man was admitted for relief of pain caused by carcinoma of the pancreas with metastases to the liver and mesocolon. Radon seeds and deep x-rays gave little relief. Because of severe pain he required Dilaudid $\frac{1}{3}$ gr every 1 to 2 hours; this medication kept him semi-stuporous most of the time, allowing him to wake only to demand more medication.

Operation. A bilateral partial hippocampectomy was performed on November 28, 1962, by direct approach with an estimated removal of 25% of the structures. Following the procedure, all medication was withdrawn. The patient rapidly became hypertensive, noisy, confused, and apparently without any inclination to sleep day or night. On Thorazine, 200 mg daily, he became quiet yet fully awake, though quite confused. He was aware of his environment, naming the hospital and town correctly, but he was confused in time. By December 17, he had again started to complain of pain and required codeine. By January 1, 1963, Dilaudid was necessary and eventually just before his death on January 7, the dosage of this drug had been increased to the preoperative level.

Autopsy showed relatively small parts of both hippocampi removed with quite appreciable damage to the adjacent neocortex of the temporal lobes.

Case 6. This 57-year-old man was in the Navy until 1946 when a lifeboat fell on him causing a complete paraplegia with a T-12 level. An exploratory laminectomy at that time produced no change in neurological status. This was followed by persistent severe pains in both legs. As a result of these complaints, he had a bilateral cordotomy in the upper thoracic region which was later followed by a cordectomy and amputation of the left leg below the knee. All of these procedures had no effect on his pain. The patient was intolerant of narcotics, which caused
nausea and vomiting, and only paraldehyde in 15 cc doses every 2 hours relieved his pain. A psychological evaluation showed some depression, good intellectual performance, and no major disturbance of personality.

Operation. On February 14, 1964, a right hippocampectomy was performed through a direct approach. An estimated 80 to 90% of the hippocampus was removed.

Postoperatively, the patient continued to ask for paraldehyde frequently enough to justify putting him back on the medication. However, there were periods of up to 12 hours when he would not ask for the drug. This was the only indication of relative improvement. No neurological or obvious men-
Effects of Human Hippocampal Ablation

Fig. 4. Brain sections in Case 3. Subtotal removal of right hippocampus with preservation of adjacent temporal lobe. On the left a large hematoma and an area of necrotic softening occupied the upper part of the temporal lobe and insula; a considerable amount of hippocampal tissue was still present on this side.

tal changes were noted, but the patient refused a second hippocampectomy and without adequate postoperative psychological evaluation had to be discharged, at his insistent request.

Case 7. In 1959, this 37-year-old man shot himself in the left lower chest. Since that time he had suffered from a persistent severe neuralgia in the T5-8 segments. This was treated by multiple rhizotomies, sympathectomy, and two cordotomies. Extensive and prolonged psychiatric investigation revealed a conversion reaction and anxiety aggravating a pain of organic origin. Prolonged psychiatric treatment in two hospitals failed to
Fig. 5. Brain sections in Case 4, showing 80 to 90% removal of the left hippocampus, plus damage to the adjacent temporal lobe.
affect the patient’s complaint. On December 2, 1963, a bilateral rostral, frontal lobotomy was performed without any obvious improvement in the patient’s condition. The lobotomy was then extended into a bilateral full lobotomy, again without significant effect on the patient’s complaint. Following these procedures, he was put on a regimen of codeine, 1 gr every 4 hours, and a variety of tranquilizers including Thorazine, 200 mg per day. A psychological consultation following the lobotomies showed an I.Q. of 109, rather haphazard thinking, and a poorly interpreted response to ambiguous stimuli, but the memory quotient was 118. Emotionally, he was depressed, antipathetic, and anxious.

Operation. On January 27, 1964, a right hippocampal coagulation was performed using 2- to 3-second periods of coagulation at a setting of 40 on the Bovie unit. The lesions were placed at 1-cm intervals along the course of the hippocampus.

Following unilateral coagulation of the hippocampus, the patient showed only slight improvement. On February 28, a left hippocampectomy was performed in the same fashion.

A psychological evaluation performed between these hippocampectomies on February 7 showed the patient to be a little more responsive and at ease than before hippocampectomy. A slight reduction of intellectual efficiency was present on the Wechsler Bellevue II and Wechsler Memory Test. The response to inkblots showed greater placidity than before and less tension.

On March 23, the psychological tests were repeated (following the second hippocampectomy) and showed no marked change in over-all intelligence, with an I.Q. of 105. Although no change in speed tests was found, the memory quotient showed a significant decrease to 91, compared to 118 before hippocampectomy; both old and recent memories were affected. A decrease of learning ability was noted. Although judgment and integration were poor to begin with, his perceptions and interpretations were more vague than ever. Changes in the emotional status were minor but he seemed less hostile than before.

The patient was discharged on July 10, 1964, complaining of the same pain; the only benefit of the hippocampectomy appeared to be a somewhat more placid state, but the improvement was insufficient for any return to productive existence.

Discussion

No mention has been made in the literature about the function of the hippocampal formation in the perception of pain. Therefore, the finding that destruction of even part of the hippocampal masses can modify intractable pain is of interest. If we accept the theory that the limbic system is concerned with the preservation of the individual and species, then it will not be surprising to find that destruction of any part of the limbic system will affect these prime goals of the system. Pain can be considered as perhaps the most important warning signal to the organism that its well-being and existence are threatened. Although no cortical projection areas for pain have ever been described, it seems possible that after surprising the thalamus, the first cortical awareness of pain may be at the level of the paleo-cortex of the limbic system. Disruption of the function of the hippocampus by hippocampectomy may produce the apparent postoperative indifference to pain shown by these patients.

Knowledge regarding the relation of the hippocampus to memory recording, or more exactly to acquisition and retention, is only beginning to accumulate. Evidence has been presented by Penfield and Milner and Scoville and Milner that the hippocampal formation and the hippocampal gyrus play a large and essential part in the recording of recent experiences. However, it can be shown that “memory recording” cannot be assigned so simply to one part of the central nervous system. In Wernicke’s syndrome, a severe memory defect is present yet no hippocampal or temporal lobe lesions can be found, most of the changes being noted in the diencephalon and the hypothalamus.

In our cases, the memory deficit varied with the size of the lesion and appeared to be more influenced by the neocortical than the paleo-cortical lesions; however, which of these definitely played a major part in the memory deficit cannot yet be stated with certainty. Certainly, bilaterally extensive hippocampal lesions did not produce the extreme memory deficits described by Penfield, Scoville, and Milner.

Whether hippocampectomy will play a role
as another surgical approach to the control of pain is not clear at this time. The procedure is admittedly complex, and evaluation of the behavioral changes is not easy. The material available remains restricted by humanitarian considerations, and much further work lies ahead. Meanwhile, we are obtaining a more detailed understanding of the fascinating activities of the limbic system as a whole.

Summary

Extensive hippocampectomy in cats, baboons, and monkeys results in a diminished reaction to pain. We have recently performed the operation on seven human patients with severe intractable pain. There was usually appreciable reduction in pain following an extensive bilateral hippocampectomy. After unilateral hippocampectomy, the effectiveness was varied and did not last for more than a period of weeks. The patients also showed flattening of affect and were relatively unconcerned about the seriousness of their condition. This was accompanied by a variable change in such intellectual functions as retention and acquisition.

Whether hippocampectomy offers a satisfactory approach to the control of intractable terminal pain cannot yet be decided. However, it may provide an insight into the function of the hippocampus.

References