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Gold Medal Lecture

Engrams in the Human Brain

Mechanisms of Memory

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'I sometimes feel, in reviewing the evidence on localization of the memory trace, that . . . learning is just not possible.'

With these words Karl Lashley, Harvard's Professor of Psychology, laughed at himself, frustrated by failure. His paper, written in 1950, was entitled 'In Search of the Engram'. Thirty years of experimental work (on rats, monkeys and chimpanzees) had, to quote again, revealed 'a good bit of information about what and where the memory trace is not . . . nothing of the real nature of the engram'.

These negative findings have caused many investigators to turn away from study of the brain as a whole and to content themselves with a search for the secret of learning and of memory in the possible encoding of information on macromolecules, following the geneticists there. Or, like John Eccles, they sought the answers in the single neurone and its connexions.

'Engrams' is a word psychologists use frequently although what they mean by it neither they nor the physiologists have, as yet, quite decided. One dictionary's definition of the word 'engram' is this: 'A permanent impression left on protoplasm as the result of a stimulus.' Again, it is defined as 'a lasting trace . . . left in an organism by psychic experience'.[1] I would myself be satisfied to define it as – the writing left behind in the brain by conscious experience.

[1]From Webster's New International Dictionary, 1960. The Oxford English Dictionary (Supplement, 1933) refers to 'engram' as a change wrought by a stimulus and adds: 'The sum of such engrams in an organism may be called its engram store'

It is my purpose to point out that those things which constitute a man's awareness, those things that enter the focus of his attention, *are* recorded by neuronal mechanisms in the human brain and we can now begin to point out where. On the contrary, the passage of nerve impulses that have to do with what a man ignores leave little or no lasting record. Something more than the passage of nerve impulse is involved in the establishment of the 'memory trace'.

Two fields of study and two questions present themselves to those who search for the engram in the brain: (1) What are the basic protoplasmic alterations that make permanent recording of experience and memory recall possible? I shall have nothing to say of this basic problem. (2) How and where does the neurone transaction take place that constitutes the record of experience and makes possible its reproduction or recall? To this second question, we can make some clear-cut answers, although they may seem no more than a beginning of a final explanation.

The Royal Society of Medicine's invitation to give this lecture has brought me back from other preoccupations to what, I now see, was an unfinished study – back too, in time and place, to this Society. I return to you with a deep sense of gratitude. How often, as a graduate student, I scanned the weekly list of clinics and lectures posted in the hall outside this room! How many winter afternoons I read in the library where silence was broken only by the muted sounds of Wimpole Street! I remember the comfort of a pot of tea that could be had hot, on one's reading desk, for threepence.

It is a matter of history that clinicians have always shared (with philosophers, on the one hand, and laboratory men on the other) the search for an understanding of the mind and the

brain of man. The Father of Scientific Medicine himself started off that search:

'Eyes, ears, tongue, hands, and feet act in accordance with the discernment of the brain', he said. 'Therefore I assert that the brain is the interpreter of consciousness.' Thus Hippocrates defied the philosophers of his day and, stating his hypothesis, turned to a discussion of epilepsy.

Little further advance was made until about a hundred years ago. Paul Broca, a surgeon and pathologist of Paris, demonstrated then that a relatively discrete destruction of the third frontal convolution in the left hemisphere had resulted in aphasia. The loss of speech occurred without other significant disability. This argued for a separable mechanism that had to do with the understanding and the use of words. It contradicted the idea that the brain, as the 'organ of the mind', acted as a whole.

Neurologists at the Salpêtrière in Paris and the Queen Square Hospital in London began to publish what patients were teaching them. John Hughlings Jackson, like Hippocrates before him, made shrewd assertions from the bedside. 'Epilepsy', he said, 'is the name for occasional sudden, excessive, rapid and local discharges of grey matter.' Convulsive twitching of the hand, he pointed out, could only be due to circumscribed 'discharge' in a hand-control area of the brain. The epileptic illusions and hallucinations – Jackson called them 'dreamy states' – were, he said, psychical seizures as distinguished from motor seizures. They were, he pointed out, associated with local discharge in one 'temporosphenoidal lobe'. He suggested that a third type of seizure was the fit characterized by initial loss of consciousness. It might be, he suggested, due to discharge in the 'highest level' of nervous integration. This, he suspected, might be due to discharge in a frontal region. We know now that there is, in many of these fits, electrical discharge that originates in higher brain stem, conducting to the frontal areas.

Neurophysiologists, headed by Charles Sherrington and studying monkey and cat, described inborn reflexes and how they were integrated. Pavlov described the establishment of acquired or 'conditioned' reflexes in the dog and showed that what the dog learned could be abolished by removals of cerebral cortex. These reflexes, he said, formed the basis of learning. He adopted the working principle that mental phenomena accompanied a corresponding activity in the brain. But contemporary political philosophers took his work as evidence in favour of their materialist philosophy and a Marxian state with an atheist outlook.

Eight years after Lashley reported on his search for the engram, he made a final survey of the problem of cerebral organization and behaviour. That was in 1958. The behaviourist school in America, he observed, had carried Pavlov's idea of 'psychophysical parallelism' to 'its logical conclusion [by asserting that mental phenomena] do not provide a basis for any scientific study whatever. Their position', he added cynically, 'still leaves them with the problem of how man ever developed the delusion that he is conscious.'

Then he turned toward London: 'Three leaders in neurology,' he wrote, 'specialists in different fields, have asserted that mind cannot be explained by the activities of the brain and have sought to reseat the little man on his throne in the pineal gland' (Sherrington 1941, Eccles 1953, Walshe 1953).

'Sherrington,' he pointed out, 'after demonstrating that mind is not a special form of energy', proceeds to describe the possibility of assuming that 'the theoretically impossible happens' . . .

'Eccles', he remarked, 'accepts Sherrington's conclusion that the mind is not a form of energy, then evolves an elaborate theory as to how non-energy mind can act on matter, appealing to telepathy as supporting evidence.' Lashley dismissed all telepathic studies and extrasensory perception with characteristic glee: 'I still consider', he wrote, 'the gambling-house odds more reliable . . .'

'Walshe', Lashley continued, 'bases his argument for reviving the soul chiefly upon the assertion that man is more wonderful and more dignified than the earwig.' Without discussing earwigs, Lashley quoted from Archy the cockroach. (This cockroach, called 'Archy', is a character in the satires of the American humourist, Don Marquis.) 'a man', Archy once said, 'thinks he amounts to a great deal but to a flea or a mosquito a human being is merely something good to eat.'

Finally Lashley concluded: 'I am not ready to accept these doctrines of scientific despair and Christian hope.' Then he proceeded to speak of his own hope: 'The problem', he said, 'requires . . . a thorough analysis of the phenomena of consciousness, oriented with reference to the phenomena of neural activity. . . . The correlation may eventually show a complete identity of the two organizations.'

One must agree with him that, some day, correlation may show that the organizations are, somehow, one. But that 'some day' is far away. Indeed, in my opinion it may never dawn. In the meantime it is well to adopt the 'doctrine', as Charles Symonds expresses it, of an approach to the problem 'from two sides'.

Sherrington, choosing his own personal philosophy as every thoughtful human being must, did write in 'Man on His Nature': 'Let me prefer

to think that the theoretically impossible does happen.' Seven years later, when his 'Integrative Action of the Nervous System' was published a second time by the Physiological Society, he wrote from his place of retirement at Eastbourne these words: 'That our being should consist of *two* fundamental elements offers I suppose no greater inherent improbability than that it should rest on one only.' This, to my mind, is the way to leave the matter.

Some philosophers declare today that there is no brain-mind problem, stating that the answers are self-evident. Very well! There were philosophers who made similar assertions in Ancient Greece. If Hippocrates had accepted their dicta, he would never have pointed the way toward a science of man and nature. In the Hippocratic school, truth was sought through observation of man and in critical examination of phenomena. This was done in defiance of the 'unprovable hypotheses' of the philosophers and the superstitions of current religion.[1]

It is significant that Hippocrates himself, the founder of medical science, had his personal philosophy. It lives on today in every land as the physicians' own philosophy – compassion and honourable service to fellow man, a *religio medicinæ*.

It is time to have done with quibbling criticism. We all know there is no 'little man' sitting in the pineal gland where the seventeenth century philosopher, René Descartes, seemed to visualize him. Consciousness is not something to locate in space. But the neuronal activity that accompanies it is.

Sensation and movement and speech and perception are not located in special areas of the cerebral cortex. But there are cortical areas that can be delimited with increasing exactness for each of these functions. These cortical areas are parts of special mechanisms. In each of them one may identify the neurone transactions without which the corresponding mental phenomena are impossible. The action of each mechanism depends upon the cortical area, together with its connexions to underlying thalamus and other parts of the higher brain stem. Interference with brain-stem action results in unconsciousness. Cortical removals deprive a man only of one or more of his functional capacities. These are facts, not theories.

In the brain of man, the cerebral cortex plays a far more important role than it does at lower levels in the mammalian scale. There is, here, a greater amount of irreplaceable specialization. I would like to remind you briefly of three thalamocortical mechanisms which serve the purposes of learning and memory and then pass on to the engram of the stream of consciousness.

First, the motor skills. They are developed in both hemispheres. Second, a thalamocortical system for the ideational transactions of speech, developed in one hemisphere. Third, a perception mechanism that makes use of the interpretive cortex of the temporal lobes in both hemispheres.

It is now possible to delimit, at least partially, the cortical frontiers of these functional areas (Fig 1). They are created and elaborated as part of the learning process. Specialized memories are not stored but the corresponding neurone patterns are. The learned performance is normally reproduced by the automatic neurone action of each functional unit. What is learned of motor skill, of speech or of perception, leaves its accumulating 'memory trace' in each respective unit. But what has been learned is evident only when the mechanism is called upon. Each has, then, its own peculiar form of engram.

Electrical Stimulation

Let me make a short digression to discuss the material to which I must refer, and the theory of the meaning of cortical stimulation. Stimulation, with a gentle electrical current from point to point over the cerebral cortex of a conscious patient, serves as a most useful practical guide to functional boundaries and to the therapeutic excision of cortex. The material that had to do with experiential responses was summarized in the Lister Lecture (Penfield 1961).[1]

In the cortical areas from which positive responses are produced, the electrode demonstrates only what the functional corticofugal connexion is. For example: from the motor cortex, cell groups in lower brain stem and spinal cord are activated. No signal enters consciousness except indirectly as the patient becomes aware that certain crude movements which he did not himself command have taken place. From the sensory areas, somatic, visual or auditory neuronal conduction evidently leads inward into the organizing circuits which lie subcortically and centrally. The patient is conscious of only the most elementary sensation. The electrode does

[1]Hippocrates, with an English translation by W H S Jones (1948) Cambridge, Mass. & London; 1, 8

[1]With the help of my associate, Phanor Perot (Penfield & Perot 1963), I reviewed a case series in which 1,132 operations under local anæsthesia had been carried out. The purpose of the operations was to free the patients from focal epileptic seizures, if possible. The cerebral cortex was stimulated electrically in all cases and the responses of the conscious patient were carefully recorded by the surgeon's running dictation.

In 520 of these operations, one or other temporal lobe was explored by gentle electrical stimulation at various points as desired. Forty patients (7·7%) reported 'flashbacks' during stimulation (experiential responses). There were no such responses in the remaining 612 cases where other parts of the cerebral cortex were explored. Fifty-three of the temporal lobe patients complained of flashbacks of previous experience in their spontaneous fits

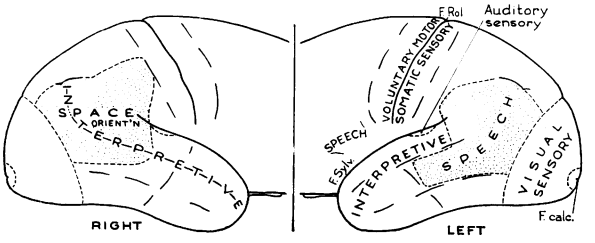

Fig 1 *Lateral surfaces of man's brain. Language learning and recall depend, to a large extent, upon conditioning of the thalamocortical speech mechanism in the dominant hemisphere. The interpretive cortex is part of a mechanism that scans the sequence-record of past experience and makes automatic interpretations of present experience*

not tell what is normally being added to function in the cortex.

Thus in the sensory and motor areas, the electrode produces only elementary responses. No clues as to the nature of new skills are demonstrated. But in the uncommitted cortex of the adult, if the electrode has any positive effect at all, it is illuminating and complicated.

The uncommitted temporal cortex is like a blank slate at birth. But it comes, in time, to be devoted, on the one hand, to the learning and the elaboration of language and, on the other, to perception. Perception may be defined as the automatic interpretation of the present as judged by past experience. Both of these mechanisms (that of speech and that of perception) have to do with specialized learning and with special memory stores.

In the area of cortex devoted to speech (Fig 1), a gentle electrical current produces only interference with function. That is to say, an aphasia. The aphasia vanishes instantly when the electrode is removed.

In the rest of the originally uncommitted cortex, which we may call interpretive, the electrode produces responses of two types. The effect appears in consciousness suddenly, to disappear with equal suddenness. It may be evoked in any part of the cortex that I have labelled 'interpretive' (Fig 1).

Scanning the Past

One of the two types of response is a sudden *signal of interpretation.* It is an automatic judgment of present environment such as the feeling that things are familiar, strange, coming near or becoming dangerous, &c.

The other response is an activation of the *stream of past experience.* This is what the patient often refers to as a 'flash-back' to his own past. When the electrode is applied, he may exclaim in surprise, as the young secretary, M M, did: 'Oh, I had a very, very familiar memory, in an office somewhere. I could see the desks. I was there and someone was calling to me, a man leaning on a desk with a pencil in his hand.' Or the patient may call out in astonishment, as J T did (when the current was switched on without his knowledge): 'Yes, Doctor, yes, Doctor! Now I hear people laughing – my friends in South Africa . . . Yes, they are my two cousins, Bessie and Ann Wheliaw.' Or, the patient may describe it quietly, as N C did: 'I had a dream. I had a book under my arm. I was talking to a man. The man was trying to reassure me not to worry about the book.' When a point 1 cm distant was stimulated, she spoke again quietly: 'Mother is talking to me.' Again, later, stimulation at the same point caused her to say: 'Yes, another experience, a different experience, a true experience. This man, Mr Meerburger, &c., &c.' R M said suddenly: 'A guy coming through the fence at the baseball game, I see the whole thing.' A little later he explained: 'I just happened to watch those two teams play when the fellow came through the fence . . .' T S remarked (immediately after temporal lobe stimulation) something about 'the street corner'. When the surgeon asked him 'Where?' he replied promptly, 'South Bend, Indiana, corner of Jacob and Washington.' A little later, stimulation without warning caused him to say, 'that music from "Guys and Dolls".' Then, after the surgeon had withdrawn the electrode, he remarked: 'I was listening to it . . . It was an orchestration.' These cases have been published and the same initials used (*see* Penfield & Perot 1963, also Penfield & Jasper 1954) I need give no further examples.

A good many patients were caused to hear music. In general, each of them seemed to be present while listening to orchestra or voice or choir. The same piece of music could be recalled by the electrode after a short interval and the subject, if asked to do so, could hum along, accompanying the piece that he was hearing.

The ganglion cell or cells which responded to the current applied by the electrode to the pia mater is (or are) more easily activated for some minutes after the first response. Thus the same experience, beginning at the same moment in previous time, may be summoned again even by replacing the electrode at a little distance or by using a 'weaker' current.[1]

[1]Thus, stimulation of the interpretive cortex is subject to the rules of facilitation pointed out by Brown & Sherrington (1912) for the mammalian motor cortex and for the human sensory cortex, by Penfield & Welch (1949)

In briefest summary, the experiential response to the surgeon's electrode is this – an evoked awareness of the thoughts and feelings that once moved through the subject's mind. From moment to passing moment, they move now once more with the freshness of a present experience.

The auditory or visual components are always prominent. In many instances both are prominent. But periods of silent thought or calculation or physical exercise or eating or sexual activity did not appear although they occur frequently enough in all men's lives. This may well suggest that the interpretive cortex serves a function closely related to the visual and auditory experiences that a man might understand but hardly other mammals. The experiences he might well share with dog or monkey do not appear.

Speech and Perception

In the rat there is, I am told, no uncommitted cortex between visual and auditory sensory areas (Fig 2). In the case of man, the comparatively large expanse of uncommitted cortex between the two seems to have pushed the visual cortex backward into the longitudinal fissure and to have caused the auditory cortex to disappear from the convexity in the fissure of Sylvius (Heschl's gyrus).

After the learning period of childhood, destruction of the temporal speech cortex on the dominant side produces aphasia. Removal of this area in the non-dominant hemisphere produces a reduction in capacity to interpret relationships in space that is sometimes quite marked. The patient loses capacity to perceive the scheme of things. Lhermitte called it a defect in 'pensée spatiale' and Paterson and Zangwill 'spatial thought'; George Riddoch spoke of it as 'visual disorientation', Russel Brain 'spatial disorientation' (*see* Critchley 1953, Hécaen *et al.* 1956).

One may conclude that the thalamocortical speech area and the interpretive areas make possible these specific learned functions. But where is the memory trace that preserves the sequence of the past? Certainly it is not in the temporal cortex where the electrode is applied.

In the 1957 Sherrington Lecture, I was led by study of the stimulation and clinical evidence to 'suggest that the actual ganglionic patterns of remembered experience are situated at a distance from the temporal cortex', probably in 'the hippocampus of both temporal lobes and their integrating circuits' (Penfield 1958). Perhaps I may change and, at the same time, substantiate that suggestion now.

Hippocampal System

Because it may be important for the eventua understanding of the engram mechanism, let me refer briefly to the anatomy of the rhinencephalon. In the primates and man, one may say that the ancient smell-brain has less to do with olfactory sensation and more with something else. It is represented by a much diminished olfactory bulb and by the structures in the hippocampal zone. These latter structures were once the archipallium, the mantle or cortex of the smell-brain. Now they are crowded out of sight, beneath the neocortex. The hippocampus (sometimes called

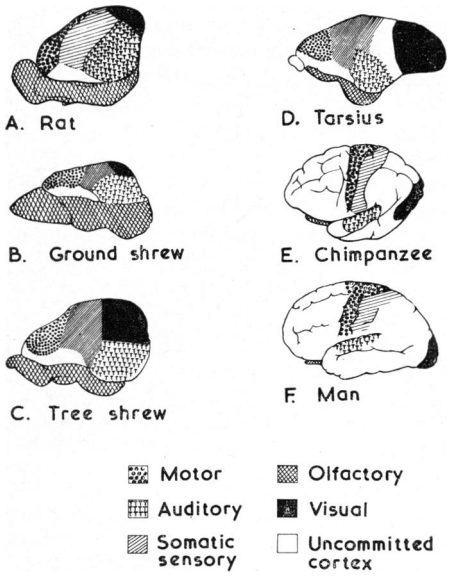

Fig 2 *Diagram of some mammalian brains, from rat to man, to show the approximate extent of uncommitted cortex as contrasted with sensory and motor cortex. Prepared by Stanley Cobb)*

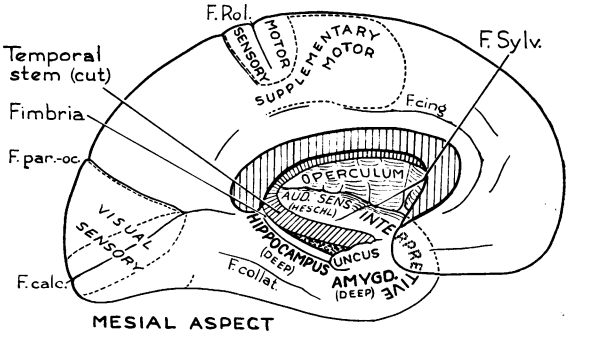

Fig 3 *Mesial aspect of the left hemisphere from which the insula (island of Reil) and the brain stem have been removed. Note that the auditorisensory cortex is on the inner surface of the temporal operculum as well as some of the interpretive cortex. The hippocampal formation is adjacent to the internal capsule (temporal stem)*

Ammon's horn) is a strangely structured organ rolled up like a rug on the floor of the inferior horn of the lateral ventricle while the parahippocampal gyrus, beneath it, forms a sort of collar that hugs the peduncles of the forebrain closely as they pass downward into the posterior cranial fossa. The parahippocampal gyrus terminates forward, on the undersurface of the temporal lobe, in a hook-shaped elevation, the uncus, beneath which is a large nucleus of grey matter, the amygdala (Fig 3).

Smell and the ability to record and to recall the memories of smell were important in the animal forms lower in the scale from which the brain of man evolved. And one might well wonder: Perhaps the memory mechanism once used in an olfactory world is being employed for memory still, by man, in his world of sound and sight and words and perceptions.[1]

Perhaps I may refer briefly to some neurosurgical observations: Electrical stimulation of the olfactory bulb as it lies on the cribriform plate invariably causes a conscious man to experience a crude odour, much like the analogous visual and auditory and somatic responses. But electrical stimulation in the hippocampus has never evoked a sensation of smell and only rarely in the amygdala. Stimulation of the hippocampus produces no observable response of any sort.

On the other hand, a stimulus in the amygdala (or peri-amygdaloid region), that is strong enough to be followed by ictal discharge, does. It results in a very peculiar epileptic attack. The discharge may, of course, involve the direct connexions with adjacent diencephalon. In any case, it is characterized by automatic behaviour and amnesia.

Hughlings Jackson recognized these attacks in clinical practice and he localized them quite accurately. He called them 'uncinate fits'. During such a fit, the patient moves about, fumbling with his clothing and smacking his lips in a state of complete confusion, resistant to reason and brooking no interference. Or, in a less severe seizure, he may carry on a line of complicated behaviour previously planned. For example, he may walk safely through busy streets. But he is an automaton, not open to new reason and not making a memory record. The invariable characteristic of such attacks is this: They are followed by complete amnesia for all that has transpired during the episode.

In 1954 my associate William Feindel and I reported twelve examples of such attacks of automatism produced by deep stimulation in the peri-amygdaloid region during operations intended to cure this condition. We concluded that the after-discharge produced in the amygdaloid area by the strength of our stimulus fired across through direct connexions into the hippocampal system of the opposite hemisphere. On the basis of this hypothesis there would be, for the duration of each seizure, complete interference with the function of the amygdala-hippocampal mechanisms bilaterally and, no doubt, their central connexions.

As worked out by Cajal and Edinger and other anatomists for the brain of lower animal forms, the afferent stream of nerve impulses passes from olfactory bulb to the amygdala and hippocampal formations on either side. An efferent stream then emerges from the hippocampal system on each side by way of nerve fibre bundles, the fimbria and the fornix. This efferent stream of impulses flows directly across into the hippocampal system of the opposite side. But it also makes crossed and uncrossed connexions with all parts of the brain and especially with the diencephalon.

Hippocampus and Memory

Gradually between 1939 and 1949 we came to realize in our clinic that the anterior half of either temporal lobe could be removed with impunity while treating temporal lobe epilepsy by excision. The hippocampus was usually left intact. During the next two years, urged on by the need of our epileptic patients, we gradually gained the courage to remove the hippocampal zone – first on the right, nondominant side and finally on the left. Indeed we were learning that this area *should* be removed as well, for here the sclerotic lesions produced by birth compression were apt to be most severe.

These more complete anterior lobectomies produced, at first, little or no loss of function except for an upper quadrantic homonymous defect in the field of vision. Then came the first example of memory loss. That was in September 1951.

Case 1 The patient was, by profession, a civil engineer. I had removed the anterior portion of the left temporal lobe in 1946, five years earlier, leaving the hippocampal formation intact. In Fig 4, the broken line and shaded areas show the extent of removal. There had been no resultant functional defect after that operation but the man was not relieved of his attacks; he still suffered from fits of automatism in which he would stare, be obviously confused, walk about unpredictably, smacking his lips and chewing. The attacks had decreased in number but they were unchanged in character. Fearing he might lose his employment, he returned in September 1951, ready, he said, to 'take a chance on anything'.

[1]In the dogfish, the olfactory brain forms the major neuronal structure. There is no more than a small beginning of a non-olfactory brain. Moving up the biological scale as far as the rat, the olfactory brain is still large by comparison. It seems to form an undercarriage for the auditory, visual, somatic and motor portions of the organ as shown in Fig 2

So, in 1951 the whole left hippocampal formation was excised as shown by the dotted line and stippled area in Fig 4. We were stunned to discover, following operation, that the patient had an amnesia which was retrograde, going back into the recent past. More than that, he could no longer remember the events of each day. His general condition was excellent and he had no aphasia although his left hemisphere was the dominant one for speech. The hippocampal zone we had removed showed incisural sclerosis.[1]

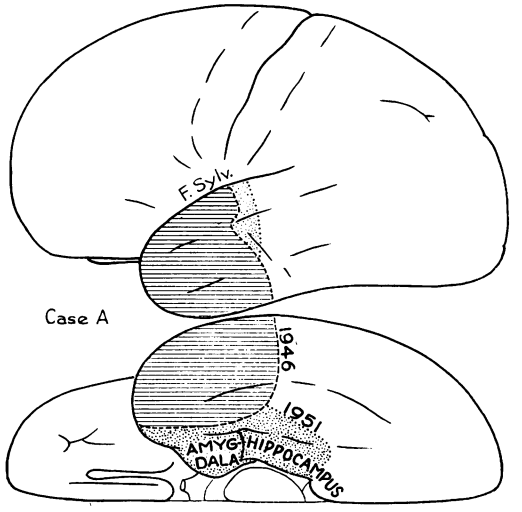

Fig 4 **Case 1** *Diagram to show the anterior tissue of temporal lobe excised in the first operation, also the hippocampal zone excised at second operation*

Was it possible that the hippocampal zone or the hippocampus on the other side had been completely destroyed at the time of birth and that our removal had thus produced a bilateral hippocampal deficit? Would such a bilateral lesion really result in memory loss? We continued to carry out these operations none the less, but with greater caution. A good many patients were cured of their seizures but, in October 1952, it happened again.

Case 2 The second case was that of a glove cutter. The left anterior temporal lobe was removed, including the whole hippocampal zone. Operation was followed by a defect in memory and learning which had the same peculiar pattern as that of the engineer. In Case 2, as in Case 1, we could only surmise that head compression, while passing through the mother's birth canal, had destroyed the hippocampal zone on the side opposite to the operation and produced no more than an epileptogenic scar on the side of our excision.[2]

My associate Brenda Milner and I followed anxiously the subsequent story of the two patients who had suffered memory loss. She studied them with the battery of psychological tests that she has adapted to clinical purposes and we planned to publish their cases in full detail. The engineer and the glove cutter were severely handicapped by the memory loss, yet each of them was able to continue to earn his living: each had preserved the memory of his special skills. The engineer continued to draw excellent blueprints. While his attention was focused on the problem in hand, he could understand and make the drawings accurately but, if he turned attention to something else and then turned back to the drawing board, all memory of what he had done and proposed to do was a blank. Thus he made copious notes by hand and substituted these for what he should have been writing down in the brain's own sequential record. The glove cutter, with less elaborate effort to compensate for his defect, was still an expert glove cutter.

Then, before Mrs Milner and I had finished our manuscript, I discovered that, without intention, the perfect experimental test of some of our theories had been made. Dr William Scoville (in his search for a better operation to replace frontal lobotomy as a treatment for otherwise hopeless psychotics) had removed the hippocampal formation completely and bilaterally in two such patients. He made his approach beneath each temporal lobe, without molesting other cerebral structures. On my suggestion, he invited Dr Milner to study his post-operative patients in Hartford and they published their evidence (Scoville & Milner 1957). Milner finished our manuscript in 1958 and described the memory loss as follows (Penfield & Milner 1958): 'Bilateral removal of the hippocampus and hippocampal gyrus in man', we concluded, 'produces loss of recent memory. As soon as he has turned his attention to something else, the patient is unable

[1]To find an explanation for this unexpected memory loss, I turned to the Laboratory of Neuropathology. We were at that time in the midst of a pathological study which was to be published by Earle, Baldwin & Penfield (1953). In this report, the examination of 157 such cases led to the conclusion that the most frequent cause of temporal lobe epilepsy, even when it made its appearance years after birth, was the sclerotic scar produced by herniation of the hippocampal margin of the temporal lobe through the incisura of the tentorium into the posterior fossa during compression of the infant's head as it passed through the mother's birth canal. Such compression of the infant's head may, of course, produce herniation, with injury, on one side or on both

[2]Since 1952, my associates, led by Theodore Rasmussen, have devised better techniques of testing patients. They can now determine whether or not the hippocampal zone can be excised without fear of serious memory defect. The *intracarotid amytal test* is particularly reassuring (Milner *et al.* 1962): Injection of amytal into one internal carotid artery paralyses function in the hemisphere on that side for a few minutes. During this period, brief memory tests can be carried out. If there is no evidence of amnesia, the hippocampus excision can apparently be carried out without fear

to remember what was happening a moment earlier. It is as though he had made no record of present experience.' Or, one might add, having made the record as usual, he had lost the mechanism that enabled him to reactivate the record by voluntary initiative. This latter explanation is made more plausible by the fact that the patient had an additional defect. He had 'a retrograde memory-loss that covers a considerable period before operation. In spite of this, memory for the distant past is not lost, nor is there corresponding loss of attention, concentration, reasoning ability, or previously acquired skills. The intelligence quotient shows no drop when compared with pre-operative testing. There is no interference with speech, and the memory of words is unimpaired.'

Final evidence that the engineer (Case 1) had a bilateral lesion has since come to light. In April 1965 he died from a pulmonary embolus. Autopsy examination of his brain, as studied by my associate, Gordon Mathieson, showed the right hippocampus (on the side opposite to the operation) to be greatly shrunken and the structure of cornu ammonis to be 'only faintly discernible'. On the other hand, the amygdala was normal and the parahippocampal gyrus grossly 'within normal limits'.

It is now quite clear that this memory defect is produced only by bilateral interference with the hippocampal mechanism. In our 1958 report (Penfield & Milner 1958), we were able to state that we had carried out careful psychological study of the cases of more than 90 patients before and after the same unilateral operation (in addition to Cases 1 and 2) and they showed no evidence of general memory loss. Under normal conditions, then, one hippocampal area can duplicate the work of the other. Either can carry on when its fellow is removed.

Pathological Evidence

These findings were a confirmation of a suggestion made by Glees & Griffith (1952). From an autopsy study of one patient with a bilateral brain lesion, those authors had suggested that 'the hippocampal formation of the adult seems to be essential for recent memory'.

Ten years later, in a comprehensive study of the 'amnestic syndrome', Raymond Adams (1962), speaking for himself and his associates, has come to the summary conclusion that even small bilateral lesions that involve the 'hippocampal formations, fornices and medial parts of the diencephalon . . . abolish general memory function. . . . Memories early in life are often retained.'

J Z Young (1965) has studied exhaustively the organization of a memory system in the octopus and Charles Symonds has made a recent 'speculative interpretation of the clinical data' to explain the oft-recurring pattern of pathological memory loss (Symonds 1967).

Conclusion

But now I shall bring this lecture to its own conclusion while my hearers can still recall the beginning. Memory is the power or the process of reproducing or recalling what has been learned. There are memory mechanisms in man, functional units that serve the purposes of *learning* and *reproducing*. They are well integrated in the total action of the brain and yet they are capable of separate action under a control that is partly conscious and voluntary, partly automatic and involuntary.

Pathological evidence and the evidence of surgical excision make it clear that bilateral interference with the function of the hippocampal system produces retrograde and antegrade amnesia of a peculiar type. There is loss of memory of events for some years previous, with a fair preservation of memory of the distant past. There is also inability to recall (or possibly to record) all the succeeding conscious states of mind from the date of the hippocampal lesion onward.

The surgical evidence indicates that a unilateral removal of the hippocampal system on one side has little or no effect on memory. Bilateral interference produces the syndrome just described. It is due to interference with mechanism A, listed in Table 1.

Table 1

Some mechanisms of memory

A.	*Sequence record of experience:*	Engram of the stream of consciousness
B.	*Sensorimotor skills:*	Conditioned reflexes . . . thalamocortical
C.	*Speech mechanism*	
D.	*Perception mechanism:*	Automatic scanning of past and interpretation of present

Consider the cases of the engineer and the glove cutter that I have described. There was no interference with sensorimotor skills or speech (except that there seemed to be no further learning that would have improved them normally). Both men continued to speak without aphasia and each could still earn his living because he retained his sensorimotor skills. The engineer was demoted as department supervisor but he continued as draftsman. He added nothing more to his skills but, as long as he kept his mind on the data presented to him, he could carry out the preparation and the drawing of blueprints; if his attention was called to something else, even for a moment, he could no longer recall what had been in his mind – he had to read his instructions and make

his own analysis all over again. There was nothing wrong with the centrencephalic organizing process that enabled him to call on his already-established, conditioned reflexes – namely, his skills and his speech mechanism and his well-established concepts. Both men could judge the orientation of objects in space. They could recognize the purposes of well-known objects in the familiar environment. And yet the glove cutter did not recognize the 'girl-friend' he had known for eighteen months before operation. This suggests that the perception mechanism could no longer carry out its automatic function of scanning the record of experience of the (recent) past.

Thus there were two defects from which each of these men suffered: (1) An inability to recall the details of recent awareness, details that should not, normally, have faded beyond recall. (2) A defect of automatic perception.

(1) In the first instance, although each could focus attention on a voluntary project as long as he held that project in view, he could not find his way back to the project after even a momentary interruption. One must assume either that he had lost the mechanism of voluntary recall or that no 'record of his consciousness' was now being made.

(2) In the second instance, automatic reflex recognition of a person (who would have been recognized before the hippocampus was removed) is no longer possible. Here, either the past record has been destroyed (A, Table 1) or the mechanism of automatic recall has been lost (D, Table 1).

Other forms of recall were still possible. There was no interference with word memory. The speech mechanisms (C, Table 1) were obviously intact. Such objects as drawing implements and glove-cutting equipment were still recognized and could be used according to his voluntary initiative. This was presumably due to the fact that the sensorimotor conditioned reflexes (B) were still intact.

These facts throw light on the function of the hippocampus system. It is conceivable that, through its two-way diencephalic connexions, the hippocampus system plays an essential role in the *recall* of past experience, whether (1) in response to voluntary initiative (through the attention-focusing mechanism) or (2) to the automatic perception mechanism (D). When the central hippocampal connexions are intact, these functions can obviously be discharged by one hippocampus as well as by both.

Each attack of automatism (which is due, we believe, to epileptic discharge in the whole hippocampal system with involvement of its central connexions) is followed by retrograde amnesia for the time of the attack. This might argue that the hippocampal system really does have something to do with the recording as well as with the recall of states of consciousness.[1]

This question of hippocampal function cannot now be given a final answer. But these facts should guide us to reasonable theories.

Engram of the Stream of Consciousness

And now for a brief concluding reference to the sequence-record of experience (Mechanism A in Table 1) and its obvious relationships to the other mechanisms (B, C, and D) which are, one may suppose, established secondarily.

In the vast circuitry of the human brain the evidence of an engram, a recording of succeeding states of consciousness, is clear. There is now a beginning of evidence as to its nature. The fact that the application of a gentle electrical current, on certain portions of the temporal cortex, can switch on the recording, suggests that the engram is, in fact, a permanent and continuous thread of facilitation. Facilitation lowers the threshold of resistance to the passage of nerve impulses.

This should not suggest to us that the engram and its thread of facilitation are localized in the temporal cortex beneath the surgeon's electrode. Indeed it suggests only that there is a scanning mechanism, in the temporal cortex, that is capable of activating the thread of facilitation at a distance.

This sequence is the sort of thing for which Lashley was hoping to find evidence in pursuit of the engram by means of brain-removals. But if he had destroyed it in the animals he studied, they might well have preserved (like the engineer and the glove cutter) the conditioned sensorimotor reflexes acquired in their training and thus they would have continued to behave normally in the test environment.

The engram of the stream of consciousness is the sequence record of what came within the focus of a man's attention – his awareness, his thoughts, and his emotions. No one can prove that the record is complete for the whole of man's conscious past, although it is difficult to conceive why it should be discontinuous. As to localization, there are two possibilities: Either (*a*) this permanent path of facilitation runs like a thread or a bundle of threads through the inner labyrinth of the human brain, reproducing the neurone action that made the former states of consciousness possible. It was, one may suppose, the passage of electrical potentials through this 'inner labyrinth' that was the basis of consciousness once and becomes so again when the electrode is applied to a man's temporal cortex. Or

[1]An alternative suggestion is logical, however unlikely it may appear: The hippocampus system could actually contain the neuronal records of the sequence of conscious experience (A, Table 1). In that case, the record is a double one, duplicated in the two hippocampuses

(*b*) there is, in some region of the brain (such as the hippocampus), a special recording-mechanism which (like a wire-recorder or a tape-recorder) can somehow cause the former thought-sequence to march again through a man's consciousness. If the hippocampal system is actually such a recorder, the record is duplicated in the hippocampus of the two sides.

The focusing of attention, as described in the case of the engineer, is a process that is not disturbed by bilateral absence of the hippocampus. Under normal conditions, the recording must, one would suppose, take place before the man's attention turns to another matter. In the absence of the hippocampus mechanism, either the record was not made or the mechanism of recall no longer functioned.

Normally, the focusing of attention has other lasting effects on the brain: There must be, at the same time, an impact on whatever conditioned reflex may be concerned, whether it has to do with motor skill or speech or altering concept. These are all things that are formed and shaped and altered in the light of focused attention. It seems to be true of these acquired mechanisms, as it is of the sequence-record. Only those things to which a man paid attention are preserved in the record or added to the automatic mechanism. The sights and the sounds and the somatic sensations that he ignored are not preserved in any engram form.

In conclusion, what can be said in regard to localization of the 'engrams in the human brain'? Four brain-mechanisms (Table 1) begin to emerge in the consideration of memory. It is obvious that no more than a comparative delimitation and cerebral localization will ever be possible.

Motor skills disappear when areas of motor cortex are excised but the automatic reflex action of these areas is also clearly dependent upon acquired connexions through the thalamus to various other functional areas of the brain. The patterns of thalamocortical organization, for any skill, must continue to alter as long as a man continues to learn. Thus they are, in fact, sensorimotor skills and the 'sensory' refers to auditory and visual sense as well as somatic.

The speech mechanism is somewhat more clearly delimited than the others as far as the cortical areas are concerned and it is localized to one hemisphere, at least in the great majority of people. Language, none the less, is learned in a manner not unlike the other skills. Speech might be looked upon as a special conditioned reflex. In a certain sense, it is a collection of conditioned reflexes that enable a man to write and to speak and to use that special skill that makes possible the interpretation and the understanding of the spoken and the written word.

Finally, perception mechanisms make use of certain areas of the temporal cortex which, for lack of a better name, we have called interpretive cortex. It seems evident that the interpretive area of cortex is part of an automatic mechanism which scans the record of the past. It makes subconscious automatic judgments that have to do with the individual and his environment. The basis for perception of the meaning of things must be learned, as that of words and language are learned.

To what extent concept formation and remembered generalizations and memorization by repeated review may also be served by other special mechanisms are matters of present surmise and future test.

The engram is the permanent impression left behind by psychical experience in the brain's cellular network. This 'memory trace' makes all that came within the focus of a man's attention memorable in one way or another. It may modify or reinforce a skill. It, also, forms a part of the record of the stream of consciousness and may be summoned consciously or automatically for the purpose of recognition, interpretation, perception. What a man has ignored leaves no discoverable trace.

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