STRUCTURE AND FUNCTIONS OF THE LIMBIC SYSTEM ("VISCERAL BRAIN") : A REVIEW

By

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There can be no better introduction to the subject of *limbic system* than in the words of Fulton (1951) in "*Frontal Lobotomy and Affective Behaviour*". "Among the most significant developments in modern neurology–if not in all scientific medicine–has been the gradual recognition of the existence of vast areas in the forebrain in subserving autonomic function and forming the structural background not only of emotional expression, but of affective behaviour in the broadest sense. In every field of human endeavour new knowledge unfolds slowly, and so it has been with the autonomic nervous system. I know of no more revealing theme in the whole range of medical history than that of how the functional significance of autonomic nervous system has come to be recognised, particularly in its bearing upon the phenomena of human behaviour. Human behaviour, indeed, can no longer be considered a thing apart and unrelated to anatomical structures and physiological function ; by the same token the science of psychiatry has become one in which we are now forced to correlate structure with function." It will be endeavoured to trace in this review the circumstances which have brought this about.

The most important recent disclosure relating to the physiology of the nervous system has been the recognition of the functional importance of the limbic system. The limbic system was first defined by Paul Broca in 1878 and his original definition is given below :—

i.e. "*Le nom de circonvolution limbique que j'ai adopte indique les rapports constants de cette circonvolution avec le limbe de l'hemisphere ; il n'implique aucune theorie ; n'exprimant has une forme determinee ; il est applicable a tous les cerveaux des mammiferes, a ceuz qui on un vrai corps calleux comme ceux dont le corps calleux est nul ou rudimentaire (lyencephales d' Owen), a ceux qui ont un vrai lobe olfactif, comme a ceux dont le lob olfactif n'est qu'al'etat de vestige. Enfin, il a l'avantage de permettre de designer sans changement d'adjectif les parties quise rettachent a la description de cette circonvolution : le grand lobe limbique, la scissure limbique, Parc limbique superieur or inferieur, etc.*"

"The name of limbic convolution that I have adopted indicates the constant ratio of proportion of this convolution with the limb of the hemisphere. It does not imply anything theoretical and does not express a definite form. It is applicable to all the brains of the mammals ; to those who have a true corpus callosum, as well as to those in whom the corpus callosum is absent or

> rudimentary (brain of Owen). It is also applicable to those who have a true olfactory lobe, as well as to those in whom the olfactory lobe is not prominent. It is advantageous to designate, without change of the objective, the parts which are linked to this convolution as the big limbic lobe, the limbic incissura, the superior and inferior limbic arcs, etc."

Broca thus demonstrated that a large convolution which he called the great limbic lobe is found as a common denominator in the brains of all mammals. He chose the word limbic to indicate that this lobe surrounds the brain stem. In accordance with the theory of Papez (1937), experimentation in recent years has shown that the limbic lobe is also, physiologically speaking, a common denominator of a variety of viscerosomatic and emotional reactions in the mammal. Furthermore, it has been found that the limbic lobe and its subcortical cell stations constitute a functionally integrated system which may be appropriately designated as the '*limbic system.*

Broca was thus primarily concerned with the gross morphological relations of the limbic lobe, and it remained for Ramony Cajal to give the first adequate analysis of the finer structure and connections of this phylogenetically ancient part of the forebrain. Cajal (1903 ; and translations by Kraft 1955) was aware that all parts of the limbic system were interconnected, the pyriform with the hippocampus, the cingulate with the parasplenial and sub-callosal gyri, and that the limbic system as a whole projected to subcortical nuclei such as the amygdala, anterior thalamic nuclei, hypothalamus, and basal ganglia. He was not fully aware, however, of the major afferent connections of the limbic system from spinal cord and midbrain. Indeed, the afferent supply of the limbic system has been further clarified only within the last few years.

It remained, however, for a comparative neurologist to call attention again to the forgotten cortex in the limbic lobe and to give the most comprehensive formulation to date of its possible role in emotional behaviour. This was in 1937, when Papez, in a remarkable paper entitled "A proposed mechanism of emotion," drew extensively from his own researches and the literature to show that the so-called rhinencephalic structures (limbic system) constituted a "harmonious mechanism which may elaborate the functions of central emotion, as well as participate in emotional expression".

Early in this century it was recognized that the "higher" brain centres of the neocortex represent autonomic as well as intellectual and sensorimotor functions. The implicated areas then were the sensorimotor and premotor cortices. The evidence for their involvement in autonomic functions was summarized thoroughly by von Bechterev (1911). Through the later work of both Ranson and his colleagues (1935 ; 1938 ; 1939 ; 1940 ; 1942) and Hess (1945; 1947, 1948, 1949) the hypothalamus came to be regarded as a central effector organ of the autonomic nervous system. Sherrington (quoted by Fulton 1951) designated it as the "*head ganglion*" of the autonomic nervous system.

However, many areas of incomplete knowledge remained. The interconnections between hypothalamus and frontal cortex were not clear. The mechanisms of conscious, preconscious, and unconscious, and the manner in which they influenced and were influenced by autonomic phenomena, were unknown ; and until recent years the problems which arise out of the translation of symbolic functions into autonomic reactions had not even been clearly formulated.

The reason why the limbic system has now assumed such conspicuous importance lies in the fact that phylogenetic and cytoarchitectural studies together with recent physiological investigations have suggested that this system represents an early neural development involved in the higher control of autonomic nervous system and affectively determined behavior (MacLean 1949). It influences many phases of autonomic function as well as patterns of emotional behaviour. It perhaps also serves to integrate the higher intellectual functions of the neocortex with the more primitive visceral functions. As a result of recent studies, the limbic lobe has emerged as a distinct functional entity concerned primarily with the regulation of visceral organs and elaboration of affective behaviour, while the neocortex is recognized as presiding in large measure over conscious sensory perception and the more purely intellectual functions of the brain. MacLean (1949) draws the conclusion that this phylogenetically old limbic system "appears to be so strategically situated as to be able to correlate every form of internal and external perception, and the possibility exists in this region for bringing into association not only oral (smell, taste, mouth) and visceral sensations, but also impressions from sex organs, body wall, eye and ear. In contrast to the *neopallium* (*neocortex*), this region has many significant connections with the hypothalamus for discharging its impressions. Intellectual functions, on the other hand, are associated with the newest and most highly developed parts of the brain (neocortex). This situation provides a clue to understanding the difference between what we *'feel'* (limbic system), and what we *'know'* (neocortex)". On the basis of these conclusions, MacLean (1949) has given the designation of "*visceral brain*" collectively to all the structures included in the limbic system.

I. LIMBIC SYSTEM–COMPONENTS.

The limbic system comprises the cortex contained in the great limbic lobe of Broca, and its associated subcortical cell stations. The limbic lobe, including the infolded hippocampus, was so named by Broca because it completely surrounds the hilus of the hemisphere.

The important components of the limbic cortex are the orbitomesial surface of the frontal lobes, the anterior cingulate gyrus, the anterior insular area, the temporal polar area, the pyriform (periamygdaloid) area, the

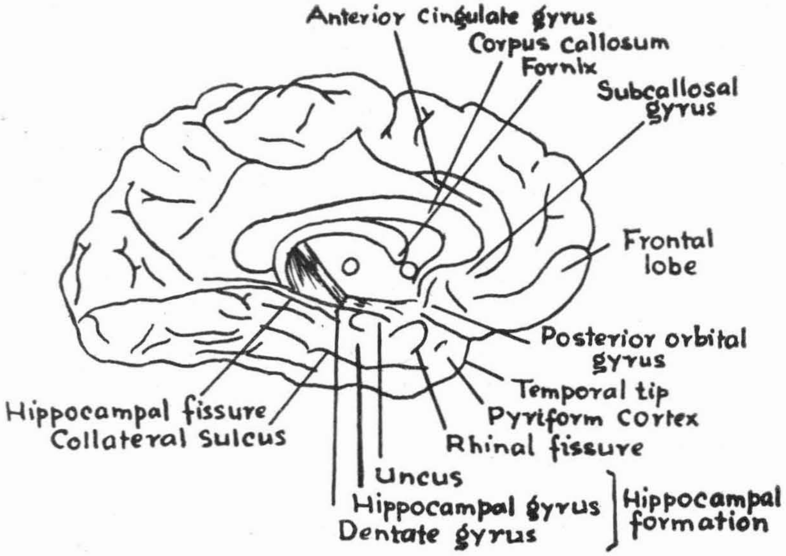

Fig. 1

Semidiagrammatic representation of different parts of the limbic system on the medial and ventral surfaces of the cerebral hemisphere. Cortical areas surrounding the hilum constitute the great limbic lobe of Broca.

hippocampal and dentate gyri, and the uncus (Fig. 1). These cerebral cortical regions are phylogenetically more primitive and fall within the classification (Cobb 1950) of *archipallium* or *allocortex* (primitive rhinencephalon–simple and principally two to three layered cortex), and *mesopallium* or *transitional cortex* (six layered but more simple than the neopallium), as differentiated from the well developed six layered *neopallium* or *neocortex* which is phylogenetically more recent in origin. These limbic cortical regions can thus be differentiated from neocortex both phylogenetically as well as cytoarchitecturally. Its subcortical cell stations include the amygdaloid nuclei (further subdivided into anteromedial group and basolateral group, the hippocampus (Ammon's Horn) (Fig. 2), the septal nuclei, the hypothalamus, the anterior thalamic nuclei, parts of the basal ganglia, and perhaps also the epithalamus.

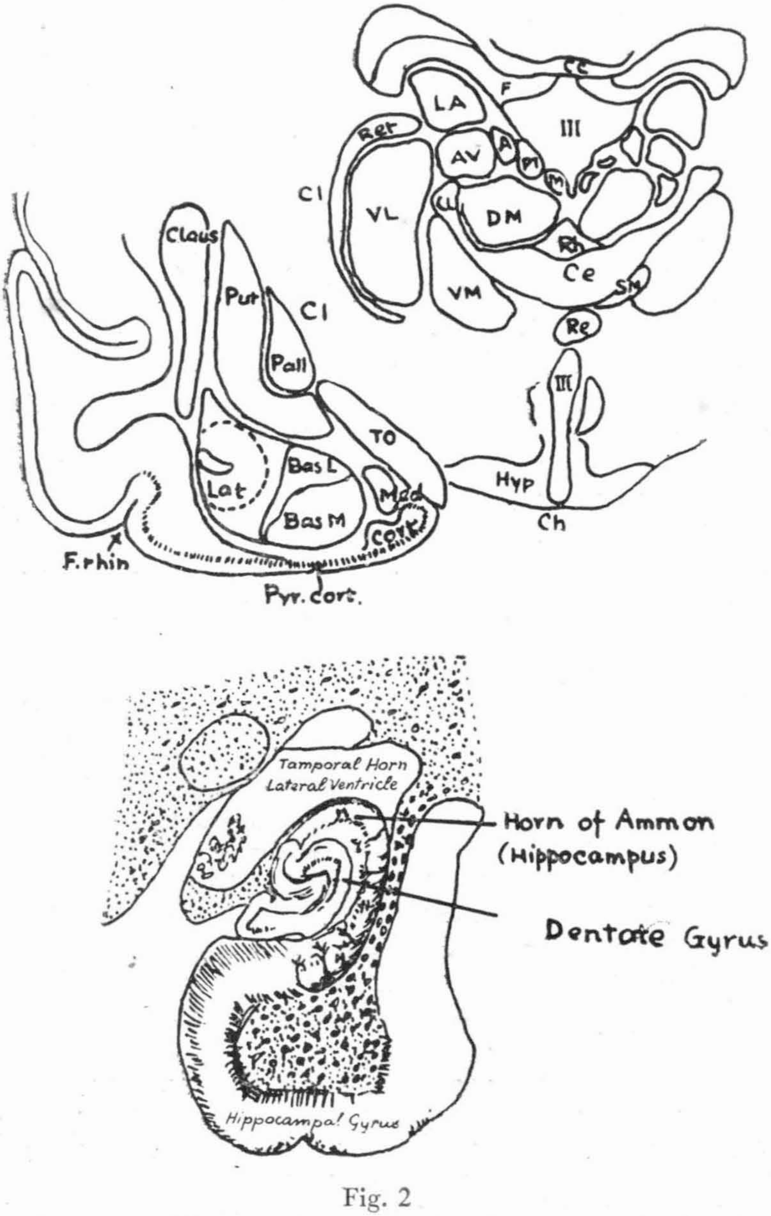

Fig. 2

Upper figure is a semidiagrammatic representation of transverse section through temporal lobe and diencephalon, showing the arrangement of amygdaloid nuclei in relation to hypothalamus and thalamus. Lower figure is a transverse section of temporal lobe through hippocampal and dentate gyri, showing the arrangement of hippocampal formation. Abbreviations used are : Med.—Medial nucleus of amygdala, cort.—cortical nucleus of amygdala, Lat.—lateral nucleus of amygdala, Bas. L. and Bas. M.-basal nucleus of amygdala (lateral and medial parts), Pyr. Cort.—pyriform cortex, F. Rhin.—rhinal fissure, G. I.—internal capsule, Pall.—globus pallidus, Put.—putamen, Claus.—claustrum, To.—optic tract, Hyp.—hypothalamus, III—third ventricle.

As Broca pointed out, the limbic lobe forms a common denominator in the brains of all animals. The experimentation of the last 15 years suggests that the limbic system also provides a common denominator for a variety of emotional and viscerosomatic reactions in the brains of all mammals. Its relative constancy of gross and microscopic structure throughout the phylogeny of the mammal contrasts strikingly with the structure of the neopallium that mushrooms around it.

II. PHYLOGENETIC DEVELOPMENT AND CYTOARCHITECTURE.

A perspective of phylogeny indicates that the design of the neural chassis included within the brain stem and spinal cord is essentially similar in all animals. This neural chassis provides the mechanism for integrating and acting reflexly upon the messages coming from the internal and external environment. But as the resulting behaviour is largely of the reflex type, it means that it is also stereotyped. The neural chassis, therefore, "is in some way analogous to the chassis of an automobile. What it lacks, really, is a driver at the wheel, to give it direction and to decide on alternative courses of behaviour" (MacLean 1954).

It is the development of such a driver that represents in evolution the chief modification, and addition to, the central nervous system. Its harbinger is found in the hypothalamus and olfactory apparatus of fishes, two structures so closely allied in some of these primitive forms that they are practically indistinguishable (Herrick 1924).

The elaboration of the forebrain is presumed to have resulted from the wide range of adjustments that faced the animal after he left the relatively stable environment of the water for a more unpredictable life on the land (Johnston 1923). It is significant that the new formation is organised around the sense of smell, a sense that is unique by being intero-and exteroceptive, and one that is vitally concerned in "feeding, nutrition, reproduction," and avoiding what is harmful (Herrick 1933). It was as though Nature, in fashioning the new driver, had sought to compromise on one who would ensure a homeostasis between the new demands of the outside world and the continued needs of the inside world.

In phylogeny the distinguishing feature of the budding driver–a cortex with a distinctive layering of the neural elements–is not found until the appearance of the reptile. Microscopic examination shows that such a sheet of cells practically covers the entire hemispheres which in this form have ballooned out to considerable size in the region of the olfactory apparatus. By the use of silver stains comparative neurologists have shown that the pathways projecting on these sheets of cells are predominantly those relaying viscero–olfacto–gustatory incitations, together with somaesthetic appreciations from the head and mouth (Johnston 1906). But there is evidence that the visual and, probably, the auditory systems also find some representation. The inference is made that the structural innovations provided by the evolutionary development of the cortex allow a great increase in the range of the animal's comprehension and decisions and thereby emancipate him, in part, from the chains of stereotyped reflexes "soldered" into the neural chassis.

The cortex on the medial and dorsal surface of the hemisphere, arising in association with the medial olfactory tract and pathways ascending from the hypothalamus (Johnston 1906), is called the *archipallium,* a term that originated with Edinger and his followers (Elliot Smith 1910). On the lateral surface, and related to the lateral olfactory tract, is what Ariens Kappers (1909) named the *paleopallium.* Between these two fields of cortex there is a less differentiated form that Elliot Smith (1910) believed to be a transitional type. Comparative neurologists spoke of the archicortex and the palecortex as being, respectively, olfacto-visceral and olfacto-somatic correlation centres.

There is no evidence of the gradational changes that took place in the cortex of forms intermediate between the reptile and the mammal. But on examination of the brains of the lowliest mammals one finds there has been a striking development. In what was the region of transition in the cortex of the reptile there has ballooned out what Elliot Smith (1901) called the *neopallium.* And separating the neopallium from the archi-and paleo-cortex is a transitional form to which Rose's term *mesopallium* might be applied (Yakovlev 1948). As will be emphasized, the neocortex surpasses all the others in comlexity. Yet equally significant is the finding that on this new cortical screen are projected predominantly impressions from the eye, ear and body wall. These are the impressions that are obviously most suited to giving the animal an accurate orientation to the external environment in the terrestrial world.

Comparative neurologists consider the archicortex of the reptile to be the counterpart of the dentate gyrus and the hippocampus in mammals. The paleocortex, on the other hand, presages the pyriform lobe and its caudal continuation in the hippocampal gyrus. The bulk of the so-called transitional or mesocortex is found in the cingulate gyrus (interhemispheric cortex of Cajal 1903). Together these structures form what Broca (1878) called the great limbic lobe, because they completely surrounded the hilus of the hemisphere (Fig. 3). In phylogeny it is a striking fact that this lobe, though it undergoes some expansion and reaches its greatest development in man, retains essentially its position and structural characteristics throughout the

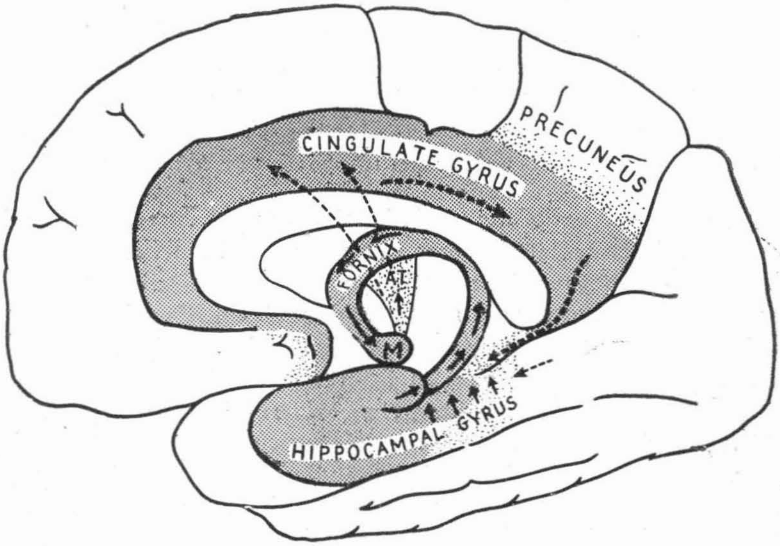

Fig 3

Diagram of medial aspect of brain. The shaded area shows schematically some of the circuits in the limbic system that were emphasized by Papez. As indicated, the outer surface of the limbic lobe is comprised chiefly of the cortex of the cingulate and hippocampal gyri; the two other main divisions of the lobe, the hippocampus and the dentate gyrus, are folded into the medial part of the temporal lobe in such a way as to defy representation. The amygdala lies beneath the rostral part of the hippocampal gyrus. M. mammillary body, hypothalamic recipient of the bulk of the fornix projecting from the hippocampus; AT, anterior thalamic nuclei, way station between mammillary body and cingulate gyrus.

entire mammalian series (Fig. 4). The neopallium, on the other hand, continues an exuberant growth, becoming, in the higher subhuman primates and in man, a massive tucked-up sheet that folds over and crowds the limbic lobe into the cellar, as it were, of the brain.

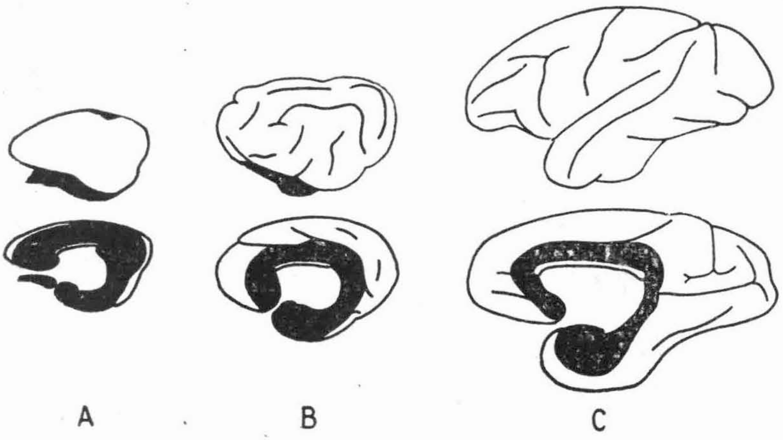

Fig. 4

Brains of rabbit (A), cat (B), and monkey (C), drawn roughly proportional to their respective sizes, and showing both the lateral (top) and medial (bottom) surfaces. The brains of these three commonly used laboratory animals are taken as examples of how the limbic lobe, represented in black, surrounds the hilus of the hemisphere and forms a common denominator of the cerebrum throughout the mammalian series.

It is opportune at this point to contrast briefly the cytoarchitecture of the cortex contained in the limbic lobe with that of the neopallium. Ariens Kappers (1928) in an over-simplification, has pointed out that the cellular elements of the archicortex and palecortex form essentially two layers that correspond functionally to the receptive granular layer IV and the efferent pyromidal layer V, of the neocortex. In the archicortex, he notes that the arrangement of the granular layer in the dentate gyrus and the pyramidal layer in the hippocampus "is such that the latter only for a short distance extends below the former as subgranular pyramids". The palecortex of the olfactory area, on the other hand, "shows a higher stage of development" in so far as the receiving layer is entirely superimposed on the one giving rise to the "large efferent tracts." The cortex of the limbic lobe is comprised essentially of the two foregoing primitive types, together with the transitional or mesopallial cortex developing adjacent to them. In some respects the outer lamina of the entire limbic lobe is comparable to layer IV of the neocortex because of the distribution of the afferent plaxus, (Lorente de No 1934, 1934a, 1949). On the other hand, one of the most striking features distinguishing the neocortex is the great elaboration of the so-called supragranular layers in the outer lamina. Also of great note is the large number of cells with short axones in the neocortex, a finding that to Ca'jal (1903) "was the anatomical expression of the delicacy of function of the brain of man".

Elliot Smith (1901, 1910, 1919) was probably one of the first comparative neurologists to derive, on the basis of comparative studies, generalizations that bear on the problem of behaviour. He postulated, for example, that the cortex developing in association with the olfactory apparatus and the hypothalamus provided a system for integrating the animal's various sensory impressions and imparting to them the quality of emotion. On the other hand, he referred to the neocortex as the "organ of the mind" because he presumed it to be primarily concerned with higher symbolic processes. Herrick (1933) is another eminent person among comparative neurologists, who sought an explanation for the difference between intellectual and affective functions in terms of the respective development of the primitive and phylogenetically newer portions of the cortex.

But the tradition in anatomy and the course taken by physiological investigation conspired to postpone interest in the concepts expressed by these workers in regard to the part played by the primitive cortex in emotional behaviour. Impressed by the relationship it bore in development to the olfactory apparatus, many anatomists looked upon the entire limbic lobe as subserving primarily the function of smell. By the end of the nineteenth century, this notion had become so well entrenched that several authors of textbooks extended the meaning of Turner's (1890) term "*rhinencephalon*" to apply to the whole structure.

Nor were findings in physiology conducive to making an appraisal of the possible role of the limbic lobe in emotional behaviour. Following Bard's (1928) demonstration that the well-integrated manifestations of sham rage depended on the posterior hypothalamus, there was an increasing tendency on the part of many to infer that this little neural structure was the chief central mechanism, not only for integrating emotional expression, but also the elaboration of emotional experience. This line of thinking was calculated to have particular appeal for workers in psychosomatic medicine, because of the known strong inter-relationship of the hypothalamus, autonomics, and endocrines and the abundant evidence that their joint activities were responsible for much of the symptomatology and observed changes in the so-called psychosomatic affections.

In this scheme of things, the cerebral cortex was considered to be "above" emotional participation. Like a judge removed from the "maddening crowd" (MacLean 1954) it was presumed to hand down decisions that were predominantly inhibitory for the tendencies of the hypothalamus to run irrationally and emotionally wild. Despite its ancestral relationship and strong reciprocal connections with the hypothalamus, it is probable that the limbic lobe was not included in people's mind when they referred to the foregoing functions of the cerebral cortex, because it had too long been entrenched in tradition as being a *smell brain.* And smell was thought to be unimportant in man.

Attention was focussed on the forgotten cortex in the limbic lobe by Papez in 1937, who in a paper entitled "*A proposed mechanism of emotion*" gave the most comprehensive formulation to date of its possible role in emotional behaviour. He showed that the so-called rhinencephalon (smell brain) elaborated the function of central emotion, as well as participated in emotional expression. Significant developments since 1937 have provided substantial evidence of the general validity of Papez thesis. The limbic lobe, maintaining as it does the same gross and micro-anatomical organization throughout the mammalian series, provides the common denominator of emotional mechanisms in all mammals, whereas the neocortex might be looked upon as an expanding numerator representing the growth of intellectual functions. "This situation provides a clue to understanding the difference between what we '*feel*' (limbic system) and what we 'know' (neocortex)" (MacLean 1949). Because in evolution the functions of the limbic lobe appeared to be oriented primarily towards the internal and affectively experienced needs of the animal, it has been referred to as the "*visceral brain*". This has been done to help dispel the notion that it had primarily to do with the sense of smell.

III. CONNECTIONS OF THE LIMBIC SYSTEM.

The limbic system, or 'visceral brain', is a very well integrated, and interconnected unit. This unit receives afferents from the viscera, as well as some external (somatic) sensations. It, on the other hand, sends out efferents by its intimate connections with the autonomic outflow, both sympathetic and parasympathetic, as well as it has some somatic efferent connections (e.g. involvement of facial muscles in emotional exteriorisation). The various components of the limbic system are intimately interconnected.

(1) **Interconnections** :

Most of the ascending impulses of visceral origin first impinge upon the hypothalamus (Fulton 1951). After impinging upon the hypothalamus, they divide into two groups : (i) One group goes from here to the anterior thalamic nuclei (via mammillo-thalamic tract). From there it projects to the cingulate gyrus. Cingulum is further connected to the hippocampus, which through fornix projects back to the hypothalamus, and also to the convexity of the cerebral cortex. (ii) The second group of projections from the hypothalamus passes to midline and dorsomedial thalamic nuclei. From here they project to the transitional cortex of the posterior orbital anterior insular, and temporal polar regions. These regions are reciprocally connected (Bailey et al. 1943 ; Petr et al. 1949 ; MacLean & Pribram 1953), as well as project into the cingulum and the amygdala, which further are connected to the rostral hippocampus and hypothalamus. The transitional cortex directly also projects into the hypothalamus and parts of basal ganglia (Wall et al. 1951; Adey 1951). Thus it will be seen that not only are the various structures of the limbic system interconnected, but they are connected in a cyclic manner with the hypothalamus, which is the predominant receiving (sensory) as well as effector (motor) structure of this system.

On the basis of their extensive studies, MacLean and Pribram (1953), and Pribram and MacLean (1953) have divided this system into the following five regions (Fig. 5):

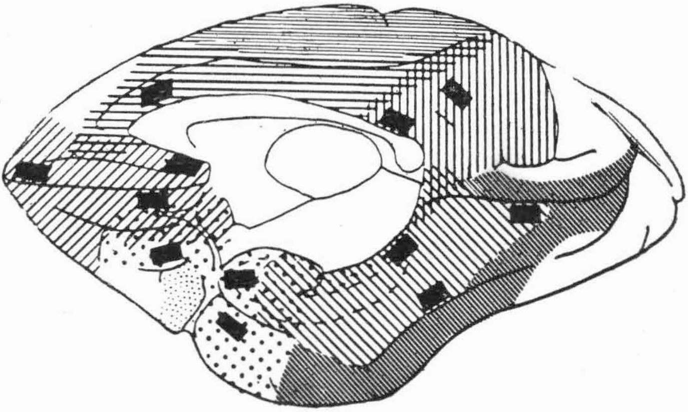

Fig. 5

- This figure, depicting the lateral and inferomedial aspects of monkey's brain, shows diagrammatically the distribution of regions and segments referred to in text. Stippling ⁘ frontotemporal; rostroventral striations \\\\ : medial occipitotemporal; vertical striations IIII : medial parieto-occipital; horizontal striation ☰ : medial frontoparietal; dorsorostral striations /// : medial frontal.

(i) Frontotemporal
(ii) Medial occipitotemporal
(iii) Medial parieto-occipital
(iv) Medial frontoparietal
and (v) Medial frontal

(2) **Afferent Connections**:

The classic spinothalamic system arising in the spinal cord and projecting to the ventral nuclei of the thalamus, and thence passing in precise topographical fashion to the cerebral cortex, was long thought to be the chief, if not the only, afferent supply of the forebrain. However, Kappers et al. (1936) and others described spino-hypothalamic connections in fish and certain other lower forms, and they pointed out that this ascending system, completely independent of the spinothalamic system, passed to the hypothalamus via the mammillary peduncle. In 1935 Ibanez of the Ca'jal Institute found ascending peduncle fibres from the ventral tegmental nucleus, and in 1936 Tello demonstrated in the 14 mm. cat foetus the entire course of the mammillary peduncle from the ventral tegmental nucleus to the mammillary body in a single sagital section. In 1940 Bronk and his associates found electrical evidence of an ascending system from medulla to hypothalamus in the higher animals. Now, thanks to the investigations of Dell (1951, 1951a and 1952), Downman (1952), Amassian (1951), and Aider et al. (1952), we know that two large extralemniscal systems of autonomic afferents ascend from the spinal cord through medulla and midbrain to hypothalamic and adjacent nuclei, and that some of the ascending medullary connections project directly to the limbic system of the forebrain. One system of fibres is slow, and these appear to terminate subcortically in hypothalamus and adjacent structures; some of the more rapid fibres proceed directly to the posterior orbital gyrus.

French, Verzeano and Magoun (1953) have now disclosed (through the use of evoked electrical potentials) that a large portion of the extralemniscal system terminates in the reticular formation and projects from there to various parts of the forebrain, including the limbic cortex. This newly recognised system of afferent fibres is being emphasized because the fibres are severed in the now classical lobotomy procedure, and it is believed that this circumstance accounts for the dramatic relief which a lobotomy may confer on a patient suffering from intractable visceral pain. When these fibres are severed, pain communications to the sensorium from various visceral organs are interrupted with the result that fewer pain impulses can impinge upon the sensorium in a given time. The patient may still be conscious of pain because all pain fibres cannot be severed, but pain ceases to disturb the patient because the number of intact pain fibres has been curtailed. French et al. (1953) also point out that this extralemniscal system is selectively blocked by anaesthetic agents, as are cortical internucials, long before there is interruption of the spinothalamic system, and they suggest that this may be responsible for the anaesthetic state.

In this connection it is of great interest that MacLean et al. (1952) have obtained conspicuous electrical responses of the pyriform area to noxious stimuli (pricking ear or foot), indicating that pain stimuli are, in fact, transmitted to the limbic system. The reactions were in every way similar to those evoked by olfactory stimuli. Green and Arduini (1954) have reported that stimulation of the reticular activating system of French, Amerongen and Mogoun (1952) evokes a train of slow waves in the hippocampus. Liberson and Akert (1952), and Green and Arduini (1954) have noted that when an animal shifts or focuses attention, synchronised activity is manifested in the hippocampus at the sametime, as the neocortical activity becomes desynchronised. Green and Arduini have emphasized that synchronised activity can be initiated in the hippocampus by stimuli too weak to 'arouse' the 'sleeping' cortex. Visual, auditory, olfactory, and other types of sensory stimulation may evoke the same type of response.

Hippocampus thus has been shown to receive in addition to visceral sensations, external (somatic) sensations (MacLean 1949) of smell, taste, mouth, sex organs, body wall, eye and ear. This, therefore, is an important region for integration of 'external' and 'internal' sensations.

Evoked potential studies being conducted in our laboratory these days (unpublished) tend to show that different regions of the limbic system, especially orbital cortex and hippocampal formation, receive afferents from the paleocerebellum (old parts of cerebellum).

(3) **Efferent connections** :—

The limbic structures send out efferent impulses to the viscera via the autonomic outflow, with which it must have intimate physiological connections. Experimental studies have shown that stimulations of different limbic structures produce marked changes in the activity of different viscera, which are both sympathetic and para-sympathetic in nature (vide infra), in addition to producing changes in the affective behaviour.

Langley (1921), when he published his celebrated monograph on the autonomic nervous system, defined this system as a group of myelinated and unmyelinated fibres which innervate blood vessels and glands. This system was envisaged by him to be a purely peripheral motor system, and he did not think of a functional relationship with other parts of the brain and spinal cord. The beginnings of our more intimate knowledge of the part played by the forebrain in the integration of autonomic function came with the studies of Karplus and Kriedl (1909, 1910, 1912), who observed striking effects, autonomic in nature, as a result of stimulation of the hypothalamus. The studies on hypothalamus were further extended by Hess, Bard, Bailey and Bremer, Beatie, Brow and Long, and many others and it came to be regarded as the *'head ganglion'* of the autonomic (Sherrington). Thus it was concluded that the hypothalamus is intimately connected with the autonomic outflow. Hypothalamus was also shown to produce various visceral changes by its regulation of endocrine activity of the body, which it does by influencing the activity of the pituitary gland. Not only that, but it also must have some connections with the centres regulating the activity of somatic structures involved in the exteriorisation of emotion.

Recent experimental studies on the regulation of visceral activity and affective behaviour from the other structures belonging to the limbic system, have shown that these structures also must have efferent connections with the autonomic and endocrine system. These might be operating through the connections of these regions with the hypothalamus; or some of these regions may be sending direct efferents to the reticular formation. It is interesting to note here that there is similarity between psychiatric aberrations seen in patients with epilepsy secondary to lesions in frontotemporal portion of limbic cortex, and cases of encephalitis lethargica reported by von Economo (1931) due to involvement of central grey and reticulum. Gloor (1954) has also reported physiological studies that show that amygdala projects to the midbrain tegmentum (reticular formation).

IV. EXPERIMENTAL STUDIES.

(1) **Hypothalamus.**

(i) *Early studies* :—

The early history of the hypothalamus is of some interest. In the first place nearly all the original disclosures concerning hypothalamic function were made by Austrian investigators working in Vienna ; indeed, it has been well said that the hypothalamus was "born" in Vienna. The first to take notice of this part of the brain was the eminent pathologist, Carl Rokitansky, who, in 1842 in his "*Handbuch der Pathologischen Anatomie*', pointed out that acute perforating ulcers of the stomach and haemorrhagic erosions were often associated with meningitis affecting the base of the brain. He believed that this caused abnormal innervation of the stomach through overaction of the vagus nerve. This, as Harvey Cushing pointed out in his paper on "*Peptic Ulcers and the Interbrain*" (1932), was the first suggestion of a neurogenic origin of gastric affections. Many years later Mauthner (1890) ascribed the somnolence of encephalitis to an infection of the base of the brain, a conclusion which was supported by the Italian neurologist Righetti (1903), who observed somnolence in 115 of 775 cases of cerebral tumor, and that 61 per cent of those showing somnolence had tumors affecting either the pituitary or the third ventricle. At the turn of the century Babinski (1900) and Alfred Frohlich (1901) independently reported upon cases of expending pituitary tumours associated with adiposity and sexual infantilism. They did not, however, attribute the syndrome to an involvement of the base of the brain, but rather to the destruction of the pituitary.

The first experimental studies on the hypothalamic region also emanated from Vienna at the hands of Karplus and Kreidl whose studies appeared in a series of papers published between 1909 and 1937. They found that electrical stimulation of the walls of third ventrical both in the cats and in monkeys caused changes in heart rate and blood pressure as well as other signs of sympathetic activity, including dilatation of the pupils, sweating, piloerection, and retraction of the nictitating membrane. Later they observed effects on gastric motility and secretion. Fearing that they might be stimulating fibres of passage rather than nerve centres, they removed the cerebral hemispheres and three weeks later, after all degeneration would have taken place, the reactions still occurred ; but they disappeared if the walls of the third ventricle were locally anaesthetized. Karplus and Kreidl also proved that these responses depended upon the existence of the peripheral outflow of the sympathetic system, for they disappeared when this was removed. They also disappeared after high cervical section of the spinal cord and section of the upper thoracic ventral nerve roots. They further found that reflex dilatation of the pupil depended upon the integrity of the hypothalamus and was not affected by removal of the cerebral cortex. They concluded that the hypothalamus contained centres regulating the activity of the sympathetic nervous system.

In 1912 Cushing and his associates observed the adiposogenital syndrome after removing the pituitary gland, and also after dividing the pituitary stalk. They believed at first that the sydrome was due to removing the pituitary, as Frohlich originally contended, being unaware that pituitary removal had caused concomitant injury of the base of the brain. Camus and Roussy (1913) were the first to place lesions deliberately in the hypothalamic area. They reported in 1913 that this was followed by transitory polyuria and they also encountered one instance of permanent polyuria associated with adiposogenital dystrophy—this even though the pituitary was intact and uninjured.

The experiments of camus and Roussy were not described in detail until after World War I (1920), and in 1921 Bailey and Bremer published their important paper on experimental diabetes insipidus reporting that lesions restricted to the hypothalamic area invariably caused polyuria and that polyuria was permanent if the lesion was large; they also recorded that the adiposogenital syndrome usually associated with hypersomnia was also observed in their dogs. It is interesting that Dr. Cushing was at first opposed to publication of their results because he was still of the view that the pituitary was primarily concerned; but in his Balfour Lecture published in 1932 he altered his position and became a determined advocate of the importance of hypothalamic function.

(*ii*) *Recent studies :*

The more recent history of hypothalamic function begins in 1928 when Bard disclosed that the caudal hypothalamic area is concerned with the phenomenon of "sham rage", the behaviour pattern which develops in cats following decortication, and which continues so long as the posterior hypothalamus remains intact. Keller (1930, 1933) drew attention to the fact that the hypothalamus was also essential for heat regulation. It was at this time that Ranson became interested in the subject and in collaboration with Magoun, Ingram, Fisher, Kabat, Clark, Hetherington, Harrison, Brobeck, to mention only a few, published during a twelve year period a series of most important papers on hypothalamia function, establishing the importance of the hypothalamus in heat regulation, water metabolism, pathological somnolence gastrointestinal function, and cardiovascular reflexes. All these functions of the hypothalamus are so well known by now as not to merit any further detailed repetition.

(*iii*) *Food intake and metabolism* :

Recent studies have thrown further light on hypothalamic control over some other activities. Hypothalamus emerged as an important centre in the regulation of food intake. Hetherington working in Ranson's laboratory (1940, 1941, 1942, 1944) showed that lesions in the ventromedial nucleus produced obesity in the rat. It was also concluded that the obesity of Frohlich's syndrome was due to hypothalamic involvement and not due to involvement of the anterior pituitary. Brobeck and others (1943, 1946) showed that the obesity after ventromedial hypothalamic lesions was due to hyperphagia (over-eating) rather than due to any disturbance in metabolism. Anand and Brobeck (1951, 1951a) further showed the presence of a "feeding centre" in the development of complete aphagia and death due to starvation. In a series of further studies Anand and his associates (Delgado and Anand 1953 ; Anand, Dua and Shoenberg 1955; Anand and Dua 1955a ; Anand, Dua and Chhina 1957b) have confirmed the presence of the 'feeding' (lateral) and 'satiety' (medial) hypothalamic centres in higher mammals like cat and monkey. The stimulation of these two centres in conscious animals, on the other hand, leads to a marked increase and decrease in the food intake respectively. It has also been postulated that these hypothalamic centres operate as 'fascilitatory' and 'inhibitory' mechanisms for feeding reflexes mediated through lower centres in response to various sensory stimuli. Added proof to this concept of hypothalamic centres have been provided by the studies of Mayer et al. (1951) that the activity of these centres depends upon blood sugar levels ; the studies of Larsson (1954) who showed that in the hungry state the neurons of 'feeding centre' pick up more of labelled phosphorus and thus increase A.T.P. activity ; and the studies of Brobeck et al. (1955) that amphetamine decreases appetite by increasing the activity of 'Satiety' centre as recorded electroencephalographically by depth electrodes. E.E.G. studies on the activities of these centres by means of depth electrodes under various changes produced in blood chemistry, are being conducted these days in our laboratory, to throw more light on the mechanism of these centres.

It has also been shown that in the higher mammals (monkey), who have a higher degree of encephalisation, control over food intake is exerted from cortical regions (Anand, Dua, and Chhina 1957b). Frontal lobe lesions including posterior orbital cortex lead to decrease in food intake, while those which spare the orbital cortex are followed by an increase in intake. Amygdaloid and periamygdaloid lesions produce an increase in intake (see also Pribram and Bagshaw 1953). It is concluded that cortical structures have a discriminative mechanism ("*appetite*"), in contrast to the primitive urge ("hunger") which originates at hypothalamic levels (see also Bruce and Kennedy 1951).

(*iv*) *Autonomic control :*

In a recent study conducted by stimulating different hypothalamic regions in concious animals, Dua (1956) has mapped out hypothalamic regions influencing cardiovascular activity and blood pressure, respiration, eye changes, gastric activity, and some somatic manifestations, and concluded that although there was some overlapping of functions in different hypothalamic regions, the anteromedial regions of hypothalamus were predominantly parasympathetic. The same conclusions were drawn in terms of blood sugar changes induced by stimulation of hypothalamus (Anand and Dua 1955b). It is interesting to note here that reserpine, the drug for lowering the blood pressure, has been shown to inhibit the posterolateral hypothalamic regions (sympathetic) and facilitate the anteromedial regions (parasympathetic) (Anand, Dua and Malhotra 1957). Sen (1956) has shown that stimulation of the pre-optic region of the hypothalamus produces acute haemorrhagic ulcers in gastric pouches.

(*v*) *Endocrine control* :

Hypothalamus has also emerged as a pivot for the hypothalamo-endocrine system. It thus constitutes an important station for two major homeostatic mechanisms which are associated inseparably in function–the autonomic and the endocrine systems. It influences the other endocrine organs through its connections with the pituitary gland, whose trophic hormones in turn activate the target glands, the adrenal cortex, thyroid, and gonads. The processes thus affected are those concerned with birth, growth, maturation reproduction and nutrition, and include various self-preservative reactions, and electrolyte balance (Glaser 1955, Cleghorn 1955). The control of posterior pituitary secretion by fibres arising from supraoptic nuclei of hypothalamus has long been well known. In recent years the more complex control of the anterior pituitary has been clarified. The nerve supply from hypothalamus to anterior pituitary is not particularly significant or does not exist, but the hypophyseal portal system of vessels between hypothalamus and anterior pituitary is regarded as the most important link between these two structures (Harris 1952).

There is now general agreement that the hypothalamus is capable of stimulating ACTH secretion from anterior pituitary, whenever the individual is exposed to a stressing agent. Hume and Wittenstem (1950) reported that in dog the anterior portion of the median eminence of tuber cinereum takes part in this response, while Groot and Harris (1950) in rabbits put this in the posterior part of tuber cinereum or mammillary body. Porter (1952, 1953) also located such an activity in the posterior hypothalamus. Anand, Raghunath, Dua and Mohindra (1953), and Anand and Dua (1955) by ablation and stimulation studies showed that the medial part of the anterior and middle hypothalamic regions are concerned with ACTH secretion.

Secretion of Gonadotropic hormones from the anterior pituitary is also influenced from the hypothalamus. The rabbit ovulates only after copulation and this can be prevented either by stalk section (Brooks et al. 1940) or by barbiturates (Kasdon 1949). Markee et al. (1946) reported ovulation by stimulating hypothalamus in rabbits. Everett (1952) has suggested the presence of a rhythmically acting centre in the hypothalamus of those animals who ovulate spontaneously. Dempsey and Rioch (1939) have located the integrating area for oestral behaviour in the posterior hypothalamus. Anand, Malkani and Sikand (1957), and Anand, Malkani, and Dua (1957) have shown that the hypothalamic regions involved in the secretion of gonadotropins from the anterior pituitary are the same which are concerned with ACTH secretion (medial part of the anterior and middle hypothalamus). This region lies just above the anterior pituitary and probably would be directly connected through portal vessels. Destruction of this region disturbs the poestrus activity in the rat, and stimulation of this during different phases of the cycle in concious monkeys can precipitate both ovulation and menstrual flow.

To what extent the thyrotropic hormone (TSH) secretion under different conditions, is mediated through the hypothalamus is still uncertain. Scow and Greer (1953) have shown that intact mice have a higher I^{131} uptake than hypophysectomised mice with functioning intraocular implants. Hypothalamic lesions behind the supraoptic nucleus in rats prevents the compensatory hypertrophy of thyroid following thiouracial. Levine and Goldstein (1952) concluded that thyroxine deficiency acts in certain hypothalamic areas to control TSH release.

When Ranson died in 1942, the hypothalamus had emerged as one of the primary centres of autonomic function. Since his death, the relation of the hypothalamus to other levels of nervous function has been further clarified, especially in its relations with the limbic system. It has become clear that while the hypothalamus is an important element in the regulation of autonomic and endocrine function, it is subservient to autonomic centres situated more rostrally in the forebrain.

(2) REST OF THE LIMBIC SYSTEM (RHINENCEPHALON "VISCERAL BRAIN")

Phylogenetic and cytoarchitectural studies (enumerated above), together with extensive recent physiological investigations have brought out the fact that this system is involved in the higher control of autonomic nervous system and the affectively determined behaviour (emotional behaviour). The physiological investigations have depended, in the beginning, mainly on surgical ablations and electrolytic lesions of these regions, and studying their effects on the affective behaviour. Later on stimulation studies, both electrical and chemical, of portions of the limbic system resulted both in autonomic and behavioural changes. These usually were carried out in anaesthetised animals, and could not therefore be expected to produce ideal results. More recently studies on both autonomic as well as behavioural changes have been carried out by electrical and chemical stimulation in unanaesthetised animals, by means of permanently implanted electrodes and needles. Although efforts have been made to identify specific parts of the limbic system responsible for the various somatic, autonomic, and behavioural changes, the physiological studies have always shown a remarkable wide spectrum of activities influenced by different limbic structures. (Bailey and Sweet 1940 ; Ward 1948 ; Kaada 1951a ; Gastaut 1952 ; MacLean & Delgado 1953 ; Koikegami et al. 1953, 1954, and 1955). In this respect the limbic system has the characteristics of "unspecificity". It is not within the scope of this review to summarize all the extensive evidence collected so far bearing on this subject, although an attempt will be made to give some of the main features of the limbic control. Excellent reviews on this subject have been written by Kaada (1951a), Fulton (1951), Gastaut (1952), MacLean (1954), and Pribram and Kruger (1954) and the readers are referred to them. Further evidence for similar effects produced in man also has been added by recent studies (Chapman et al. 1954 ; Baldwin et al. 1954 ; Pool 1954).

As one cannot investigate simultaneously the physiological functions of the entire limbic system, it would obviously be advantageous to have some basis for concentrating attention on specific parts. Frontotemporal region of this system has been most extensively investigated and more information has accumulated about the function of this region than the others.

(*i*) *Autonomic* (*visceral*) *responses :*

Various autonomic responses, both 'sympathetic' and 'parasympathetic' are induced by stimulation of almost all the different regions of the limbic system, both in anaesthetised, as well as unanasthetised animals. The 'unspecificity' of these responses has been already commented upon. This is in contradistinction to the responses obtained on stimulation of the hypothalamus; where a 'demarcation' between sympathetic and parasympathetic areas can be obtained. Ablation (lesion) studies involving these regions, on the other hand, produce only a slight change in the autonomic responses. A multiplicity of responses are obtained and these vary from lachrymation, pupillary changes, movements of nictitating membrane, changes in the heart rate, blood pressure, respiration, blood sugar level, salivation, gastrointestinal motility and secretory activity, even urination and defaecation can be produced (Anand and Dua 1956). Some of these functions have been investigated more than others, and they are summarised below.

(*a*) *Cardiovascular activity* :

Spencer in 1894 was the first to report a fall of blood pressure on farradisation of the posterior part of the orbital surface of the frontal lobe. Bailey and Sweet (1940) on the other hand demonstrated a rise of blood pressure on such stimulation, and the same was confirmed by various workers in animals

(Livingston et al. 1947 ; Delgado and Livingston 1948 ; Kaada et al. 1949 ; Sachs 1949), as well as in human beings (Livingston et al. 1947; Champan et al. 1949, & 1950). Smith (1945) and Ward (1948) obtained a rise of B. P. from stimulation of cingulate region also. These studies were all carried out in anaesthetised animals. Anand and Dua (1956c) obtained the same response on stimulation of both the orbitomesial cortex and anterior cingulate gyrus in unanaesthetised animals, except in two animals which actually registered a fall in B. P. There were also changes produced in heart rate, which did not show any relationship to the rise or fall of B. P. On the other hand lesions produced in these frontal lobe structures showed only a very slight drop in B.P. in some animals (Anand, Dua, and Chhina 1957), with the majority of these animals developing an increase in the heart rate (which may be compensatory). Rectal temperature also dropped after frontal lesions, possibly due to peripheral vasodilatation.

Kaada et al. (1949) extended these studies to the temporal lobe structures and anterior perforated space in monkeys. Chapman et al. (1950) obtained a rise of B. P. from temporal tip in humans. Chapman et al (1955) also reported rise of B. P. on stimulation of amygdala in humans. Anand and Dua (1956c) on the other hand observed that in unanaesthetised monkeys and cats, stimulation of all the temporal lobe limbic structures (except the polar region) including amygdala, hippocampus, and pyriform cortex produced a fall in B. P., with variable changes in the heart rate. Temporal polar stimulation on the other hand produced a rise of B. P. in monkeys and a fall of B. P. in cats. This probably is due to phylogenetic differences. In higher mammals (monkey) temporal tip is allied to posterior orbital cortex. Ablation studies restricted to the temporal limbic regions (Anand, Dua and Chhina 1957) produced a definite rise of B. P. and decrease in heart rate after amygdaloid lesions.

These results definitely indicate the involvement of limbic structures in the regulation of B. P. and the possible effects which might be expected from involvement of these regions in lobotomies and other pathological conditions. The psychosomatic approach to the question of hypertension is also indicated.

(*b*) *Respiration* :

Spencer in 1894 also first reported complete arrest of respiration on farradisation of posterior orbital cortex, confirmed later by Bailey and Sweet (1940) and many others (Livingston et al. 1949 & 1952 ; Turber 1954). On the other hand, in unanaesthetised animals the stimulation of orbitomesial cortex and the anterior cingulate produced an increase in the depth and rate of respiration (Anand and Dua 1956c). Stimulation of temporal lobe limbic structures mostly lead to inhibition of respiration–even apnoea in some cases (Kaada et al 1949 & 1952 ; Turner 1954 ; Anand and Dua 1956c).

Anand, Dua and Chhina (1957), on the other hand, have reported a general decrease in respiration rate after both frontal as well as temporal lobe lesions.

(*c*) *Gastro-intestinal activity*:

After Cushing (1932) reported that organic lesions of the central nervous system may produce ulceration of the mucosa of upper gastro-intestinal tract, many other workers have noticed ulcerations, haemorrhages and changes in the secretion in clinical cerebral damage as well as experimental studies. Most of this work had mainly focussed the attention on the hypothalamus (loc. cit). Watts and Fulton (1934), and Davey et al. (1950) obtained increased gastric secretion from stimulation of frontal cortex. Anand and Dua (1956b) obtained appreciable changes in the secretion of gastric juice both in volume as well as HCl and pepsin content–after stimulation of different limbic structures, but could not elicit any definite localisation in these regions so far as the increase or decrease of secretion is concerned.

Changes in the motility are also observed as a result of limbic stimulation. Eliasson (1952) elicited vigorous contractions of the stomach on stimulation of amygdala, while no change in motility followed stimulation of hippocampus. Kaada (1951) obtained inhibition of motility on stimulation of temporal polar and pyriform cortex. Bailey and Sweet (1940), and Babkin and Kite (1950) have reported decreased motility on stimulation of posterior orbital cortex. Anand and Dua (1956b) obtained inhibition of movements on stimulation of temporal lobe limbic structures, and mostly increased motility on stimulation of orbital surface and anterior cingulate. They also observed marked balooning of the gut after hippocampal lesions in a monkey (1957), and hyperaemic and ulcerative changes in the mucosa in most of the animals with frontal and temporal lesions.

(*d*) *Blood chemistry:*

Heath (1954) has reported a gradually Increasing fall in blood sugar and tissue glycogen, marked decrease in plasma sodium, poikilothermia, and loss in body weight after lesions in the septal region of the forebrain. Allot (1939) and Sweet et al. (1948), on the other hand, reported retention of sodium in the presence of frontal lobe damage. Tokay (1931) described increased salt out put after stab wounds in the region of the caudate nucleus. Majority of animals of Anand et al. (1957) after frontal and temporal lesions showed some rise in blood sugar and blood sodium, while some showed a fall in both these. These changes may be due to some metabolic changes, or may be due to endocrinal involvement (vide infra). Stimulation of these regions on the other hand produced a rise in blood sugar in all the animals, except after anterior cingulate stimulation in cats, which led to a fall in blood sugar (Anand and Dua 1956a).

(*ii*) *Somatic responses :*

Various somatic movements have been described on stimulations of limbic structures in unanaesthetised animals (MacLean and Delgado 1953; Anand and Dua 1955c and 1956; Kaada 1953). These usually involve ipsilateral facial, eyelid, orbital and oral muscles. These are easier to elicit from the anteromedial amygdala, than from the basolateral amygdala and other limbic structures. (Phylogenetically anteromedial group of amygdaloid nuclei is old (Fox, 1940) and the basolateral group is younger). Kaada (1953) has stressed the contraversive (contralateral) turning of the head as a response from the amygdala, and this has been suggested as of diagnostic importance in temporal lobe epileptic seizures (Magnus et al. 1952)

Coordinated oral responses relating to 'eating' are also produced by stimulation of limbic system. Stimulation studies in the anaesthetized animal were the first to show the oral-visceral motor·functions of the frontotemporal region. Many years ago Ferrier (1876), using a variety of animals, stimulated the limbic cortex in this region and reported responses which he related to smelling, tasting and eating. Schaltenbrand and Cobb (1931) and Rioch and Brenner (1938) obtained similar results in cats after they removed the entire neocortex and stimulated the limbic structures in the frontotemporal region. Experiments by Smith (1944) and Sugar et-al. (1948) have demonstrated that signs of vocal activity can be elicited from both the limbic and extralimbic postions of the frontotemporal region. MacLean and Delgado (1953) studied the effects of either electrically or chemically stimulating the limbic portion of the frontotemporal region and obtained responses which were usually automatisms, seemingly related to eating, or to the situations of defence and attack that one associates with the animal's search for food and his struggle for survival. The 'eating automatisms' included sniffiing, licking, biting, chewing, chop-licking, gagging, retching. As a rule these components of eating processes appeared repetitiously as long as the stimulation was applied. Anand and Dua (1956) obtained such responses of 'eating automatisms' after stimulation of all the regions of the limbic system. Delgado and Anand (1953) had shown that on stimulation of the lateral hypothalamus (feeding centre) 'eating automatisms' were produced which were accompanied by increased food intake even while the stimulation was taking place. On limbic stimulation, only the 'eating automatisms' are observed without any accompanying increase in food intake.

There is an extensive representation of what may be called succinctly the "oral senses" (Edinger 1899) in the frontotemporal region. Anatomical (Clark 1947 ; Meyer 1949), physiological (Fox 1944 ; Berry 1952), and clinical observations (Penfield 1951), all concur in placing the cortical representation of the sense of smell in the pyriform and prepyriform areas. As regards taste, neither the usual anatomical methods nor the evoked potential technique (Patton 1950 ; Patton and Amassian (1952) have given definitive information about its cortical representation ; but clinical observations (Penfield 1951) and ablation studies in animals indicate that it resides somewhere in the region of the insula. Thus, Ruch and Patton (1946) have shown that lesions placed in the region of the insula result in the inability of the monkey to discriminate among different concentrations of quinine solutions. As for the oral-tactile sense it is evident, in the cat atleast, that part of the sensory cortex so concerned overlaps the frontotemporal region (Woolsey 1947). This region therefore could be expected to correlate oral-visceral activities of the animals.

The association between autonomic and emotional processes, with somatic motor processes, in the functions of the limbic structures has been emphasized by Pribram. That there is a close relationship between voluntary and autonomic control of visceral functions is obvious from general considerations of body physiology. For example, in the control of the bladder voluntary activity of striated muscles initiates the act, before the autonomic nervous system takes over. Occasionally with excessive filling the autonomic system may start the sequence ; but the striated system then takes over briefly, to be followed again by autonomic control. Stimulation of most of the structures in the limbic system results in respiratory, vascular, and somatic motor effects. The somatic movements are massive and diffusive ; therefore, it would appear that the control of striated as well as smooth muscle by the rhinencephalic structures is massive and diffuse, as contrasted with the more discrete control exerted by neocortical structures.

(*iii*) *Endocrine control* :

Recent investigations have shown that the limbic system is related to the mechanisms of neuroendocrine integration. In view of the wide spectrum of somatic and autonomic functions activated by the limbic stimulation, the extension of this spectrum into the endocrine field could almost be predicted. The actual demonstration of this relationship started with the work of Schreiner and Kling (1953), who demonstrated marked hypersexuality in cats after bilateral removal of amygdala and periamgdaloid region. This release of sexual drive was suggestive of a functional derangement in the hypothalamo-pituitary control of gonadal functions. Later on Schreiner and Kling (1954) demonstrated this hormonal link, since castration in these amygdalectomised animals was followed by disappearance of the abnormal sexual behaviour. It was thus assumed that the amygdala inhibits gonadotrophin secretion by the pituitary in acting on hypothalamopituitary mechanisms.

Other experimental studies demonstrated that the amygdala can exert an activating influence upon this system as well, thus adding another example to the dual effects of limbic activity upon visceral and somatic functions. Koikegami et al. (1954) produced ovulation in the female rabbit by amygdaloid stimulation. Sawyer (1955) confirmed the involvement of limbic system in the rabbit's ovulation mechanism.

The endocrine functions of the limbic system, however, do not seem to be restricted to the sphere of gonadotrophin secretion. Koikegami et al. (1955) have reported that growth was markedly slowed in young puppies after bilateral amygdalectomy suggesting some interference with hormonal mechanism. The endocrine glands in these puppies also showed marked atrophy.

This was very apparent in anterior pituitary, and there was colloid retention in thyroid gland, decrease of Langerhan's islets in the pancreas, and atrophy of adrenal cortex, especially of zona and fasciculata.

MacLean (1955) has put forward the hypothesis that the frontotemporal region of limbic system may exert a discriminatory influence over the release of such hormones as ACTH by the hypothalamopituitary system during times of stress, whereas the medial parieto-occipital region may serve in a parallel capacity in regard to sexual hormones.

(*iv*) *Affective Behaviour*:

A large number of workers, as a result of studies which were originally restricted to ablations and later extended to stimulations both electrical and chemical, have shown that many structures in the frontal and temporal regions of forebrain, alongwith the hypothalamus, take part in the elaboration of affective behaviour. The frontal and temporal lobe structures bring out an integration of affective behaviour and take part in the '*feeling*' of emotions, while the hypothalamus possibly is meant for the '*exteriorisation*' (expression) of emotion. Bard's (1928) and Bard and Mountcastle's (1948) classical studies on 'sham rage' pointed to hypothalamus being the centre for 'emotion', which was inhibited from cortical levels. Evidence against a subsidiary role of the cortex in emotional experience was provided by Masserman (1943). It is most significant that, in experiments in which he stimulated the hypothalamus in chronically prepared and unanaesthetized cats, he could elicit the manifestations of sham rage and diffuse sympathetic activity and yet the animal would go on lapping milk. Furthermore, he demonstrated that these animals could not be conditioned to becoming alarmed at the prospect of hypothalamic stimulation. These findings indicated that the structures essential to the elaboration of the experience of emotion were represented at a higher level. As is well known, in recent years abundant evidence has accumulated that the frontal lobes are somehow implicated in the elaboration of affective behaviour (Fulton 1951). With this realization it has become the consensus of opinion that the cerebral cortex is essential to appreciating the various affective qualities of experience and combining them into such states of feeling as fear, anger, love, hate, etc.

(*a*) *Temporal lobe* :

Kluver and Bucy's (1939) epical findings were, in part, a rediscovery of those described by Brown and Schafer in 1888. Bitemporal lobectomy, provided it included limbic structures,resulted in an apparent taming of wild, ferocious monkeys, a compulsive type of oral behaviour, and bizarre sexual activity. To the casual observer theoral behaviour is reminiscent of the human infant, in so far as these animals will examine everything,noxious or otherwise, with their mouths. Though ordinarily frugivorous, they will, after operation, eat meat or fish. Rosvold and Pribzam (reported by Fulton 1951) had the same experience with dogs. Bard and Mountcastle (1948) produced sham rage in cats on removal of these temporal regions, and it was suggested that this opposite response in cat from that of monkey was possibly due to cat being carnivorous. Schreiner et al. (1952), on the other hand, found that ablation of the amygdala and overlying cortex in the cat also leads to manifestations of the Kluver and Bucy syndrome, the oral manifestations and hypersexuality being particularly conspicuous. Schreiner and Kling (1956) showed that after amygdaloid lesions, even some of the ferocious animals became docile. Similarly Anand and Brobeck (1952) reported that rats, which developed viciousness after hypothalamic lesions, became non-vicious after amygdaloid lesions. Anand, Dua and Chhina (1957a) observed that restricted amygdaloid lesions as well as surgical temporal lobectomies generally made both monkeys as well as cats fearless, non-aggresive and calm. These animals also showed loss of distinction between edible and non-edible objects, and put even noxious objects into the mouth, just like Kluver and Bucy animals. In a psychological study of humans with bilateral temporal ablations Rosvold (personal communication) has noted the tendency of some patients to eat both food and non-food objects. One patient, for example, finished a bag of potato chips and then ate the bag. Others consumed toilet paper, orange peels, etc. In general, they appeared as though they did not know when to stop eating.

By stimulation studies on the temporal lobe structures in unanaesthetized animals by MacLean and Delgado (1953), they have reported that this region is involved in drives that are necessary to the self preservation of the animal. They also reported 'alerting' reactions from the hippocampus. Anand and Dua (1956) reported that stimulation of amygdala, the pyriform cortex, and the hippocampal formation in unanaesthetised monkeys as well as cats produced a picture in which majority of animals appeared frightened and tried to run away into a corner, while a few would sit quietly. On the other hand they observed that stimulation of the temporal polar region (temporal tip) made the animals very much irritable and also violent.

(*b*) *Anterior cingulate gyrus* :

Smith (1945), Ward (1948), and Glees et al. (1950) have reported that cingulate ablation in animals produces greater tameness and loss of preoperative fear of man and other animals. Kennard (1955) has shown that such a lesion in cats makes them confused, and they exhibit a plastic tendency. They also show hypomotility. Anand, Dua, and Chhina (1957a) observed that restricted anterior cingulate lesions in both monkeys and cats mainly led to fearlessness and docility and made them hypomotile.

Stimulation of anterior cingulate in unanaesthetised cats (Anand and Dua, 1956) made them very vicious and violent, and some of these would go into convulsions. Monkeys, after such stimulation, merely developed more irritable and angry behaviour, but did not develop a typical rage reaction. Delgado (1955) on the other hand has shown that stimulation of the ventromedial quadrant of the frontal lobes, the anterior part of the cingulate gyrus, or the fornix, produces a similar picture; the ferocious male macaque may become completely docile at the moment that stimulation is applied, and resumes ferocious behaviour the moment that stimulation is stopped. This is not an arrest reaction, because the animals are able to move and regain equilibrium if they are pushed ; the effect seems to be connected with a decrease of the aggressiveness.

(*c*) *Posterior orbital gyrus* :

Ruch and Shenkin (1943), and Livingston et al. (1948) have reported hyperactivity after lesions of the orbital surface. Davis (1951) concluded that hyperactivity after lesions of this region, although possibly an affair of the orbital surface, is also in someway linked with the head of the caudate nucleus. Anand, Dua and Chhina (1957a) also observed hyperactivity in some of the animals with lesion in this region, and found that the head of caudate was damaged in most of them.

Anand and Dua (1956) showed that monkeys and cats, with electrode locations in the posterior orbital cortex, became very quiet during stimulation in the unanaesthetised state.

(*d*) *Psychiatric implications* :

Summarising the psychiatric implications of the different regions of the limbic system demarcated out by MacLean and Pribram (Fig. 5), MacLean (1955) has put forward the following suggestions.

Frontotemporal region :

The stimulation studies suggest that this region is concerned with the organization of the oral activities of the animal as they pertain to feeding and to the search, vocalization, angry attack, and defence involved in obtaining food. It therefore appears to be a region that is involved in drives that are necessary to the self preservation of the animal. This possibly accounts for the fact that clinically the emotional auras associated with discharges in the region are generally of a fearsome and unpleasant nature. As one might be led to predict on the basis of the stimulation studies, bilateral ablations of this region in the animal appear to result in an agnostic apraxia in matters concerning self preservation. At the same time, there is an apparent release of sexual mechanisms.

Medial parieto-occipital region :

The studies on this region, difficult as they are to evaluate, suggest that this part of the limbic system exerts an influence over grooming and sexual behaviour and the associated affective states. In other words, in contrast to the frontotemporal region this part of the brain appears to bear on activities that are directed for the purpose of preserving the species rather than the self.

Medial occipitotemporal region :

Little is known about the functions of this cortex. Both anatomical and physiological studies show that it is strongly associated with the cortical regions considered above, and which are allegedly concerned respectively with oral and sexual functions. It is also but one synapse removed from a large expanse of parieto-occipitotemporal cortex to which Penfield (1952) ascribes the functions of memory and dreaming.

(*e*) *Application in frontal lobotomy:*

In 1935, Egas Moniz introduced the operation of frontal lobotomy as a therapeutic procedure, and induced his colleague Almeida Lima to undertake the procedure, after hearing a report on behavioural changes produced in two chimpanzees which had been subjected to a cerebral ablation, which was presented by Jacobson and Fulton. They interrupted the frontal projections in patients suffering from mental diseases and reported favourable results. When this lobotomy operation was started in 1935-36, knowledge of frontal lobe function both in man and in animals was limited, and the procedure of lobotomy which gained wide acceptance was in large measure empirical. As a result of extensive studies (vide supra) the dichotomy of function between primitive structures of archi- and mesopallium (limbic system) and neopallium has been well brought out. The limbic system has been identified with 'emotional'experience and expression, and the neopallium with 'intellectural' function. In any lobotomy operation, the changes in affective behaviour would result from involvement of the limbic structures. In *radical lobotomy* operations (Freeman and Watts 1946; Lyerly 1938), large areas of neocortex are also involved in addition to the limbic structures, and therefore these suffer from the unfortunate side effects of conspicuous deterioration in intellectual function.

On the basis of extensive experimental studies on the limbic system, it has been suggested (Fulton 1951) that the *radical* lobotomy operation should be abandoned and in its place *selective* lobotomy, involving only an appropriate part of the limbic system depending upon the nature of mental aberration, should be undertaken. This has been taken up at some centres with very good results.

On the basis of the studies on affective behaviour mentioned above, it might be suggested that the depressed patient and the schizophrenic with subnormal psychomotor activity should have a resection of the posterior orbital gyrus or an interruption of its projections; while the agitated, aggressive, and overactive psychotic should have a cingulectomy. With these lesions, there is no intellectual impairment.

(*v*) *Psychosomatic Implications*:

It has been said that "information is information, not matter or energy" (Weiner 1948). One might also say, psyche is information, not matter or energy. This proposition, arising out of the trenchant statement by Wiener, presents the imponderable with which anyone has to deal who tries to correlate psychological phenomena with structure and physiological events. In the field of psychosomatic medicine the crux of the problem is to ascertain how the organism derives information and so acts upon it as to give rise to physical symptoms and, at times, detectable lesions.

The subject of implications of the information given above to psychosomatic disorders is so vast as to merit only a passing reference to it in this review. Not only one expects the involvement of these structures in psychosomatic disorders, but this new knowledge can be of great assistance in the rational treatment of the whole subject of psychosomatic medicine.

Aside from its academic interest, the limbic system is of great immediate practical importance because of its bearing on psycho-motor epilepsy. Although foreseen in the observations of several workers of the last century, it remained for present-day electroencephalography to establish that epileptogenic foci within or neighbouring the limbic cortex of the frontotemporal region are responsible for a large proportions of seizures now classified as psychomotor epilepsy. This common form of epilepsy has protean-ictal and inter-ictal manifestations, but in line with experimental findings, it is to be emphasized that it reveals itself conspicuously in viscerosomatic and emotional disturbances.

It should be remembered that in this system (limbic) of central structures the entire body image as a whole may be represented (Glaser 1955); and since the controls which are exercised by these structures are massive and diffuse, entire organ systems appear to be represented rather than specific muscles or movements. This differentiates such controls sharply from those exercised by the neocortex. This would also explain the differences in epileptic seizures from the limbic system and neocortex.

In psychomotor epilepsy a great variety of emotional manifestations can be correlated with epileptogenic foci in the frontotemporal region. In view of the recent physiological findings in regard to the projection of the "pneumogastric" nerve (vide supra), the so-called epigastric aura deserves particular attention. This aura, when followed by automatisms, can frequently be linked to discharges in the limbic portions of the frontotemporal region. Patients commonly refer to it as an indescribable "funny feeling" in the pit of the stomach. Significantly, it is often associated with a number of other feeling components that include: a feeling of fear or terror, "nervous," "shivery" or "chilly" feelings, a sensation of choking, a feeling of hunger or thirst, a "sinking" or "faint" feeling, a "paralyzed" feeling, nausea, etc. (MacLean 1954a). Attendant on such feelings may be a number of autonomically related manifestations such as headache, vomiting shivering, urination, etc. More rarely the aura is experienced not in the epigastrium but higher up in the precordial region. In such instances the patient may have the sensation his heart is racing, although there is no objective evidence of it. Here presumably is a primitive part of the brain that integrates and interprets experience in a language of feeling, not in the languauge of symbolic thought.

Gastaut et al. (1953) have reported that injections of alumina cream in either the pyriform-amygdalo-hippocampal region or the tegmentum of the cat result in seizures that from a clinical point of view resemble psychomotor epilepsy.

Thus the accumulation of knowledge about the physiology of the limbic system, which though old anatomically is very new from the point of view of our knowledge of its function, has a direct bearing on many branches of clinical medicine, and is of immediate importance both to the general physician and to the neurologist.

(*vi*) *Involvement in Consciousness, Memory mechanisms, and Symbolic process :*

The problem of 'consciousness' and its mechanisms is stlll elucive. In the past this was usually looked upon as a function solely of the neocortex. In recent years with the work of Magoun (1952) and Penfield (1952), the role of the brain-stem 'activating machanisms' and of the 'centrencephalic system' have become clearer. These regions fire into neocortex, as well as limbic system (especially hippocampal formation) as brought out in the section on afferent connections. Cobb characterises consciousness as implying a simultaneous awareness of environment and self; and in the integration of such functions limbic system (hippocampal formation) is also involved. Thus the brain-stem mechanisms, along with their reverberating connections with the neocortex and limbic system form the basis for consciousness.

It is also essential to bear in mind the fact that the central mechanisms controlling states of consciousness, also are involved in memory functions as well (Glaser 1955). For example, peculiar disorders of memory occur with lesions in and around the third ventricle in cases of Korsakoff's syndrome. The disturbances in memory that occur in psychomotor seizures have been correlated with lesions in the limbic areas of the temporal lobe, and in their connections with the upper brain stem or centrencephalic region (Penfield (1952). Penfield's studies of deep temporal stimulation, and the correlation of lesions with various types of memory deficit, suggest that three areas are involved in the memory process–the temporal lobes, the upper brain stem or the centrencephalic system and the periaqueductal region.

Kubie (1953 and 1953a) points out that the ancient brain (limbic system), much of which lies in the depths of the temporal lobe, has an extensive relationship with both the neopallium and the hypothalamus, becoming in this way a cross road or association area for both internally and externally derived perpetual processes. Here then, in the depths of the temporal lobe, with its intricate connections, is a cross-road where the multipolar functions of the symbolic process can be integrated. The temporal complex constitutes a mechanism for integrating the past and the present, the phylogenetically old and the external and internal environments of the central nervous system. It is precisely here that the multipolar areas of reference of the symbolic function can be served.

On our present concept of the interaction between limbic system and neocortex in determining behaviour, I can do no better than to cite Mac Lean's (1954) colourful simile:—

"One might imagine that the neopallium and the limbic system function together and proceed through the world like a man on a horse. Both horse and man are very much alive to each other and to their environment, yet communication between them is limited. Both derive information and act upon it in a different way. At times the horse may shy or bolt for reasons at first inexplicable to his rider. But the sympathetic horseman will try to find out and understand what it is that causes the panic so he can avoid the disturbing situations in the future or reassure and train the beast to overcome them. One may think of psychotherapy as serving in a similar capacity, helping the intellectual faculties of the patient to ferret out the disturbing factors in his life's situation so they can be dealt with and controlled in an intelligent fashion. In the case of the psychosomatic patient one suspects this helps to prevent excessive 'neighing' along the streets of slow-moving traffic to the viscera."

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