leospinal fibres originate in the ventral part of the locus coeruleus and in the subcoeruleus area [460, 473, 862, 1205, 1495], descend in the lateral funiculus of the cord [1496], and terminate in the ventral parts of the dorsal horn (laminae IV, V, VI), the intermediate grey matter and the central horn [794, 1496]. Onuf's nucleus receives a particularly dense noradrenergic innervation [701, 702, 922], but the projection descending to this nucleus from the pontine L-region also contains non-noradrenergic fibres [537]. The locus coeruleus complex does not innervate the sympathetic intermediolateral column in the thoracic cord [247, 1016, 1496]; however, in the rhesus monkey the parasympathetic preganglionic neurons in the sacral cord have been shown to receive a major noradrenergic input from the locus coeruleus [1496]. The projection to these neurons from the pontine M-region, on the other hand, is non-noradrenergic [810]. According to the earlier studies of Dahlström and Fuxe [280] the *non-coerulean noradrenergic fibres* descending to the spinal cord originate mainly from the lower medullary A1 and A2 groups. However, more recent experimental investigations have revealed that this projection arises largely, if not exclusively, from the pontine groups A5 and A7 [127, 795, 808, 1494, 1495] (Fig. 189). This pontospinal projection presumably descends in the longitudinal catecholamine bundle and enters the deeper part of the lateral funiculus of the spinal cord [808, 1205]. Its fibres terminate in the superficial layers of the dorsal horn, in the area around the central canal and, with great density, in the thoracic sympathetic intermediolateral column [230, 271, 808, 1495). The fibres projecting to the sympathetic preganglionic neurons originate mainly from the A5 group, which presumably represents a vasomotor centre [808, 1524].

The nucleus of the solitary tract and the dorsal vagal nucleus, both in the caudal rhombencephalon, and the intermediolateral nucleus in the spinal cord all show a high density of adrenergic terminals [530]. Exact knowledge of which adrenergic cell groups give rise to which terminal networks is lacking. However, Hökfelt and colleagues [531] have presented experimental evidence indicating that the projections to the spinal cord originate mainly from cell group C1 (Fig. 154A). The experiments of Ross et al. [1157] have also shown that adrenalin-containing neurons in the C1 group project to the thoracic cord.

Physiological experiments [281, 282, 869, 870] have shown that the ventrolateral portion of the medulla oblongata contains a circumscribed and highly sensitive vasopressor area, and evidence has been presented suggesting that this centre corresponds to the adrenergic C1 group [420]. Thus it seems likely the noradrenergic A5 group and the adrenergic C1 group both project to the sympathetic preganglionic neurons in the thoracic spinal cord and that both provide a portion of the anatomic substrate of vasomotor control.

Olfactory and Limbic Systems

Introduction

Certain territories of the diencephalon, the telencephalon and the mesencephalon are structurally and functionally so closely interrelated that they may be considered a single functional complex, which has been designated as the limbic system. In most general terms, this complex may be characterised as being directly involved in processes aimed at the survival of the individual (organism) and of the species. As such, the mammalian limbic system plays a key role in [825, 842, 843, 844, 977, 982, 986, 997, 1337]:

1. The maintenance of homeostasis, a complex task accomplished by
   (a) Activation of visceral effector mechanisms
   (b) Modulation of hormone release from the anterior and posterior pituitary
   (c) The initiation of feeding and drinking and the related foraging behaviours.
2. Agonistic (i.e. defense and attack) behaviour.
3. Sexual and reproductive behaviour.

At the telencephalic level, the limbic system is represented by the septal and preoptic regions, the hippocampus and some adjacent cortical areas, the amygdala and the bed nucleus of the stria terminalis. The diencephalic components include the epithalamus, the hypothalamus and the subthalamic zona incerta. In the midbrain, the limbic system comprises a number of cell masses, all of which lie in or close to the median plane. In the present section, an attempt will be made to survey the structure and fibre connections of all of these territories. Brief consideration will also be given to the olfactory system, which is intimately related to some components of the limbic system. Indeed, an earlier generation of neuroanatomists considered most of the structures referred here to as limbic, as forming parts of the rhinencephalon. The intricacy of the relationship to be dealt with require, as far as the illustrations are concerned, a three-step procedure. Figure 190 presents the various moieties of the limbic system and their fibre connections in an extremely schematised fashion. This figure will serve as an introductory key diagram. In Fig. 191 the major limbic conduction channels are shown semidiagrammatically. This figure is intended as a link between the key diagram Fig. 190 and Figs. 193–213, which show the limbic structures and connections in greater detail. Before commencing a concise appraisal of the limbic system, two general remarks should be made. First, the relevant literature has grown so overwhelmingly in the past 10 years that any attempt at completeness has been necessarily abandoned. Second, as in previous sections, with regard to the fibre connections we have relied heavily on the published results of experimental work on laboratory animals. It is by no means unlikely that several or even many of the hodological data presented do not apply to the human brain, the more so since (a) most experimental studies of limbic pathways have been carried out using rats rather than primates and (b) certain limbic structures show considerable interspecies differences [1330, 1529].
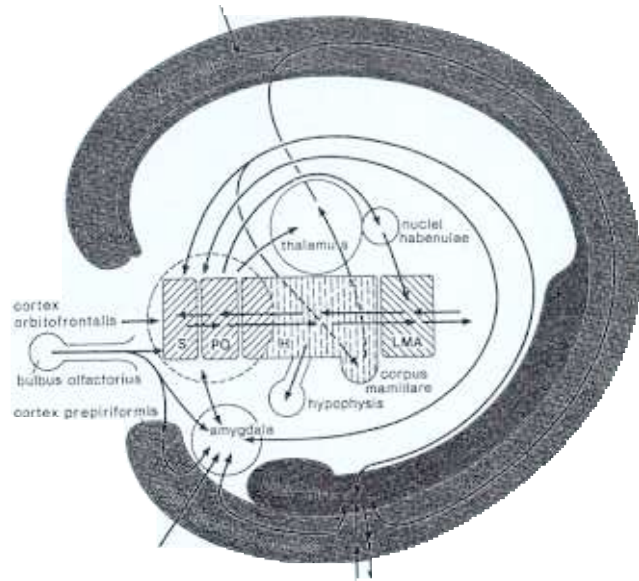
Fig. 190. Summary of the limbicohypothalamic complex. Subdivision of the area into central units and limbic rings, *H* hypothalamus; *LMA* limbic midbrain area; *PO* preoptic region; *S* septum
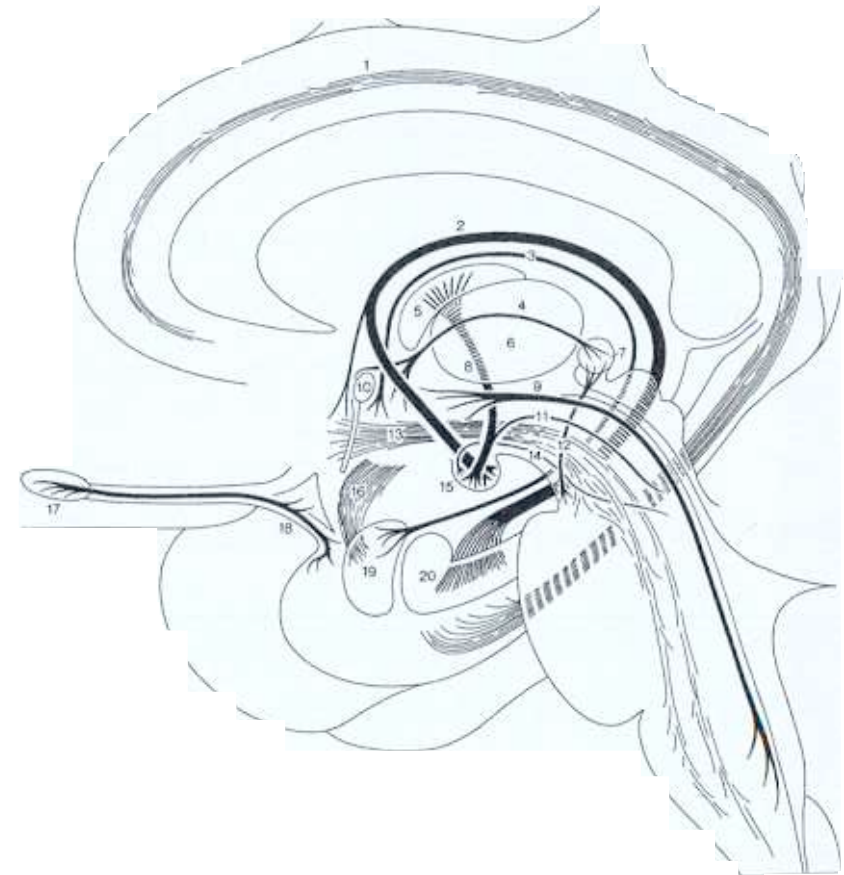
1 Cingulum	11 Tractus mamillotegmentalis
2 Fornix	12 Tractus habenulointerpeduncularis
3 Stria terminalis	13 Fasciculus telencephalicus medialis
4 Stria medullaris thalami	14 Pedunculus corporis mamillaris
5 Nucleus anterior thalami	15 Corpus mamillare
6 Nucleus medialis thalami	16 Ansa peduncularis
7 Nuclei habenulae	17 Bulbus olfactorius
8 Tractus mamillothalamicus	18 Stria olfactoria lateralis
9 Fasciculus longitudinalis dorsalis	19 Corpus amygdaloideum
10 Commissura anterior	20 Hippocampus

Fig. 191. The major pathways of the limbic system and the rhinencephalon

The Central Limbic Continuum: Sections and Centres

(Figs. 192–195; see also Part IV, Figs. 88–109)

The septal region (septum verum or pre-commissural septum) forms part of the medial wall of the cerebral hemispheres. It is situated directly rostral to the lamina terminalis within the paraterminal gyrus (Fig. 11). It is bordered dorsally by the corpus callosum, rostrally by the precommissural portion of the hippocampus, and caudally by the anterior commissure and the preoptic region. Ventrolaterally it borders on the nucleus accumbens, a large cell mass that in location and function occupies a position intermediate between the limbic and striatal or "extrapyramidal" systems. Contrary to the prevailing opinion, the septal region is well developed in the human brain [42]. It contains a number of rather poorly individualised cell groups, among which the medial and lateral septal nuclei may be mentioned. The ventromedial part of the septum is occupied by an aggregation of large cells which forms the dorsal or septal limb of what is known as the nucleus of the diagonal band of Broca. The ventral or tubercular limb of this nucleus extends caudolaterally along the ventral surface of the hemisphere and marks the caudal boundary of the olfactory tubercle. As its name implies this nucleus is embedded in a fibre bundle, the diagonal band of Broca.

The preoptic region, which flanks the rostral end of the third ventricle, is a rather narrow vertical strip of tissue that extends from the anterior commissure to the rostral edge of the optic chiasm. Although this region is of telencephalic origin, it is closely related structurally to the hypothalamus. The three rather poorly differentiated cell masses present in it – the preoptic periventricular nucleus, the medial preoptic nucleus and the lateral preoptic nucleus – may be considered rostral extensions of the three hypothalamic cell zones. Notably, the human preoptic region contains a sexually dimorphic nucleus. In men, this nucleus is considerably larger and more cellular than in women [1318]. Comparable differences have been found in the rat preoptic region [423, 524, 1251].

The epithalamus comprises, apart from the pineal gland, the habenular ganglion. Within this cell mass, separate medial and lateral nuclei can be distinguished. The two habenular ganglia are interconnected by the habenular commissure.

The subthalamic zona incerta is situated in the caudal part of the diencephalon, just ventral to the thalamus. Its rostral part occupies a position dorsal to the subthalamic nucleus (corpus subthalamicum), whereas its caudal part is ventrally bounded by the cerebral peduncle. The most caudal part consists of a cell mass known as the peripeduncular nucleus [1130], which receives a multifarious input from many different parts of the neuraxis. According to Roger and Cadusseau [1140] the zona incerta can be subdivided into a ventral and a dorsal sub-zone, the former receiving afferents predominantly from somesthetic centres, the latter being the target of limbic projections.

The hypothalamus encompasses the most ventral part of the diencephalon, where it forms the floor and contributes to the lateral walls of the third ventricle. Its upper boundary is marked on the ventricular side by a shallow groove, the hypothalamic sulcus. Caudally the hypothalamus passes gradually over into the periventricular and tegmental grey matter of the mesencephalon. It is, however, customary to define the posterior margin of the hypothalamus as a vertical plane passing just caudal to the mamillary bodies. The latter are paired small eminences located on the basal aspect of the brain. The rostral boundary of the hypothalamus coincides with a vertical plane passing from the foramen of Monro to the middle of the optic chiasm. The infundibular stalk, which is situated directly posterior to the optic chiasm, connects the funnel-shaped rostroventral part of the hypothalamus with the pituitary gland.

Within the hypothalamus three medio-laterally arranged zones can be recognised
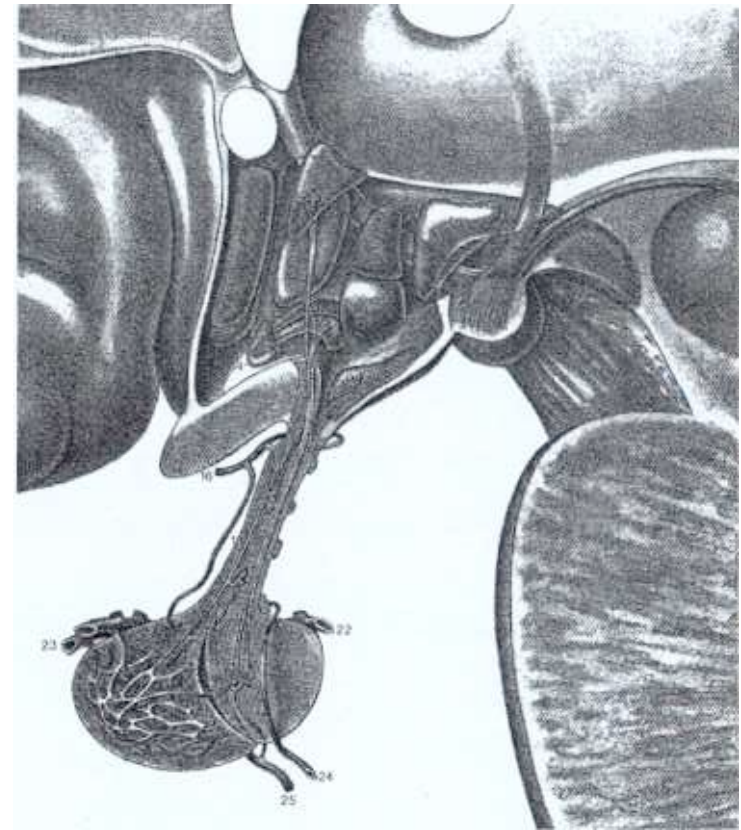
1 Columna fornicis	13 Nucleus supraopticus
2 Nucleus paraventricularis	14 Nucleus suprachiasmaticus
3 Area lateralis hypothalami	15 Nucleus infundibularis
4 Nucleus posterior hypothalami	16 Arteria hypophyseos superior dextra
5 Area tegmentalis ventralis	17 Infundibulum
6 Nucleus preopticus medialis	18 Pars infundibularis ⎫
7 Nucleus anterior hypothalami	19 Pars distalis ⎬ Lobus anterior hypophyseos
8 Nucleus dorsomedialis	20 Pars intermedia ⎭
9 Nucleus ventromedialis	21 Lobus posterior hypophyseos
10 Fasciculus mamillaris princeps	22 Sinus intercavernosus posterior
11 Corpus mamillare	23 Sinus intercavernosus anterior
12 Nucleus preopticus lateralis	24 Arteria hypophyseos inferior sinistra
	25 Arteria hypophyseos inferior dextra

Fig. 192. The hypothalamic nuclei and the relationship between the hypothalamus and the pituitary gland (4/1 ×)
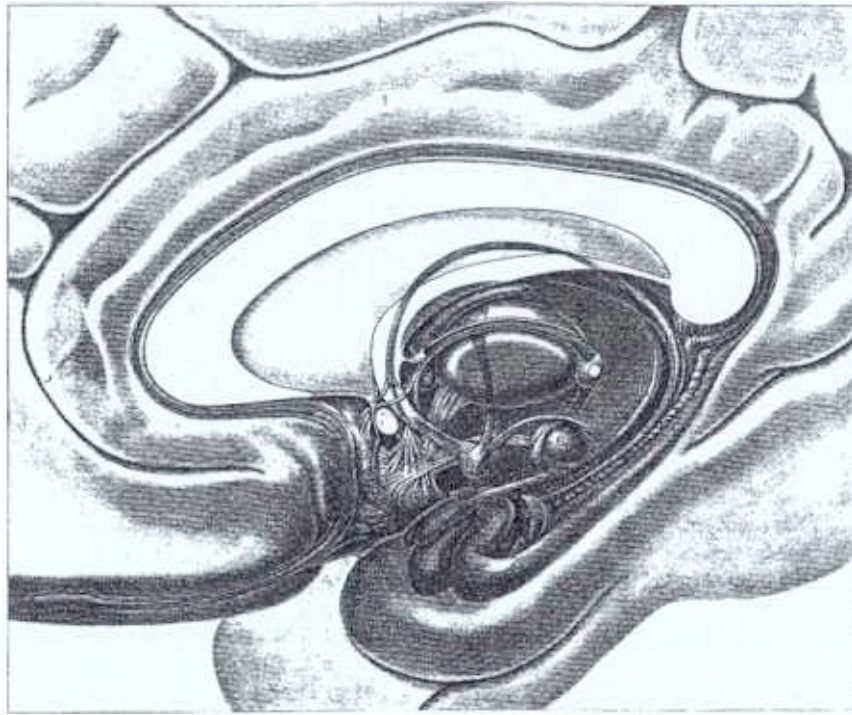
1 Gyrus cinguli	13 Crus fornicis
2 Indusium griseum	14 Gyrus fasciolaris
3 Stria terminalis	15 Fasciola cinerea
4 Nucleus medialis thalami	16 Fissura choroidea
5 Nuclei habenulae	17 Gyrus dentatus
6 Nucleus ruber	18 Subiculum
7 Fasciculus telencephalicus medialis	19 Cornu ammonis
8 Corpus mamillare	20 Site of limbus Giacomini
9 Septum verum	21 Nucleus corticalis amygdalae
10 Area subcallosa	22 Nucleus anterior amygdalae
11 Gyrus diagonalis	23 Nuclei basalis + lateralis amygdalae
12 Fibrae amygdalofugales ventrales	24 Cortex prepiriformis

Fig. 193. The structures of the limbic and olfactory systems and some input-output pathways as seen in a medial view (3/2×). Some displacement of structures serves to bring other structures in view. The walls of the third ventricle and the brain stem have been omitted almost completely; of the thalamus only the anterior, medial and habenular nuclei are illustrated
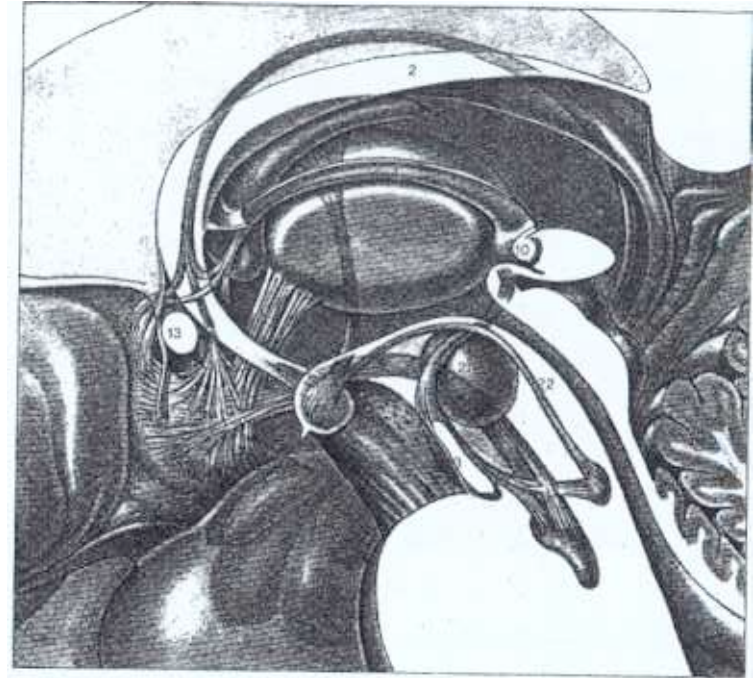
1 Stria terminalis	14 Precommissural components of { stria terminalis / stria medullaris thalami / fornix
2 Fornix	
3 Commissura fornicis	
4 Stria medullaris thalami	15 Stria terminalis postcommissuralis
5 Nucleus anterior thalami	16 Septum verum
6 Tela choroidea ventriculi tertii	17 Lamina terminalis
7 Nucleus medialis thalami	18 Fasciculus telencephalicus medialis
8 Tractus mamillothalamicus	19 Fasciculus mamillaris princeps
9 Nuclei habenulae	20 Corpus mamillare
10 Commissura habenulae	21 Nucleus ruber
11 Tractus habenulointerpeduncularis	22 Tractus mamillotegmentalis
12 Pedunculus thalami inferior	23 Nucleus interpeduncularis
13 Commissura anterior	24 Nucleus tegmentalis dorsalis
	25 Nucleus centralis superior

Fig. 194. The central part of the limbic area; medial view of nuclei and tracts (5/2×)
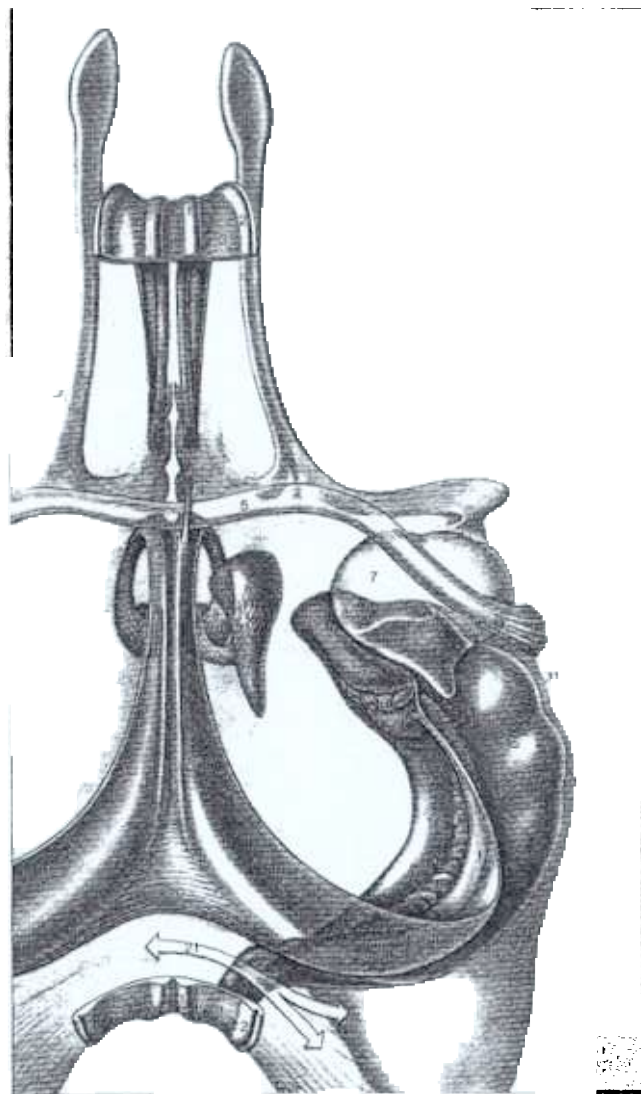
1 Stria longitudinalis medialis
2 Stria longitudinalis lateralis
3 Indusium griseum
4 Fornix precommissuralis
5 Commissura anterior
6 Columna fornicis
7 Corpus amygdaloideum
8 Nucleus anterior thalami
9 Tractus mamillothalamicus
10 Subiculum
11 Ventriculus lateralis, cornu inferius
12 Cornu ammonis (gyrus uncinatus)
13 Limbus Giacomini
14 Cornu ammonis (gyrus intralimbicus)
15 Cornu ammonis (digitationes hippocampi)
16 Corpus fornicis
17 Fimbria hippocampi
18 Gyrus dentatus
19 Crus fornicis
20 Commissura fornicis
21 Site of corpus callosum
22 Gyrus fasciolaris

Fig. 195. The limbic structures isolated from most of their surroundings, seen from above (2/1 ×)
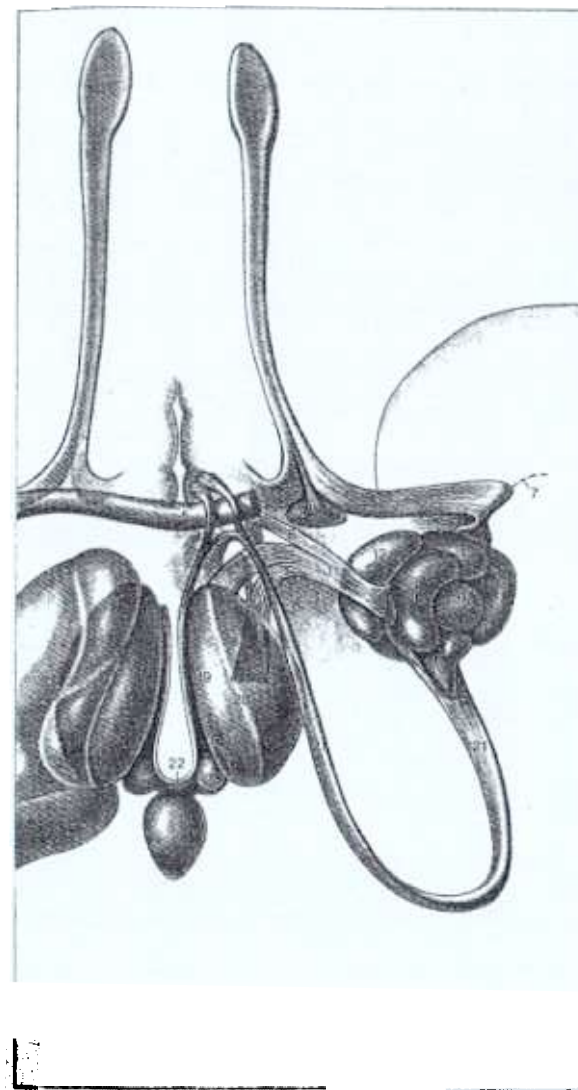
1 Bulbus olfactorius
2 Tractus olfactorius
3 Stria olfactoria medialis
4 Stria olfactoria lateralis
5 Commissura anterior
6 Tuberculum olfactorium
7 Limen insulae
8 Bandeletta diagonalis
9 Pedunculus thalami inferior
10 Fasciculus telencephalicus medialis
11 Fibrae amygdalofugales ventrales
12 Nucleus corticalis
13 Nucleus anterior
14 Nucleus lateralis   Corpus
15 Nucleus centralis   amygdalo-
16 Nucleus medialis   ideum
17 Nucleus basalis (accessorius)
18 Area lateralis hypothalami
19 Stria medullaris thalami
20 Nucleus medialis thalami
21 Stria terminalis
22 Commissura habenulae
23 Nuclei habenulae

Fig. 196. The rhinencephalic structures isolated from most of their surroundings, seen from above (2/1 ×). The *interrupted line* indicates the limen insulae and its continuation around the "hilus" of the temporal lobe

[267], a periventricular, a medial and a lateral zone. The periventricular zone consists of a few layers of small cells arranged parallel to the ventricular surface. These layers alternate with thin sheets of fine, mostly unmyelinated fibres. The nucleus infundibularis, a cell mass in the basal hypothalamus, may be considered a derivative of the periventricular zone. The medial zone, which is relatively cellular, contains a number of variably discrete cell masses. The latter are usually placed in three groups, an anterior, an intermediate and a posterior group. The anterior group is formed by the rather ill-defined anterior nucleus [1194], the distinct, magnocellular supraoptic and paraventricular nuclei, and the small suprachiasmatic nucleus. The intermediate group consists of the dorsomedial and ventromedial nuclei, which are poorly delimited from each other. The posterior group includes the medial, intermediate and lateral mamillary nuclei and the diffuse posterior nucleus. The latter nucleus, which contains numerous scattered large cells, is caudally continuous with the periventricular and tegmental grey matter of the midbrain. The lateral hypothalamic zone is partly separated from the medial zone by the postcommissural fornix, a large bundle connecting the hippocampal formation with the mamillary body. The medial surface of the internal capsule and of the subthalamic region form the lateral boundary of the lateral hypothalamic zone. Caudally this zone passes imperceptibly over into the mesencephalic ventral tegmental area; rostrally it is continuous with the lateral preoptic area. Although the lateral hypothalamic zone contains a few local condensations of cells, most of its territory is occupied by a diffuse neuronal matrix known as the lateral hypothalamic area (LHA). This area constitutes, together with the lateral preoptic area, the bed nucleus of the medial forebrain bundle (see below).

The so-called *limbic midbrain area* [977] encompasses two groups of nuclei, both of which occupy a paramedian position. The first group consists of the ventral tegmental area of Tsai – a poorly defined cell mass that

is rostrally continuous with the lateral hypothalamic area (Fig. 97) – and the interpeduncular nucleus. The latter is an unpaired median structure which lies in the caudobasal region of the midbrain. The second group is composed of the central grey matter, the dorsal raphe nucleus, the superior central nucleus (of Bechterew) and the dorsal tegmental nucleus (of Gudden). The mesencephalic central grey matter is formed by a mantle of densely packed, mostly small cells surrounding the cerebral aqueduct. Rostrally it is directly continuous with the subependymal grey matter of the third ventricle and caudally it blends into the central grey matter of the pontine tegmentum. In humans, the dorsal tegmental nucleus is a small, diffuse cell mass, which flanks the caudal part of the dorsal raphe nucleus at the level of the trochlear nucleus. The two raphe nuclei which form part of the limbic midbrain area, i.e. the dorsal raphe nucleus and the superior central nucleus, have already been discussed in the section concerning the ascending reticular system.

The Central Limbic Continuum: Circuitry and Major Conduction Channels
(Figs. 197, 198)

Experimental hodological studies have shown that all of the structural entities involved in the limbic system are interconnected by short and long, ascending and descending fibres. Taken together, these fibres constitute one large functional system, which Nauta [980, 986] has designated as the 'limbic system-midbrain circuit'. Schematising somewhat, it may be stated that the septal, preoptic and anterior hypothalamic areas form the rostral pole of this circuit, whereas the paramedian midbrain area represents its caudal pole. The hypothalamus may be characterised as a nodal way station interposed between these rostral and caudal poles. Two large telencephalic parts of the limbic system, namely the amygdala and the hippocampal

formation, as well as the olfactory system, are reciprocally connected with the rostral pole of the circuit (Figs. 190, 191). These structures and their fibre connections will be discussed below. The caudal pole of the circuit may be considered as a paramedian subdivision of the brain stem reticular formation [321, 986]. The centres forming this pole are largely integrated into both ascending and descending pathways. The ascending pathways connect the lower parts of the reticular formation, and the visceral sensory centres situated in the caudal part of the medulla oblongata, with the hypothalamus. The descending pathways convey impulses from the hypothalamus to the visceral and somatic motor centres in the brain stem and spinal cord.

The mamillary body, which is situated in the caudobasal part of the hypothalamus, receives a large projection from the hippocampal formation and sends most of its efferents to the anterior nucleus of the thalamus. These two connections form part of a closed hippocampo-mamillo-thalamo-cingulo-hippocampal system known as the circuit of Papez (Fig. 206; [1051]).

The effector mechanism of the hypothalamus include, apart from fibre systems descending to the brain stem and spinal cord, two hypothalamohypophyseal pathways. One of these, the partly neural and partly humoral tuberoinfundibulohypophyseal system, is the means by which the hypothalamus controls the production of the various anterior pituitary hormones. Most fibres that interconnect the rostral and caudal poles of the limbic forebrain-midbrain continuum traverse the hypothalamus. The descending limb of this transhypothalamic projection is, however, supplemented by a notable dorsal conducting route that bypasses the hypothalamus. This route, which is synaptically interrupted in the epithalamic habenular nuclei, is formed by the habenulopetal stria medullaris and the habenulofugal habenulo-interpeduncular tract (Fig. 155B).

After this introductory survey of the central circuitry of the limbic system (Fig. 190), brief consideration will be given to some of the major conduction channels involved in this circuitry.

The *fasciculus medialis telencephali* or *medial forebrain bundle* (MFB) (Fig. 191) may be considered the central longitudinal pathway of the limbic forebrain-midbrain continuum. It is an assemblage of loosely arranged, mostly thin fibres, which extends from the septal area to the tegmentum of the midbrain. It traverses the lateral preopticohypothalamic area, the scattered neurons of which are collectively designated as the bed nucleus of the medial forebrain bundle. The bundle is highly complex, comprising a variety of short and long ascending and descending links [998, 1438, 1445, 1446]. In the transitional area of the diencephalon and the mesencephalon, the MFB fibres are rearranged into a smaller medial and a larger lateral stream [534, 557, 983]. The medial fibre stream roughly maintains the sagittal orientation of the hypothalamic trajectory of the bundle. It passes through the medial parts of the mesencephalic and rhombencephalic tegmental areas, just next to the raphe nuclei. The medial stream is composed of descending fibres, by which several hypothalamic centres project to the raphe nuclei and to the adjacent parts of the medial reticular formation [534, 983], and also comprises fibres which ascend from the raphe nuclei to the lateral hypothalamus, from where they pass to a variety of diencephalic and telencephalic centres (cf. the section on ascending reticular systems). The lateral stream of fibres extending from the MFB to the brain stem sweeps laterally and caudally over the dorsal border of the substantia nigra into a ventrolateral tegmental position immediately caudal to the substantia nigra; at this level it curves dorsomedially and then descends through the mesencephalic central tegmental area to the lateral tegmental field of the pons and the medulla oblongata. This fibre stream contains fibres descending from the central nucleus of the amygdala [550, 1103, 1412], the bed nu-

A

B

C
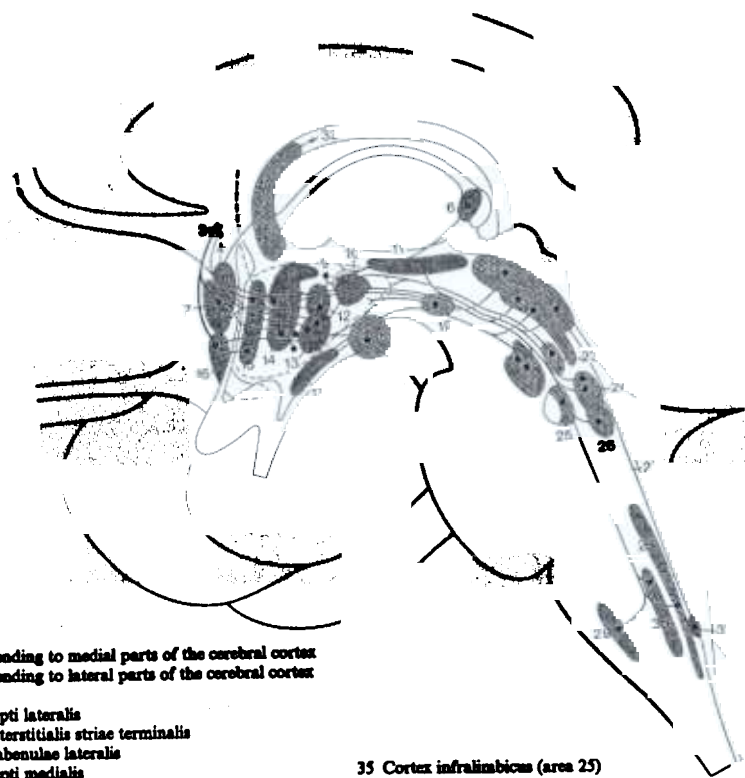
1 Fibres ascending to medial parts of the cerebral cortex
2 Fibres ascending to lateral parts of the cerebral cortex
3 Fornix
4 Nucleus septi lateralis
5 Nucleus interstitialis striae terminalis
6 Nucleus habenulae lateralis
7 Nucleus septi medialis
8 Nucleus paraventricularis
9 Area lateralis hypothalami
10 Nucleus posterior hypothalami
11 Zona incerta
12 Nucleus dorsomedialis
13 Nucleus ventromedialis
14 Nucleus anterior hypothalami
15 Nucleus preopticus medialis
16 Nucleus gyri diagonalis
17 Nucleus infundibularis
18 Corpus mamillare
19 Area tegmentalis ventralis
20 Griseum centrale mesencephali
21 Nucleus raphes dorsalis
22 Nucleus centralis superior
23 Nucleus tegmentalis dorsalis
24 Nuclei parabrachiales
25 Locus coeruleus
26 Griseum centrale pontis
27 Fasciculus longitudinalis dorsalis
28 Nucleus solitarius
29 Noradrenergic cell group A1
30 Noradrenergic cell group A2
31 Area postrema
32 Fibres passing to the nucleus medialis and nucleus centralis amygdalae
33 Fibres originating from the nucleus medialis and nucleus centralis amygdalae
34 Nuclei mediani thalami

35 Cortex infralimbicus (area 25)
36 Cortex prelimbicus (area 32)
37 Medial and orbital regions of cortex prefrontalis
38 Nucleus accumbens
39 Tuberculum olfactorium
40 Stria medullaris thalami
41 Nucleus habenulae medialis
42 Nucleus peripeduncularis
43 Fasciculus telencephalicus medialis
44 Nucleus interpeduncularis
45 Nucleus tegmentalis pedunculopontinus
46 Area subcoerulea
47 Nucleus raphes magnus
48 Formatio reticularis metencephali
49 Formatio reticularis myelencephali
50 Adrenergic cell group C2
51 Nucleus reticularis parvocellularis
52 Nucleus raphes pallidus
53 Adrenergic cell group C1
54 Area reticularis superficialis ventrolateralis
55 Nucleus raphes obscurus
56 Nucleus dorsalis nervi vagi
57 Fibrae hypothalamospinales
58 Organum subfornicale
59 Organum vasculosum laminae terminalis
60 Nucleus supraopticus
61 Nucleus suprachiasmaticus
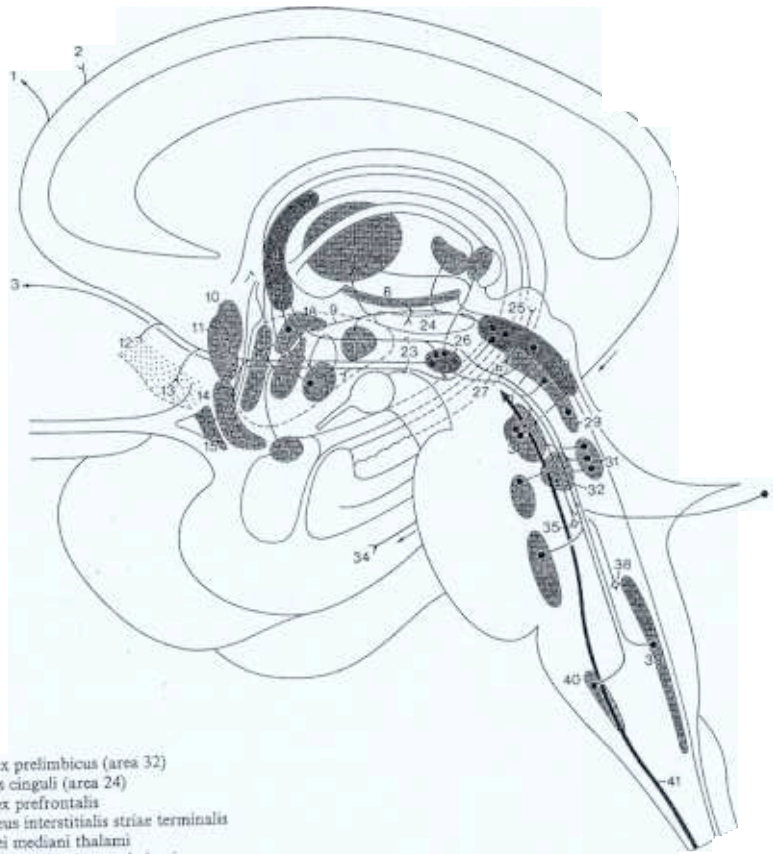62 Fibrae retinohypothalamicae
63 Eminentia mediana
fi Foramen ventriculare
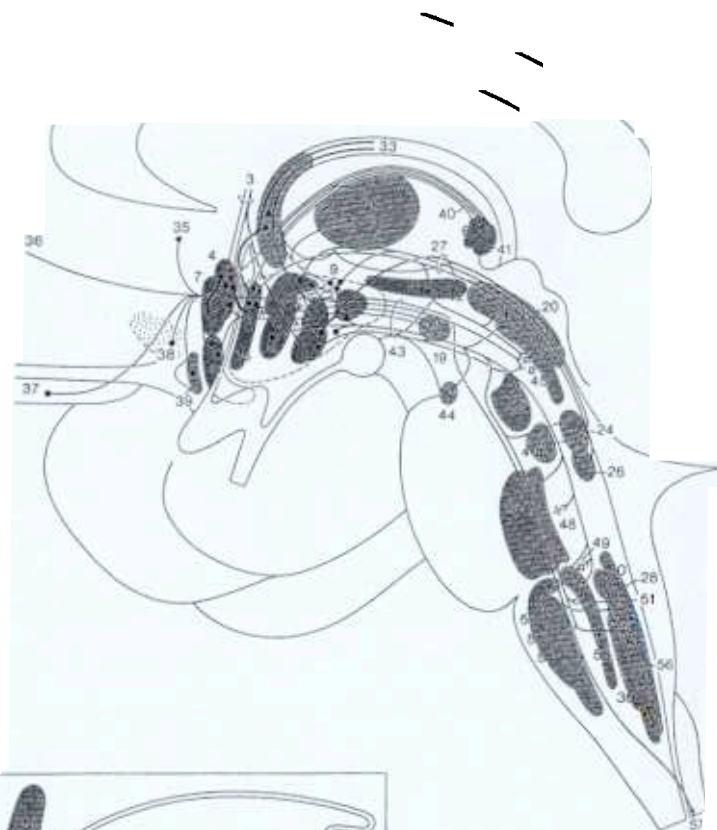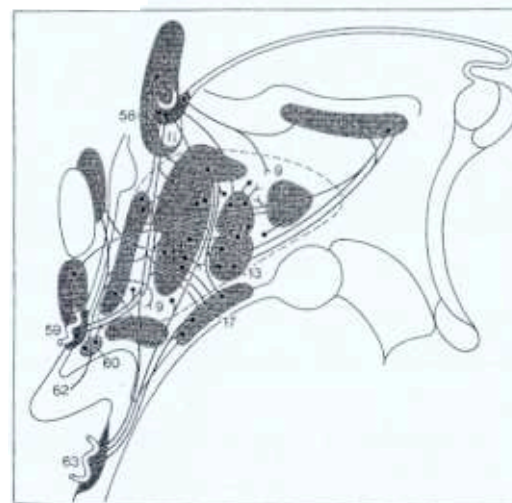
Fig. 197A–C. Fibre connections of the telencephalic and diencephalic portions of the central limbic continuum; A ascending projections; B descending projections; C short connections

1 Cortex prelimbicus (area 32)
2 Gyrus cinguli (area 24)
3 Cortex prefrontalis
4 Nucleus interstitialis striae terminalis
5 Nuclei mediani thalami
6 Nuclei intralaminares thalami
7 Nucleus habenulae lateralis
8 Nucleus reticularis thalami
9 Fasciculus longitudinalis dorsalis
10 Nucleus septi lateralis
11 Nucleus septi medialis
12 Nucleus caudatus + putamen
13 Nucleus accumbens
14 Nucleus gyri diagonalis, pars dorsalis
15 Tuberculum olfactorium
16 Nucleus gyri diagonalis, pars ventralis
17 Nucleus preopticus medialis
18 Nucleus paraventricularis
19 Nucleus anterior hypothalami
20 Nucleus centralis amygdalae
21 Nucleus ventromedialis
22 Nucleus posterior hypothalami
23 Fasciculus medialis telencephali
24 Zona incerta
25 Colliculus superior

26 Area tegmentalis ventralis
27 Formatio reticularis mesencephali
28 Griseum centrale mesencephali
29 Nucleus raphes dorsalis
30 Nucleus centralis superior
31 Nuclei parabrachiales
32 Locus coeruleus
33 Noradrenergic cell group A7
34 Cortex entorhinalis (area 28)
35 Formatio reticularis metencephali
36 Nuclei centrales cerebelli
37 Noradrenergic cell group A5
38 Formatio reticularis myelencephali
39 Nucleus solitarius
40 Noradrenergic cell group A1
41 Fasciculus anterolateralis

42 Cortex frontalis (areae 6 + 8)
43 Cortex prefrontalis (areae 9, 10, 13)
44 Cortex insulae
45 Substantia innominata
46 Corpus mamillare
47 Substantia nigra, pars compacta
48 Substantia nigra, pars reticulata
49 Nucleus interpeduncularis
50 Nucleus medialis amygdalae
51 Nuclei basalis + lateralis amygdalae
52 Subiculum
53 Nucleus tegmentalis dorsalis
54 Area subcoerulea
55 Griseum centrale pontis
56 Nucleus raphes magnus
57 Nucleus prepositus hypoglossi
58 Nucleus raphes pallidus
59 Nucleus reticularis parvocellularis
60 Nucleus dorsalis nervi vagi
61 Area reticularis superficialis ventrolateralis
62 Fibrae mesencephalospinales

Fig. 198A, B. Fibre connections of the bed nucleus of the stria terminalis and of limbic midbrain centres; A ascending projections; B descending projections

cleus of the stria terminalis [542, 1412] and several hypothalamic areas [534, 557, 825, 1184]. These descending fibres terminate in a variety of brain stem centres, among which the substantia nigra (pars compacta) parabrachial nuclei, locus coeruleus, nucleus subcoeruleus, the noradrenergic A1, A2 and A5 groups, the superficial ventrolateral reticular area and the dorsal vagal complex may be especially mentioned. Most of these descending MFB projections are reciprocated by corresponding ascending projections [1445, 1446]. Indeed, the MFB is a major descending and ascending link between the forebrain and the brain stem.

The *dorsal longitudinal fasciculus of Schütz* is, much like the medial forebrain bundle, a composite system consisting of thin ascending and descending fibres. This fascicle extends from the posterior part of the hypothalamus to the caudal medulla oblongata and occupies a periventricular position over its entire length. Rostrally its fibres become incorporated into the hypothalamic periventricular system (Fig. 191). In the older literature [266, 986], it has been reported that most of the ascending and descending projections contained within the dorsal longitudinal fascicle are synaptically interrupted in either the central grey matter of the midbrain or in the dorsal tegmental nucleus of Gudden. More recently it has, however, been established that substantial fibre contingents passing directly from the forebrain to the autonomic centres of the lower medulla oblongata and vice versa are also present [472, 1124, 1190).

The *mamillotegmental tract*, containing the efferents of the mamillary nuclei, constitutes a large, compact bundle known as the principal mamillary bundle (fasciculus mamillaris princeps). This bundle passes dorsally for a short distance and then splits up into two components, the larger mamillothalamic and the smaller mamillotegmental tract (Fig. 191). The mamillothalamic tract, which passes to the anterior thalamic nucleus, forms part of the so-called Papez circuit. The mamillotegmental tract curves caudally into the tegmentum of the midbrain and termi-

nates in the dorsal tegmental nucleus and in the nucleus reticularis tegmenti pontis of Bechterew [269, 1123].

The *mamillary peduncle* receives fibres from the dorsal tegmental nucleus. It passes ventrally and then ascends along the ventral surface of the midbrain to the mamillary body, where most of its fibres terminate. Some of its fibres join the medial forebrain bundle and spread to the lateral preopticohypothalamic zone and the medial septal nucleus [946, 987].

It has already been mentioned that the *stria medullaris thalami* and the *habenulointerpeduncular tract* together constitute a dorsal diencephalic conducting system that is synaptically interrupted in the habenular nuclei [1317]. The fibres constituting the stria medullaris assemble in the area behind the anterior commissure and pass along the dorsomedial border of the thalamus to the habenular nuclei (Fig. 194). The habenulointerpeduncular tract descends from the habenular nuclei to the basal region of the midbrain, where part of its fibres terminate in the interpeduncular nucleus. The two epithalamic cell masses, i.e. the medial and lateral habenular nuclei, represent mutually isolated processing stations in the dorsal diencephalic route. Their connections will be considered in the next section.

Hypothalamohypophyseal pathways are shown in Figs. 192 and 197C. The magnocellular nuclei of the anterior hypothalamus, i.e. the supraoptic and paraventricular nuclei, give rise to axons that descend through the infundibular stalk to the posterior lobe of the pituitary. These axons, which together form the supraopticoparaventriculohypophyseal tract, transport colloid droplets containing the hormones oxytocin and vasopressin to the posterior pituitary lobe or neurohypophysis, where they are released into the blood. The cells of the nucleus infundibularis are involved in controlling the secretion of the anterior pituitary hormones. They exert this control by means of regulating hormones that stimulate or inhibit the liberation of the hormones produced in the pituitary. Each of

the latter has a corresponding regulating hormone. The regulating hormones pass from the infundibular nucleus, along the axons of its constituent cells, to the median eminence, where they are released from the axon terminals into the capillaries of the hypophyseal portal system. The latter system forms a vascular link between the infundibulum and the adenohypophysis. It is noteworthy that the median eminence, a conspicuous neurohemal organ situated in the anterior wall of the infundibular stalk, receives (apart from the neurosecretory axons just mentioned) several other afferent fibre systems that are thought to be concerned with the release of the regulating hormones.

The Central Limbic Continuum: Functional Connections of Individual Centres

In the present section, a concise survey will be presented of the functional connections of the centres which together constitute the central limbic forebrain-midbrain continuum. This survey will be prefaced by some notes on the circumventricular organs, remarkable structures which are all either directly or indirectly related to the central limbic continuum.

Circumventricular organs (CVOs) are small loci of specialised tissue which, as their name implies, are situated in the immediate vicinity of the ventricular system. Most of these loci contain typical neurons, and all of them lie in regions of the central nervous system devoid of a blood-brain barrier. The neurons in the CVO's may be influenced by:

1. Neural afferents entering the organs from other parts of the central nervous system or from the periphery.
2. Substances carried by the cerebrospinal fluid.
3. Plasma-borne substances. The latter are generally considered to play a prominent role.

The CVOs are primarily looked upon as chemosensitive zones, which monitor the changing levels of circulating hormones and other substances. The efferent fibres of the CVO neurons pass to other neural centres and function as initial links in central regulatory circuits [159, 1123, 1253, 1336). Three important circumventricular organs, the subfornical organ, the organum vasculosum laminae terminalis and the area postrema, will now be briefly discussed. The subfornical organ (SFO) and the organum vasculosum of the lamina terminalis (OVLT) are both unpaired structures situated in the wall of the small nonevaginated portion of the telencephalon, i.e. the telencephalon impar (cf. Fig. 2), the former rostrodorsally, just between the two interventricular foramina, the latter rostroventrally, immediately dorsal to the optic chiasm.

The *SFO* is highly vascular and contains numerous receptors for angiotensin II. It receives neural afferents from the preoptic region and the anterior hypothalamic area [792]. Its efferents include fibres projecting to the paraventricular and supraoptic nuclei [916], the infralimbic prefrontal cortex, the bed nucleus of the stria terminalis, the medial hypothalamic area, the substantia innominata, the zona incerta and the lateral hypothalamic area [1336]. The SFO plays a prominent role in body fluid balance [621]. Activation of its neurons by blood-borne angiotensin II is known to lead to the release of vasopressin from the posterior pituitary, to stimulate thirst and to induce drinking behaviour. Swanson and Lind [1336] have recently indicated how the different efferent projections of the SFO might be involved in the various components of drinking behaviour. Their suggestions included the possibility that the efferents to the substantia innominata, zona incerta and lateral hypothalamic area may be involved in behavioural arousal as well as in the modulation of somatomotor control systems and that the efferents to the infralimbic cortical areas and the bed nucleus of the stria terminalis may play a role in cognitive and/or affective components of thirst.

to the mesencephalic reticular formation, including the cuneiform nucleus [234, 850, 851]. The fibres originating from the PAG which descend to the rhombencephalon pass through its tegmental field and distribute fibres to the locus coeruleus, the lateral parabrachial nucleus, the nuclei raphes magnus and pallidus, the pontine and medullary medial reticular formation, the ambiguous nucleus and the portion of the lateral reticular formation surrounding that nucleus [239, 825, 851]. A small number of PAG fibres enters the spinal cord and passes through the lateral funiculus to the intermediolateral zone of the upper thoracic segments [825]. The PAG plays an important role in a variety of 'functions and behavioural patterns, among which nociception, defense reactions, vocalisation, the lordosis reflex that forms part of female reproductive behaviour and the regulation of pancreatic and adrenal secretion may be mentioned.

As regards nociception, the PAG has been demonstrated to be an essential link in a descending pain-control system which ultimately inhibits noxiously evoked activity in spinal dorsal horn neurons (for review see Basbaum and Fields [83]). The nucleus raphes magnus, which receives a strong projection from the PAG, serves as a relay between the PAG and the spinal cord neurons.

Threatening or stressful stimuli may evoke a characteristic pattern of behavioural and autonomic responses which is commonly designated as the affective defense reaction. In cats, the somatomotor components of this reaction include ear retraction, hissing, growling and striking with the forepaw. The autonomic response pattern consists of pupillary dilatation, piloerection, increase in the rate and amplitude of respiration and a sympathetic cardiovascular reaction comprising acceleration of heart rate, elevation of blood pressure and vasoconstriction in cutaneous, renal and splanchnic beds, but vasodilation in skeletal muscles. The classical work of Hess and Brügger [516], Hunsperger [577, 578] and others has shown that this defense response can be elicited by electrical stimula-

tion of a brain area extending from the medial hypothalamus into the mesencephalic central grey matter. The caudal part of the PAG contains a small population of neurons, the excitation of which elicits both behavioural and cardiovascular components of the defense reaction [878]. It has already been mentioned that Fuchs and colleagues [365, 366] have adduced morphological and physiological evidence suggesting that an important circuit subserving feline affective defense behaviour includes an ascending component from the ventromedial nucleus to the anterior hypothalamus and a descending component from the anterior hypothalamus to the PAG. The authors emphasised that the anterior hypothalamus, which receives input from key limbic structures such as the amygdala and the septal area, may well subserve an integrating function with respect to affective defense behaviour. It is worth mentioning in this context that Luiten and collaborators [825] have stressed the potential importance of a somewhat different set of projections leading to the PAG as an essential way-station in the output channel to somatic and autonomic centres involved in agonistic behaviour. In their opinion this circuitry includes strong projections from the medial amygdaloid nucleus to the ventromedial hypothalamic and premamillary nuclei, the latter centres projecting in turn to the PAG.

The PAG also plays an important role in the vocal expression of emotion. Electrical stimulation of the PAG readily induces vocalisation, while lesions in this structure abolish it [648]. Fibres descending from the PAG to the ambiguous nucleus, i.e. the centre which innervates the striated muscle fibres of the pharynx and the vocal-cord muscles of the larynx, are considered to convey the impulses which elicit this vocalisation [649].

The lordosis reflex is elicited in sexually receptive female rodents by somatosensory stimuli which pass along spinomesencephalic fibres, forming part of the anterolateral system, to the PAG. The efferent limb of the reflex arc is presumably an indirect projection which passes from the PAG, via a relay

in the medullary reticular formation, to the spinal cord.

The PAG presumably also forms part of the control mechanisms for feeding and metabolism. Luiten and collaborators [825] recently adduced experimental neuroanatomical and neurophysiological evidence suggesting that a descending sympathetic pathway, including relay centres in the ventromedial hypothalamic nucleus, the PAG, the lower medullary reticular formation and the spinal intermediolateral column, influences the secretion of the pancreas and the adrenal medulla.

In the preceding paragraphs, the functions or possible functional roles of a number of projections descending to and from the PAG has been discussed. The dense projections from the PAG to the intralaminar nuclei have been postulated to carry or modify nociceptive inputs to these parts of the thalamus, but on the whole it should be stated that the role of the projections ascending from the PAG is largely unexplored and poorly understood [317].

The most caudal portion of Nauta's limbic midbrain area [977, 982] is the *dorsal tegmental region*, which includes the dorsal and ventral tegmental nuclei of Gudden. These two cells masses are large and distinct in rodents and carnivores, but only poorly developed in primates. In man, only a relatively diffuse dorsal nucleus can be distinguished [482, 1080]; hence, we will confine ourselves here to a brief overview of the most important connections of the dorsal tegmental region.

The dorsal tegmental region is reciprocally connected with the interpeduncular nucleus, the mamillary body and the habenular nuclei [447, 451, 483, 595, 802, 1081, 1082]; these projections constitute the major afferent and efferent systems of this region. Reciprocal connections also exist with the posterior hypothalamic area [107, 595, 802], the dorsal and superior central raphe nuclei [252, 595], the nucleus praepositus hypoglossi [451, 595] and the rhombencephalic medial reticular formation [802, 1081, 1082]. Interestingly, the dorsal tegmental region also receives direct

afferents from the prefrontal (areas 10–12) and prelimbic (area 32) cortices [595] and an anterograde tracer study [451] has revealed that in the rat the dorsal tegmental nucleus projects to widespread mesencephalic, diencephalic and telencephalic centres, among which are the superior colliculus, the premamillary nuclei, the lateral geniculate body, the midline, medial, intralaminar and anterior thalamic nuclei, the nuclei of the diagonal band, the medial and lateral septal nuclei, the medial amygdaloid nucleus, the hippocampal region and the medial frontal cortex.

The functions of the dorsal tegmental region remain to be explored; however, it may be stated that the recent experimental hodological studies cited have fully confirmed that this region represents a core structure of the limbic system.

The connections described in this section are illustrated in a schematic form in Figs. 197, 198. The main long ascending and descending pathways of the telencephalic and diencephalic portions of the central limbic continuum are represented in Figs. 197A and 197B, respectively, whereas in Fig. 197C a number of shorter connections of the same portions are depicted. Figs. 198A, B illustrate the principal connections of the centres included in the limbic midbrain area. These two figure parts also show the most important connections of the bed nucleus of the stria terminalis, a cell mass which will be discussed at the end of the next section.

The Amygdala

Introduction

It has already been mentioned that two large telencephalic components of the limbic system, namely the amygdala and the hippocampal formation are reciprocally connected with the rostral part of the central limbic continuum (Fig. 190). These two structures will now be discussed. The amygdala, or corpus amygdaloideum, is a large nuclear complex

situated in the dorsomedial portion of the temporal lobe, where it forms part of the rostromedial and rostrodorsal walls of the inferior horn of the lateral ventricle (Figs. 195, 196). Ontogenetically, the amygdala is a derivative of the caudal part of the ganglionic eminence, an intraventricular protrusion, the rostral part of which gives rise to the corpus striatum. Although the anlage of the amygdala is displaced rostroventrally during development, it retains direct contact with the striatum. The corpus amygdaloideum is divisible into a series of nuclei which may be separated into two major divisions, a corticomedial nuclear group and a basolateral nuclear group ([265, 266]; Figs. 90–93). The corticomedial group includes, apart from a number of smaller cell masses, the cortical amygdaloid nucleus and the medial amygdaloid nucleus. Together the nuclei of this group constitute the dorsomedial part of the complex (Fig. 196). The most prominent subdivisions of the basolateral nuclear group are the lateral amygdaloid nucleus, the basal amygdaloid nucleus and the accessory basal amygdaloid nucleus. A rather small central nucleus is sometimes included as part of the corticomedial nuclear group, but will be regarded here as a separate entity. This nucleus is close to the bed nucleus of the stria terminalis (which will be considered below) and the morphologically most caudal parts of the caudate nucleus and the putamen. Like the latter two cell masses, the central amygdaloid nucleus has a high content of dopamine [1402].

Fibre Systems Related to the Amygdala (Figs. 191–196)

Three large fibre bundles, the lateral olfactory stria, the stria terminalis and the ventral amygdalofugal pathway, connect the amygdala with other parts of the brain. The lateral olfactory stria carries secondary olfactory fibres to the cortical and medial amygdaloid nuclei. Its course will be considered below. The stria terminalis emerges from the caudo-

medial aspect of the amygdala, from where it runs a remarkably long curved course along the medial border of the caudate nucleus to the anterior commissure. Immediately dorsocaudal to that commissure it splits up into three components:

1. A precommissural or supracommissural component whose fibres descend in front of the anterior commissure.
2. A commissural component that enters the anterior commissure.
3. A postcommissural component that descends caudal to the anterior commissure.

The stria terminalis is composed of both amygdalofugal and amygdalopetal fibres. The ventral amygdalofugal pathway is a large assemblage of rather loosely arranged fibres which extends from the amygdaloid complex to the rostral part of the diencephalon. It arises from the dorsomedial part of the amygdala, then passes medially and somewhat rostrally through the sublenticular regions of the substantia innominata and the substantia perforata anterior. Some of its fibres pass rostrally to the mediofrontal cortex, others spread in the lateral preopticohypothalamic zone, and still others enter the inferior thalamic peduncle to terminate in the medial thalamic nucleus [986]. Contrary to what its name suggests, the ventral amygdalofugal pathway conducts impulses in both directions.

Afferents to the Amygdala (Figs. 199, 200)

The afferents of the amygdaloid complex can be grouped into the following five categories:

1. Fibres originating from the olfactory bulb and from the olfactory part of the cerebral cortex.
2. Fibres arising from the basomedial telencephalon and from the hypothalamus.
3. Thalamic afferents.
4. Direct afferents from the brain stem.
5. Projections from various (non-olfactory) areas of the cerebral cortex.

These fibre categories, which have been represented diagrammatically in Figs. 199 and 200, will now be briefly discussed.

1. Secondary olfactory fibres originating from the olfactory bulb pass by way of the lateral olfactory tract to the amygdala, where they terminate mainly in the cortical nucleus [1150, 1394]. Apart from this direct olfactory projection, several routes along which the amygdala may be indirectly influenced by olfactory impulses have been described. Thus it has been established that the prepiriform cortex distributes fibres to the basolateral complex and that the entorhinal cortex projects to the central, basolateral and cortical nuclei [1035, 1102, 1166, 1406, 1436]. Moreover it has been suggested that the deep amygdaloid nuclei receive indirect olfactory input via intrinsic connections from the cortical part of the amygdala [1035].

2. The bed nucleus of the stria terminalis and the nucleus of the horizontal limb of the diagonal band project predominantly to the medial and central nuclei, whereas the substantia innominata distributes fibres to almost the entire expanse of the amygdala [6, 262, 978, 1167]. Several hypothalamic structures, including the paraventricular, the ventromedial and the infundibular nuclei, as well as the lateral hypothalamic area (LHA) project to the medial part of the amygdala and to the central nucleus [254, 722, 1009, 1117, 1167, 1193, 1320, 1437]. In the monkey this hypothalamoamygdalar connection originates mainly from the ventromedial nucleus and from the caudal portion of the LHA [27, 889]. Experimental neuroanatomical studies in rat [253] and cat [1167] have revealed that fibres originating from the medial preoptic area pass to the amygdaloid complex, but such fibres have not been observed in the monkey [889, 1196]. The cells in the bed nucleus of the stria terminalis project to the amygdala via the bundle in which they are embedded. The fibres originating from the nucleus of the diagonal band and substantia innominata pass to the amygdala along the ventral "amygdalofugal" pathway, whereas

the axons emanating from the hypothalamic centres mentioned reach the amygdala via both the stria terminalis and the ventral pathway.

3. The amygdala receives input from dorsal as well as ventral thalamic regions. The dorsal thalamic centres that have been found to distribute fibres to the amygdala include the midline nuclear complex, the parafascicular nucleus and the medial geniculate body, all of which project predominantly to the central amygdaloid nucleus [6, 889, 1009, 1036, 1167]. In the ventral thalamus the peripeduncular nucleus has been found to project to the medial, cortical, central and lateral amygdaloid nuclei [6, 1009, 1034, 1167].

4. Brain stem neurons located in the periaqueductal grey matter (PAG), the substantia nigra pars compacta, the ventral tegmental area, the dorsal raphe nucleus, the locus coeruleus, the lateral parabrachial nucleus and the nucleus of the solitary tract project to the central amygdaloid nucleus [6, 889, 1005, 1009, 1034, 1167, 1437]. Most of the brain stem centres mentioned project to the amygdala via the ventral amygdalofugal pathway. However, the serotoninergic fibres from the dorsal raphe nucleus and the noradrenergic fibres from the locus coeruleus reach the amygdala via both the stria terminalis and the ventral pathway. It is noteworthy that the lateral parabrachial nucleus is by far the most important subdiencephalic source of amygdalar afferent connections [889, 1034].

5. The amygdaloid complex receives a powerful input from the cerebral cortex. The allocortical and mesocortical regions which have been shown to distribute fibres to the amygdala include the subiculum [1152, 1166], the anterior cingulate gyrus (area 24) [6, 1035, 1045] and the perirhinal cortex (areas 35 and 36) [6, 514, 1035, 1166]. Fibres from the anterior cingulate gyrus are distributed to the laterobasal nucleus, and fibres from the perirhinal and subicular cortices have been traced to the mediobasal nucleus [1427]. The subiculum also projects to the cortical nucleus [1166]. Neocortical afferents to the

Fig. 199. Olfactory and subcortical afferent connections of the amygdaloid body
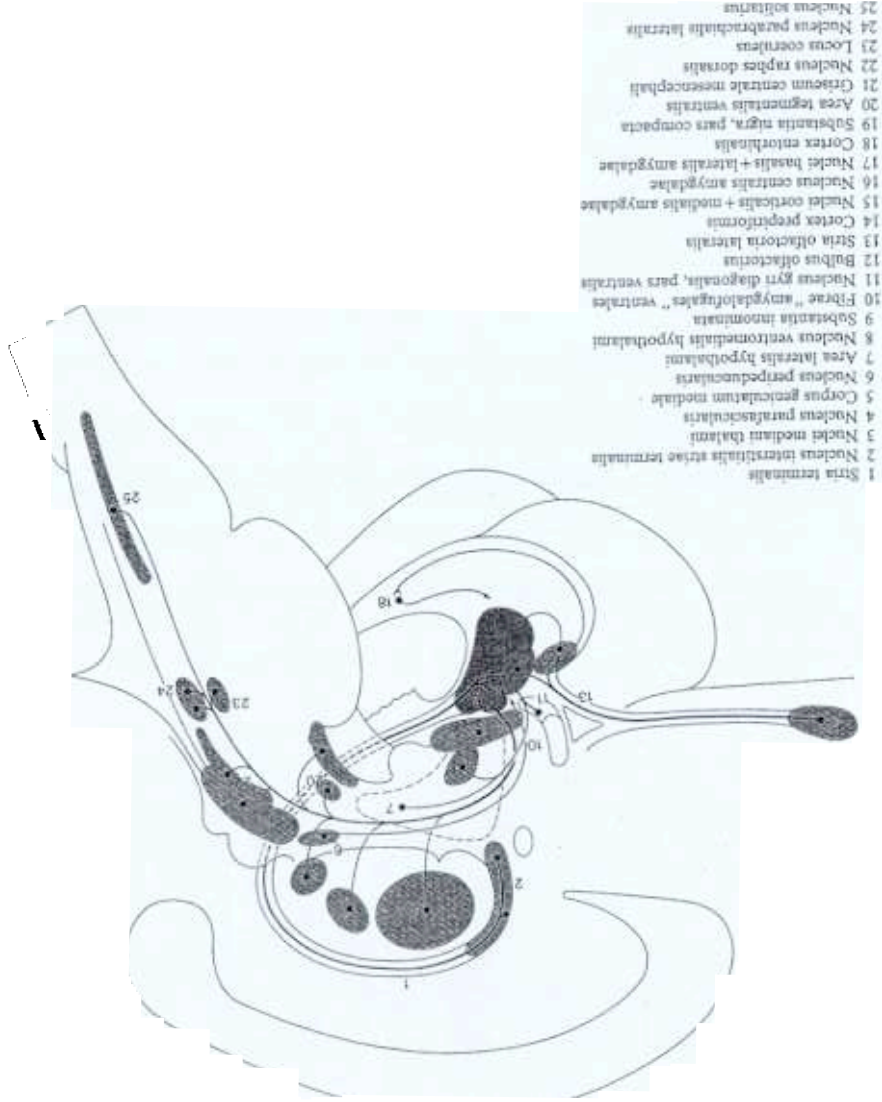
1 Stria terminalis
2 Nucleus interstitialis striae terminalis
3 Nuclei medium thalami
4 Nucleus parafascicularis
5 Corpus geniculatum mediale
6 Nucleus perpeduncularis
7 Area lateralis hypothalami
8 Nucleus ventromedialis hypothalami
9 Substantia innominata
10 Fibrae "amygdalofugales" ventrales
11 Nucleus gyri diagonalis, pars ventralis
12 Bulbus olfactorius
13 Stria olfactoria lateralis
14 Cortex prepiriformis
15 Nuclei corticalis + medialis amygdalae
16 Nucleus centralis amygdalae
17 Nuclei basalis + lateralis amygdalae
18 Cortex entorhinalis
19 Substantia nigra, pars compacta
20 Area tegmentalis ventralis
21 Griseum centrale mesencephali
22 Nucleus raphes dorsalis
23 Locus coeruleus
24 Nucleus parabrachialis lateralis
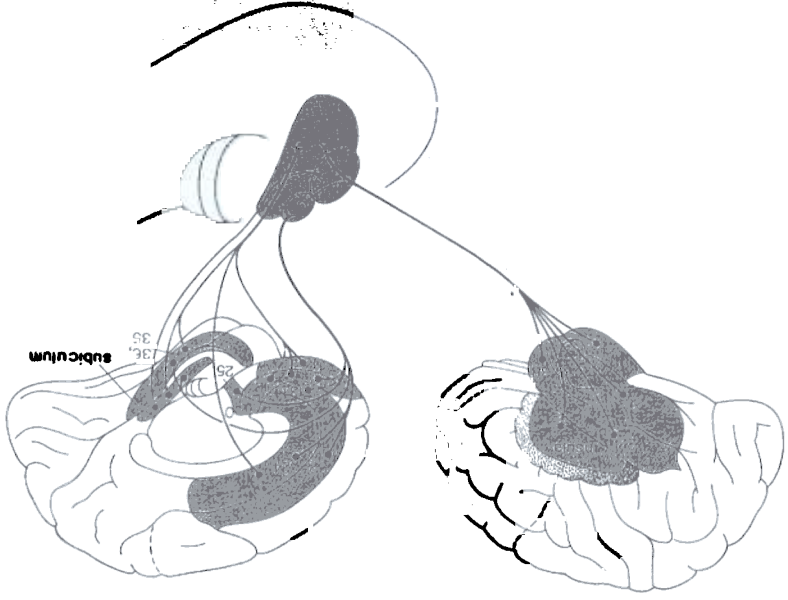25 Nucleus solitarius

Fig. 200. Cortical afferents to the amygdaloid body. *Numbers* indicate fields of Brodmann (see Fig. 5)

subiculum

amygdala originate from: the medial pre-frontal cortex (areas 11 and 12; [1427]), the caudal orbitofrontal cortex (areas 13 and 14; [6, 700, 776, 1406]), the insula [6, 661, 961, 1035, 1436], and temporal cortical regions, including the temporal polar cortex (area 38), the auditory cortex in the superior temporal lobe (area 22) and the visual association cortex in the inferior temporal lobe (areas 20 and 21; [514, 1395, 1502]). All of these neo-cortical areas project principally to the lateral and basal nuclei. It has been pointed out by Herzog and van Hoesen [514, 1427] that the cortico-amygdaloid projections are topo-graphically organised in that allocortical ar-eas project mainly to the medial and cortical nuclei, fibres from mesocortical areas project mainly to the basal nuclei, and the neocorti-cal areas project only to the lateral portion of the complex. The central amygdaloid nu-cleus is unusual in that it receives input de-rived from all types of cortex. Thus, it re-ceives input from: the allocortical prepiri-form, periamygdaloid and subicular areas; the mesocortical anterior cingular (area 24), infralimbic (area 25) and perirhinal (areas 35 and 36) regions and the neocortical prelimbic (area 32) orbitofrontal (areas 12 and 13), in-sular, and temporal (areas 20–22 and 38) re-gions [661, 978, 1035, 1166, 1427, 1502]. It has also been reported that those compo-nents of the amygdaloid complex which re-ceive neocortical afferents, such as the lateral nuclei and the basal complex, project, in turn, upon the cortical nucleus [1103].

Efferents from the Amygdala
(Figs. 201, 202)

The efferent projections of the amygdaloid complex are distributed to:

1. The septopreopticohypothalamic contin-uum.
2. The dorsal thalamus.
3. A variety of cell groups located in the brain stem.
4. The corpus striatum.
5. A number of cortical areas.

These connections will now be discussed:

1a. A large number of fibres originating mainly but not exclusively from the cortico-medial nuclear group passes with the stria terminalis to the area (directly dorsocaudal to the anterior commissure) in which the fibres, as has already been mentioned, split up into three components, precommissural, commissural and postcommissural. The pre-commissural fibres curve caudally around the anterior commissure and terminate in the me-dial preoptic and anterior hypothalamic ar-eas as well as in the paraventricular and ven-tromedial hypothalamic nuclei [107, 294, 495, 721, 873]. The commissural fibres connect the two cortical amygdaloid nuclei [752]. The postcommissural fibres spread to the bed nu-cleus of the stria terminalis, an elongated cell mass that accompanies the stria terminalis throughout most of its extent, and to the re-gion of the anterior hypothalamic nucleus. These postcommissural fibres originate mainly from the medial, basal and lateral amygdaloid nuclei [781].

1b. Fibres originating from the basolateral nuclear group and from the cortical areas surrounding the amygdala have been re-ported to pass via the ventral amygdalofugal pathway to a variety of structures, including the mediofrontal cortex, the basal septal re-gion and the lateral preopticohypothalamic zone [721, 978, 986].

2. A certain proportion of the ventral amygdalofugal fibres join the inferior tha-lamic peduncle and pass to the medial nucle-us of the thalamus [716, 719, 978]. The fibres of this projection originate principally from the basal nuclear group and terminate in the medial, magnocellular portion of the medial nucleus [7].

3. The central amygdaloid nucleus gives rise to a large projection, whose constituent fibres initially travel medially with the ventral amygdalofugal pathway and then turn cau-dally, to descend through the most lateral part of the hypothalamus and the tegmental regions of the brain stem [549, 1233, 1412]. The most caudal fibres of this so-called

amygdalotegmental projection attain the cer-vical cord [924, 1184]. Numerous fibres from the initial part of the projection are sent to the substantia innominata, the nucleus of the horizontal limb of the diagonal band, the bed nucleus of the stria terminalis and the caudal part of the lateral hypothalamic area (LHA). In the brain stem, fibres are distributed to numerous centres, including the peripedun-cular nucleus, the substantia nigra pars com-pacta, the ventral tegmental area, the cunei-form nucleus, the periaqueductal grey mat-ter, the raphe nuclei, the parabrachial nuclei, the locus coeruleus and the area subcoerulea, the rhombencephalic reticular formation, the dorsal motor nucleus of the vagus and the nucleus of the solitary tract [549, 550, 927, 1103, 1223, 1360, 1412]. The medial and lat-eral parabrachial nuclei and the dorsal vagal complex are richly supplied.

4. Fibres originating mainly from the bas-al amygdaloid nucleus pass via the longi-tudinal association bundle and the stria ter-minalis to the ventral as well as the dorsal striatum. The former includes the accumbens nucleus and certain striatal-like portions of the olfactory tubercle; the latter is composed of the nucleus caudatus and the putamen [494, 496, 497]. The fibres entering the dorsal striatum are topographically organised and terminate predominantly in the ventral por-tions of the putamen and ventral and caudal parts of the caudate nucleus [675, 1170, 1171]. This amygdalostriate projection over-laps the striatal projections from the cingulate cortex, the ventral tegmental area and the mesencephalic raphe nuclei [675]. Like the amygdalostriatal system all of these striatal afferents avoid the anterodorsolateral striatal sector, which has been shown to be the main region to which the corticostriatal projection from the sensorimotor cortex is distributed. As mentioned before, these ob-servations suggest a division of the striatum into "limbic" and "non-limbic" compart-ments [675].

5. Projections arising in specific amygda-loid nuclei terminate in distinct areas of the cerebral cortex. Thus, the lateral nucleus and
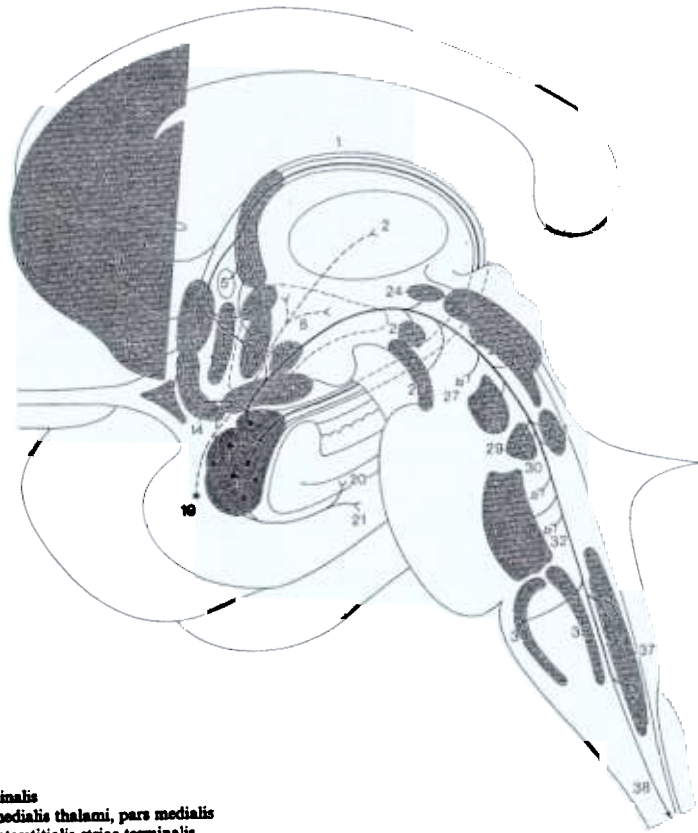
certain portions of the basal complex project strongly to the entorhinal cortex [720], which represents the principal source of cortical input to the hippocampal formation (Figs. 202–204). Additionally, the basal amygdaloid complex has substantial reciprocal intercon-nections with the subiculum, the major source of hippocampal output [720, 1427]. Certain portions of the laterobasal nucleus project to the prelimbic (area 32), infralimbic (area 25), anterior cingulate (area 24) and perirhinal (areas 35 and 36) cortices as well as to the insula [25, 719, 836, 1097]. The en-tire frontal cortex, including the motor (area 4) and premotor (area 6) regions, receives a direct projection from the basal amygdaloid nuclei [66, 606, 803, 804]. Particularly heavy projections have been traced to the lateral and medial parts of the orbitofrontal cortex (areas 12, 13a and 14) [25].

Amaral and Price [25] recently reported that all major divisions of the temporal neo-cortex receive a projection from the amygda-loid complex, with the most prominent pro-jections ending in the cortex of the temporal pole and the rostral superior temporal gyrus. These authors also found a strong projection to peristriate regions of the occipital lobe.

Comments on the Connections and Functions of the Amygdala

If we survey the fibre connections of the amygdala, it appears that this complex enter-tains reciprocal connections with numerous and widespread areas in the brain, extending from the cerebral cortex to the nucleus of the solitary tract. However, a number of con-nections are strictly unidirectional. Thus, the amygdalostriate projection and the amygda-lothalamic projection terminating in the me-dial thalamic nucleus are not reciprocated by strio-amygdaloid or thalamo-amygdaloid projections. The thalamus does send fibres to the amygdala, but these originate from the midline, parafascicular and medial geniculate nuclei, rather than from the medial nucleus.

The central amygdaloid nucleus projects directly to a considerable number of hypo-

1 Stria terminalis
2 Nucleus medialis thalami, pars medialis
3 Nucleus interstitialis striae terminalis
4 Nucleus caudatus + putamen
5 Commissura anterior
6 Nucleus paraventricularis
7 Nucleus anterior hypothalami
8 Area lateralis hypothalami
9 Nucleus ventromedialis
10 Nucleus preopticus
11 Nuclei septi + nucleus gyri diagonalis, pars dorsalis
12 Nucleus accumbens
13 Tuberculum olfactorium
14 Nucleus gyri diagonalis, pars ventralis
15 Substantia innominata
16 Nucleus centralis amygdalae
17 Nuclei corticalis + medialis amygdalae
18 Nuclei basalis + lateralis amygdalae
19 Cortex periamygdaloideus
20 Subiculum
21 Cortex entorhinalis

22 Substantia nigra, pars compacta
23 Area tegmentalis ventralis
24 Nucleus peripeduncularis
25 Griseum centrale mesencephali
26 Nucleus raphes dorsalis
27 Nucleus cuneiformis
28 Nucleus centralis superior
29 Nucleus subcoeruleus
30 Locus coeruleus
31 Nuclei parabrachiales
32 Formatio reticularis rhombencephali
33 Nucleus raphes magnus
34 Nucleus raphes pallidus
35 Nucleus raphes obscurus
36 Nucleus dorsalis nervi vagi
37 Nucleus solitarius
38 Fibrae amygdalospinales

Fig. 201. Subcortical and hippocampal efferents of the corpus amygdaloideum
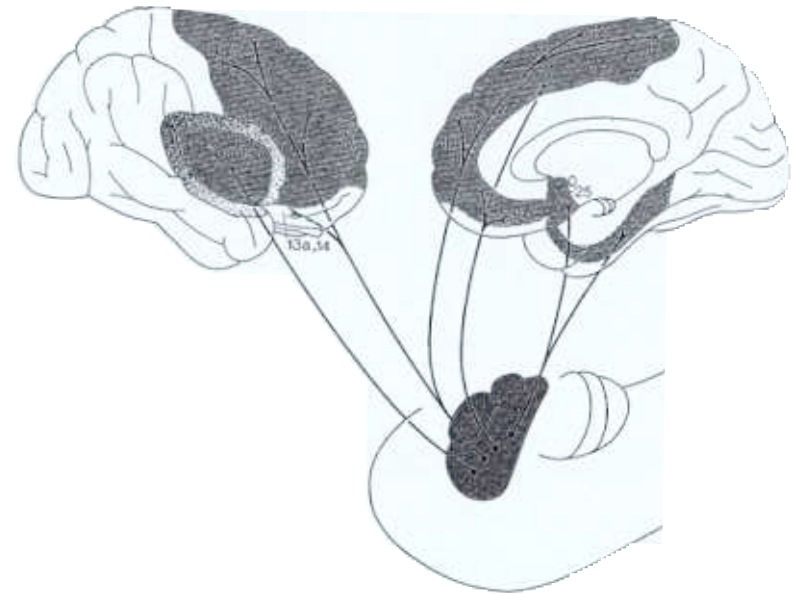

Fig. 202. Efferents of the corpus amygdaloideum to the cerebral cortex. *Numbers* indicate fields of Brodmann (see Fig. 5)

thalamic and brain stem centres, and these projections are considered to contribute significantly to the organisation of the visceral, autonomic, somatosensory and somatomotor components of affective behaviour, such as defense or flight. Electrical stimulation of the central nucleus has been shown to produce somatic, cardiovascular and respiratory components of the defense response [650, 1223], and it has been suggested by Kuypers [745] that certain components of the amygdalotegmental projection become especially active during times of emergency or extreme stress, and may be instrumental in providing motivational drive for the execution of movements. The same author also postulated that other components of the amygdalotegmental projection may activate the so-called descending pain control system, thus suppressing pain transmission during the execution of motor actions of vital priority. The various types of affective behaviour are strongly influenced by extrinsic influences, and physiological experiments have demonstrated that the amygdaloid complex receives information from all sensory modalities [101, 1185]. The pathways through which the amygdala receives olfactory, gustatory, visual and auditory impulses are well known, and these impulses may reach the central nucleus either directly, or indirectly, i.e. via intrinsic amygdaloid connections arising from the basal and lateral nuclei. The gustatory impulses originate from the insular cortex [961], and it is important to note that the visual and auditory amygdalopetal projections arise exclusively from association areas and, hence, may be expected to convey highly processed sensory information [1395]. In summary, it is reasonable to assume that polysynaptic cortico-amygdalotegmental pathways provide the anatomical substrate for the initiation and integration of somatic and autonomic responses associated with affective behaviour. Another access route along which the amygdaloid complex participates in the organisation of affective and other behaviour may well be provided by the large amygdalostriate projection [496]. It has recently been suggested that this projection is implicated in facial expression and in other forms of motor behaviour associated with the emotional and/or experiential state of the individual [1170].

The amygdala is strongly and reciprocally connected with the principal input and output centres of the hippocampus, i.e. the entorhinal cortex and the subiculum, respectively. The amygdala and the hippocampus and their respective connections with mesocortical and neocortical regions are considered to form part of an integrated system involved in the processing of long term memory [918, 919]. Clinical and experimental evidence indicates that the medial, magnocellular portion of the medial thalamic nucleus (MDmc) also has an important mnemonic role [7]. As mentioned this cell mass receives a substantial projection from the amygdala, which arises mainly from the basal nuclear group. This, of course, opens the possibility that the principal projection areas of MDmc, i.e. the medial and orbital prefrontal cortices, may likewise play a role in memory [7]. Recently, evidence has been presented that the large cholinergic cells in the substantia innominata, which receive considerable input from the basal nuclear complex of the amygdala and project in a topographically organised fashion to the cerebral cortex, are also involved in learning and memory [1168].

Bed Nucleus of the Stria Terminalis
(Figs. 91 and 198)

Before turning to the hippocampus, brief consideration will be given to the interstitial nucleus of the stria terminalis. This cell mass, which is also known as the bed nucleus of the stria terminalis (BNST) starts from the dorsal aspect of the amygdala and extends dorsomedially along and among the fibre bundles of the stria terminalis. Its intermediate part envelops the anterior commissure and its dorsal part curves alongside the rostral one-third of the thalamus. The intermediate part of the BNST is rostromedially, medially and caudomedially in direct contact with the septal, preoptic and anterior hypothalamic areas, respectively [155, 986]. Swanson and Cowan [1331] include the BNST within the septal complex, but several other authors [109, 294, 542, 622] have expressed the opinion that on both positional and connectional grounds this nucleus and the central and medial amygdaloid nuclei should be considered together as a single anatomical entity. It is noteworthy that the BNST may show marked sexual dimorphism. It has been reported that in guinea-pigs this nucleus is twice as large in males as in females [524].

The BNST receives afferents from the cerebral cortex, the amygdala, the hypothalamus and several centres in the brain stem. The cortical afferents originate from the insula [661] and from the subiculum [1330]. The BNST is one of the major terminal fields of the amygdala. Most of these amygdaloid afferents stem from the medial nucleus, but the central nucleus and the basal complex also contribute to this projection [721, 1492]. Hypothalamic afferents of the BNST include fibres originating from the paraventricular [254] and ventromedial nuclei [722, 1193]. In the brain stem the periaqueductal grey matter, the ventral tegmental area, the parabrachial nuclei and the dorsal vagal complex send fibres to the BNST [1191, 1268]. Ricardoh and Koh [1123, 1124] have emphasized that the BNST is the recipient of the most dense of the pathways that ascend from the interoceptive portion of the nucleus of the solitary tract to the forebrain.

The BNST distributes its efferent fibres to (1) the amygdala, (2) the mediobasal telencephalon and the hypothalamus, (3) the thalamus and epithalamus and (4) a considerable number of grisea located in the brain stem. These connections will now be briefly discussed.

1. A large number of fibres originating from the BNST passes, largely with the ventral "amygdalofugal" pathway, to the amygdala, where they terminate mainly in the medial and central nuclei [1331]. Fibres leading from the BNST to the lateral and basal amygdaloid nuclei have also been described [253, 254, 1011].

2. Fibres originating from the BNST have been traced to the accumbens nucleus, the substantia innominata and, via the medial forebrain bundle, to the preoptic region and to most parts of the hypothalamus, including the ventromedial nucleus, the lateral hypothalamic area, and the premamillary and supramamillary regions [1331].

3. The BNST projects to the paraventricular thalamic nucleus (one of the midline nuclei in rodents) and, via the stria medullaris, to the medial portion of the lateral habenular nucleus [253, 254, 1320, 1331].

4. Numerous efferent fibres of the BNST descend by way of the medial forebrain bundle and the mesencephalic central tegmental field to the lateral tegmental field of the pons and the medulla oblongata [542]. These fibres have been observed to project substantially to the ventral tegmental area, the substantia nigra pars compacta, the periaqueductal grey matter and the adjoining cuneiform nucleus, the dorsal raphe nucleus, the pontine central grey matter, the medial and lateral parabrachial nuclei, the locus coeruleus, the nucleus subcoeruleus, the nucleus raphes magnus and the adjacent medial reticular formation, the lateral reticular formation, the nucleus of the solitary tract and the dorsal vagal nucleus [254, 542, 1223, 1268, 1331, 1412]. The two latter centres are particularly densely innervated. As Holstege and collaborators [542] remarked, the brain stem projections of the BNST are virtually identical to the ones derived from the central nucleus of the amygdala.

Physiological experiments indicate that the BNST, with the amygdala, the septal and the preoptic regions, is involved in the regulation of somatic, cardiovascular and respiratory components of affective behaviour, particularly flight and defense [825, 1223, 1233]. The descending efferents of the BNST passing to reticular and autonomic centres in the brain stem provide an anatomical substrate

for these regulatory influences. The BNST has also been found to play an important role in male sexual behaviour [330].

The Hippocampus
(Figs. 11, 23; 93–95; 190, 193, 195)

Introduction

The hippocampus or hippocampal formation is a large "C"-shaped structure that forms part of the medial wall of the cerebral hemisphere. This structure can be subdivided morphologically into three parts, precommissural, supracommissural and the retrocommissural. The first two parts are relatively small, vestigial structures; the retrocommissural hippocampus, on the other hand, is well developed and represents the main portion of the hippocampal formation. The names of the three parts, it should be noted, refer to their position with respect to the corpus callosum. The precommissural hippocampus is a narrow vertical structure, situated in the caudal part of the area subcallosa just rostral to the septum verum. It continues dorsorostrally into the indusium griseum, a strand of hippocampal tissue which extends throughout the length of the corpus callosum. The indusium griseum represents the supracommissural hippocampus. Two small fibre bundles, the medial and lateral longitudinal striae, are embedded in it. These bundles represent a small supracallosal component of the fornix. The principal subcallosal fornix will be discussed below. Near the splenium of the corpus callosum, the supracommissural hippocampus is continuous with the retrocommissural hippocampus, the expanded morphologically most caudal end of the hippocampal formation. During ontogenesis, this structure, which is in the medial temporal lobe, rolls in on itself along a longitudinal groove, the hippocampal sulcus. This infolding causes the retrocommissural hippocampus to protrude into the inferior horn of the lateral ventricle. The most rostral portion of the retrocommissural hippocampus is recurved dorsally and constitutes a rounded swelling on the medial surface of the hemisphere, known as the uncus. On the ventricular side this part of the hippocampus is greatly enlarged and differentiated into a series of separate lobules, the hippocampal digitations. As shown by Figs. 81, 82 and 195, the most rostral portion of the hippocampal formation extends for some distance ventral to the amygdaloid complex.

The hippocampal formation constitutes the archipallial part of the cerebral hemisphere; it contains a relatively simple three-layered allocortex throughout its extent. The retrocommissural hippocampus is clearly differentiated into three longitudinally arranged structures: the fascia dentata, the cornu ammonis (Ammons's horn) and the subiculum. The fascia dentata – whose name refers to the toothed or beaded appearance of its surface – is the morphologically most medial strip of the pallium. It is laterally continuous with the cornu ammonis, which in its turn passes over into the subiculum. Due to the infolding of the hippocampus, the fascia dentata is above, and the subiculum below the hippocampal sulcus. The fascia dentata contains a granule cell layer of small neurons, whereas large pyramidal elements prevail in both the cornu ammonis and the subiculum. On the medial surface of the hemisphere the subicular cortex is contiguous with the juxtallocortex or mesocortex. The latter represents a type of cortex that is transitional between the hippocampal allocortex and the neocortex. This transitional cortex covers the parahippocampal gyrus and is also found in the supracallosal cingulate gyrus.

The cingulate gyrus, which borders on the vestigial precommissural and supracallosal parts of the hippocampus, is in the area behind the splenium of the corpus callosum directly continuous with the parahippocampal gyrus. The hippocampus, the parahippocampal gyrus and the cingulate gyrus together constitute a large arcuate convolution known as the limbic lobe (Fig. 4). The allocortical hippocampus forms the "inner ring", whereas the mesocortical parahippocampal and cingulate gyri form the "outer ring" of that lobe. Most parts of the hippocampal and parahippocampal cortices in the temporal lobe can be further subdivided on both cytoarchitectonical and connectional grounds. Without going into details it may be mentioned that within the cornu ammonis there are four different distinguishable fields which are usually designated as CA1–CA4. CA1 borders on the subiculum, whereas CA4 is an aggregation of large cells that, fills the hilus of the curved fascia dentata. Field CA1 is remarkably well developed in primates and man [1292]. The subiculum proper is separated by two strips of mesocortex, known as the presubiculum and the parasubiculum, from the entorhinal cortex. The latter largely corresponds to area 28 of Brodmann (Fig. 5) and occupies a large part of the parahippocampal gyrus. It is ventrally flanked by the so-called perirhinal cortex, which encompasses areas 35 and 36 of Brodmann.

Fibre Systems Related to the Hippocampus (Figs. 203–206)

Before focussing on the afferent and efferent connections of the hippocampus, two large limbic fibre bundles, the cingulum and the fornix, should be briefly commented upon. The cingulum is a bundle of short and long association fibres which surrounds the corpus callosum. Passing through the core of the cingulate and parahippocampal gyri, it extends from the septal area to the uncus region in the temporal lobe. The fornix is a compact fibre bundle connecting the hippocampus with the hypothalamus and various other structures. Its fibres first form the alveus, a thin white layer on the ventricular surface of the cornu ammonis, and then converge as the fimbria along the medial aspect of the hippocampus. Running posterosuperiorly, the fibres of the fimbria enter the crus of the fornix, a flattened structure that arches upwards and medially under the splenium of the corpus callosum. In this region a number of fibres decussate to the opposite side, thus constituting the commissure of the fornix. Proceeding rostrally over the thalamus, the two crura converge and join to form the corpus of the fornix, which lies immediately beneath the corpus callosum. However, at the level of the anterior pole of the thalamus the fornical corpus separates again into two bundles, the columns of the fornix, which curve ventrally in front of the interventricular foramen and caudal to the anterior commissure to enter the hypothalamus. Immediately behind the interventricular foramen a considerable number of fibres leave the column and pass backwards to the anterior nucleus of the thalamus and to the bed nucleus of the stria terminalis. Other fibres split off from the fornix just above the anterior commissure and constitute a small precommissural portion of the fornix. The main bundle of the fornix or postcommissural fornix finally traverses the hypothalamus, where most of its fibres terminate in the mamillary body.

Intrinsic Connections of the Hippocampus (Fig. 204)

A discussion of the complex intrinsic connections of the hippocampus is beyond the scope of the present work. It is, however, important to note that the main flow of information through this structure is thought to take place through a trisynaptic circuit, which begins with a projection from the entorhinal area to the fascia dentata, is relayed to field CA3 of the cornu ammonis and then proceeds to field CA1. A projection from the latter, which terminates in the entorhinal area, closes this trisynaptic circuit [1323, 1324].

The fibres destined for the fascia dentata arise from all parts of the entorhinal area and constitute the so-called temporo-ammonic or perforant path. The fibres of this large projection do not terminate exclusively in the fascia dentata, but also supply the other parts of the hippocampal formation, i.e. the subicular cortices and the various

fields of the cornu ammonis [527, 1330, 1550]. The axons of the dentate granule cells, which constitute the hippocampal mossy fibre system, project in a topographically ordered manner upon the pyramid cells in CA3 [1342]. Major intrahippocampal outputs of field CA3 are carried by the so-called Schaffer collateral system to field CA1. The direct projection from CA1 to the entorhinal area (which, as mentioned above, closes the trisynaptic principal hippocampal circuit [526, 1152, 1153] is supplemented by an indirect projection. The latter is synaptically interrupted in the subicular complex, i.e. the area where most hippocampal efferents, both cortical and subcortical, originate [88, 348, 892, 1152, 1241, 1242, 1273, 1328, 1330, 1430]. Most of the intrinsic connections just discussed are transversely arranged with respect to the long axis of the hippocampus.

Afferents to the Hippocampus
(Figs. 203, 204)

Extrinsic inputs, which are presumed to activate and modulate the intrinsic hippocampal circuitry [1324] arise from a variety of sources, including (1) various cortical areas, (2) the amygdaloid complex, (3) the medial septal – diagonal band complex, (4) the thalamus, (5) the supramamillary region, and (6) the mesencephalic raphe nuclei and locus coeruleus.

1. Pathways leading out of widespread cortical areas converge upon the hippocampus. Most of the fibres of this large cortico-hippocampal projection terminate in the entorhinal area, i.e. the site of origin of the perforant pathway [1144, 1428, 1429], others are synaptically interrupted in the perirhinal as well as in the entorhinal areas [1144, 1430, 1522], and still others bypass the entorhinal area to terminate directly in the subicular cortices [418, 979, 1232, 1430]. Substantial contributions to the corticohippocampal projection have been found to emanate from the posterior orbitofrontal (areas 12 and 13;

[1426, 1429]), infralimbic (area 25; [1148, 1426]), insular [1144], cingulate (areas 23 and 24; [1046, 1426]) and temporal polar cortices (area 38; [1426, 1428]). Several of these areas, particularly the posterior orbitofrontal, anterior cingulate and temporal polar cortex, are sites of convergence of multimodal sensory information. Pathways leading out of the primary visual, auditory and somesthetic areas of the neocortex, by way of a variable number of intercalated association areas in the parietal, frontal and temporal lobes, ultimately converge on these areas [640, 1144, 1428, 1429]. Association areas have also been found to project directly to the parahippocampal cortices. Thus, visual [105, 114, 122a, 122b] and auditory [123b] association areas project to the perirhinal and entorhinal areas [23, 1144, 1426], and fibres originating from multimodal association areas situated in the prefrontal cortex (areas 9 and 46; [418, 979]), inferior parietal lobule (areas 7 and 39; [1232]), and inferior temporal lobe terminate in the presubiculum.

From the foregoing it may be concluded that the parahippocampal cortices and ultimately the hippocampus are provided with a broad spectrum of synthetized sensory-specific as well as multimodal cortical information [1426]. Because the entorhinal area is also the recipient of olfactory information, either arising from the olfactory bulb [490, 1105, 1208] or from the prepiriform cortex (area 51; [464, 719, 720, 1146]), it seems likely that information derived from all sensory modalities is fed into the hippocampal formation.

Recent experimental neuroanatomical [1144, 1145, 1146, 1425, 1522] and physiological studies [813, 1423, 1424] have shown that along its spleniotemporal axis the hippocampus cannot be considered a homogeneous structure. There is topographical organisation of the entorhinal-hippocampal projection so that a lateromedial axis in the entorhinal cortex corresponds to the spleniotemporal axis of the hippocampus. This means that lateral parts of the entorhinal cortex distribute fibres to more splenial portions of the

hippocampus, whereas progressively more medial parts of the entorhinal cortex project to increasingly more temporal hippocampal portions. The lateral and medial parts of the entorhinal areas differ considerably with respect to their afferents. The lateral part receives predominantly cortical pathways conveying information from all sensory modalities [1144, 1522], whereas the medial parts are more influenced by subcortical centres such as the septum, thalamic midline nuclei and amygdala [1145]. These differential inputs to the medial and lateral parts of the entorhinal cortex and the topographical organisation of the entorhinal-hippocampal perforant path discussed above lead to a convergence of exteroceptive sensory information on the splenial portions of the hippocampus, whereas information derived from limbic-related subcortical centres, presumably reflecting the intrinsic status of the organism, is transmitted in particular to the temporal portions of the hippocampal formation [1522].

2. The hippocampus and the entorhinal cortex receive a substantial input from the amygdala [22, 88, 717, 719, 720, 1145]. The basolateral amygdaloid nuclei project strongly to the entorhinal cortex and also distribute numerous fibres to the subiculum [717, 719, 720, 1145]. Projections from the cortical and medial amygdaloid nuclei to the entorhinal cortex [88] and to the hippocampal formation [1427] have also been described.

3. A major projection to the hippocampus and the entorhinal cortex arises from the medial septal nucleus and the nucleus of the diagonal band [20, 22, 24, 88, 296, 310, 679, 893, 1059, 1145, 1530]. The fibres constituting this projection follow three different routes. The majority of fibres pass through the fornix-fimbria system, whereas smaller contingents enter the cingulate bundle, or take a ventral route via the medial forebrain bundle and then through the amygdaloid complex [24, 1145]. The projection to the hippocampus terminates principally in the fascia dentata and the adjacent region of the cornu ammonis [24, 227, 270, 1128]. The medial

septal nucleus and the nucleus of the diagonal band contain large numbers of cholinergic elements [904, 905, 907], and it may be safely assumed that the numerous cholinergic fibres present in the hippocampal formation originate from these neurons [1301, 1466]. The projection from the septum and diagonal band complex to the hippocampal and parahippocampal cortices is, however, only partially cholinergic [483] and several other neurotransmitters, such as gamma-amino butyric acid (GABA; [698, 1050]) and substance P [1448], may also be contained in this projection.

The hippocampus shows a characteristic slow rhythmical electrical activity, usually designated as the hippocampal *theta* rhythm. There is evidence suggesting that both the direct septohippocampal and the indirect septo-entorhinal-hippocampal projections are important in the generation of the hippocampal *theta* rhythm [813, 920].

4. Two parts of the dorsal thalamus, the anterior nuclei and the midline complex, project to the hippocampal and parahippocampal areas. The fibres originating from the anterior nuclei reach the temporal lobe via the cingulate bundle and terminate in the presubiculum, parasubiculum, and subiculum proper [17, 309, 1133, 1245]. This projection forms part of the so-called circuit of Papez, which will be discussed below. The fibres taking origin from the midline nuclei (in rat, cat and monkey most of these fibres arise from the nucleus reuniens thalami [22, 88, 296, 506, 1145, 1535]) pass to the genu of the corpus callosum, where they join the cingulate bundle [506]. After having curved around the callosal splenium, these fibres innervate the entorhinal and subicular cortices and the hippocampal CA1 field [506, 1145]. The nucleus reuniens thalami receives input from the parabrachial nuclei, which in turn receive afferents arising from the nucleus of the solitary tract, a primary viscerosensory centre. Hence, the nucleus reuniens may well help transmit information from the visceral periphery to limbic structures [506].
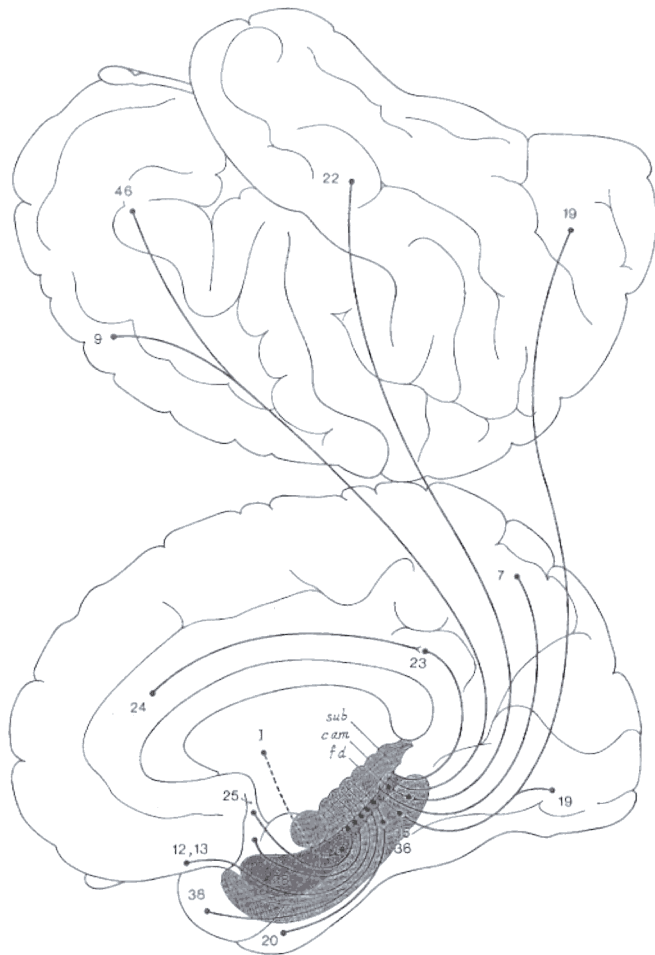
I   Insula
c am   Cornu ammonis
f d   Fascia dentata
sub   Subiculum

The numbers refer to cortical areas according to Brodmann

Fig. 203. Direct and indirect cortical afferents of the hippocampus
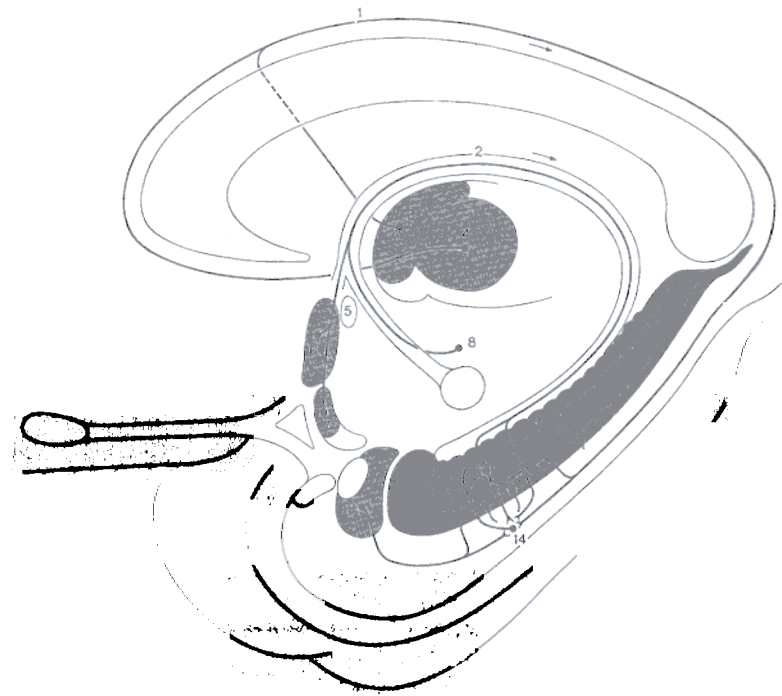
1 Cingulum
2 Fornix
3 Nucleus anterior thalami
4 Nuclei mediani thalami
5 Commissura anterior
6 Nucleus septi medialis
7 Nucleus gyri diagonalis, pars dorsalis
8 Regio supramamillaris
9 Fascia dentata
10 Cornu ammonis
11 Subiculum
12 Nuclei basalis + lateralis amygdalae
13 Tractus temporo-ammonis or "perforant pathway"
14 Cortex entorhinalis

Fig. 204. Subcortical afferents and intrinsic connections of the hippocampus

5. The supramamillary region sends, via the fornix, a substantial projection to the hippocampal region [22, 465, 1059, 1128, 1530]. Most of these fibres terminate in the fascia dentata and in the adjacent CA3 field, but the remaining fields of the cornu Ammonis and the entorhinal cortex are also supplied [465, 1145].

6. The hippocampus contains diffusely arranged noradrenergic and serotoninergic fibres, which reach this structure via the fornix as well as via longitudinal striae and the cingulate bundle. The noradrenergic fibres arise from the locus coeruleus in the upper rhombencephalon, whereas the serotoninergic fibres originate from the mesencephalic raphe nuclei, i.e. the dorsal raphe nucleus and the central superior nucleus [997]. The raphe projection to the hippocampal region contains a substantial number of non-serotoninergic fibres [699].

Efferents from the Hippocampus
(Fig. 205)

Turning now to the efferent connections of the hippocampus, it should first be stated that investigations using so-called tracer techniques have radically changed insight into the organisation of these connections. Contrary to what was believed for almost a century, the entire postcommissural fornix and a considerable part of the precommissural fornix originate from the subiculum rather than from the cornu ammonis [894, 1328, 1330]. The contribution of the latter structure to the fornix has been shown to be only minor and to be confined to the precommissural fornix. In the light of these findings, the hippocampal efferents may be grouped as follows: (1) efferents of the cornu ammonis, (2) contributions of the subiculum to the precommissural fornix, (3) contributions of the subiculum to the postcommissural fornix and (4) "non-fornical" efferents.

1. The precommissural fornix fibres originating from the cornu ammonis terminate ex-

clusively in the lateral septal nucleus [894, 1328, 1330]. These fibres, which are presumably glutamatergic [1550], arise from all cell fields of the cornu ammonis [715]. Multiple retrograde labelling studies suggest that most pyramidal cells in the cornu ammonis which project to the septum also give rise to intrahippocampal collaterals [1324]. It is of interest that the lateral septal nucleus projects massively to the medial septal – diagonal band complex [1108], which is known to project back to the hippocampal formation.

2. The precommissural fornix fibres originating from the subicular complex are distributed to the lateral septal nucleus, the accumbens nucleus, the anterior olfactory nucleus, the precommissural hippocampus, the medial part of the frontal cortex and the gyrus rectus [894, 1152, 1330].

The projection from the subicular complex to the accumbens nucleus presumably constitutes an important part of the interface of the limbic system with central somatomotor mechanisms [928, 931, 1536]. It is known that the nucleus accumbens projects massively to the ventral pallidum, and that fibres originating from the latter structure terminate in and around the tegmental pedunculopontine nucleus, i.e. in an area which has been designated as the mesencephalic locomotor region [240, 1336]. These connections between the nucleus accumbens, the ventral pallidum and the mesencephalic locomotor region are important in mediating locomotor responses associated with exploratory behaviour [928, 931]. The hippocampus probably affects the programming and execution of these responses by way of the fibres passing from the subicular complex to the nucleus accumbens. In this context it is interesting to note that these fibres synapse directly on the neurons of the accumbens-ventral pallidum projection [1536].

3. The postcommissural fornix contains, apart from some hippocampal afferents, only fibres originating from the subicular complex. Most of these fibres terminate in the mamillary body; smaller contingents are distributed to the anterior thalamic nucleus, the

bed nucleus of the stria terminalis and the cell-free capsular zone surrounding the ventromedial hypothalamic nucleus [715, 892, 894, 895, 896, 1152, 1328, 1330]. As regards the latter connection, it is worth mentioning that Ricardo [1123], considering that neurons in the infundibular nucleus send dendrites into the capsular zone of the ventromedial nucleus, suggested that the hippocampus via this particular connection, may influence the secretion of anterior pituitary hormones.

4. Fibres originating from the subicular complex project massively to the adjacent entorhinal cortex [88, 593, 1152, 1273, 1426]. As has already been mentioned, this projection is reciprocated by a strong entorhinal-subicular connection. Both projections are topographically organised, in that a lateromedial gradient in the entorhinal cortex corresponds to a spleniotemporal gradient along the longitudinal axis of the subiculum [1425]. The entorhinal-hippocampal perforant pathway shows a similar topographical organisation [1520, 1521]. Other, "non-fornical" efferents of the subicular complex include projections to the posterior cingulate (area 23) and retrosplenial (areas 29 and 30) cortices, and to the amygdala [593, 896, 1152]. It is important to note that the hippocampus, via the entorhinal (area 28) and perirhinal (areas 35 and 36) cortices, initiates a series of projections to the cerebral cortex that largely reciprocate the input pathways from the same source (Fig. 203). Thus, the entorhinal cortex is known to project to the prepiriform (area 51) prelimbic (area 32), infralimbic (area 25), agranular insular, cingulate (areas 23 and 24), retrosplenial (area 29), perirhinal (areas 35 and 36), posterior orbitofrontal (area 13) and temporal (areas 20, 22, 38 and 41) cortices [418, 708, 1272, 1426, 1521], whereas the perirhinal cortex projects to the prefrontal (areas 9 and 46), temporal (areas 20–22), parietal (area 7) and occipital (area 18) cortices [1426, 1521]. By means of these diverging projections, hippocampal output is disseminated over numerous and widespread cortical areas, including primary sensory areas (olfactory, area 51; auditory,

area 41), sensory-specific association areas (visual, areas 19–21; auditory, area 22; somatosensory, area 7) as well as multimodal association areas (areas 9, 13, 23, 38 and 46). It follows that the classical view according to which the hippocampal formation is an intermediary station in a system of connections that travel largely from cortical areas to subcortical areas has to be abandoned. The anatomical evidence clearly indicates that the key to understanding the function of the hippocampus lies in recognising that its major connections are with associational cortical areas on the one hand and with subcortical limbic structures on the other [1324].

Our understanding of the functional significance of the hippocampal formation is still fragmentary. However, clinico-pathological evidence strongly suggests that the hippocampal-parahippocampal complex and its bidirectional relationships with the associational cortical areas are prominent in learning and memory processes [316, 582, 1426, 1454]. It is interesting to note in this context that bilateral destruction of the fornix does not lead to severe memory disorders [1152].

### The Circuit of Papez (Fig. 206)

The postcommissural fornix is prominent within a system of centres and connections that involves both the inner and the outer ring of the limbic lobe. This system, which has already been briefly discussed, is known as the "circuit of Papez". It was suggested by that author [1051] to be an essential part of the structural basis of emotion. The circuit was originally considered to comprise the following structures and connections: hippocampus – postcommissural fornix – mamillary body – mamillothalamic tract – anterior thalamic nucleus – thalamocingulate projection – cingulate gyrus – cingulum bundle – hippocampus.

Experimental neuroanatomical and physiological studies have considerably increased our knowledge of the circuit of Papez. An extensive survey of the pertinent literature is
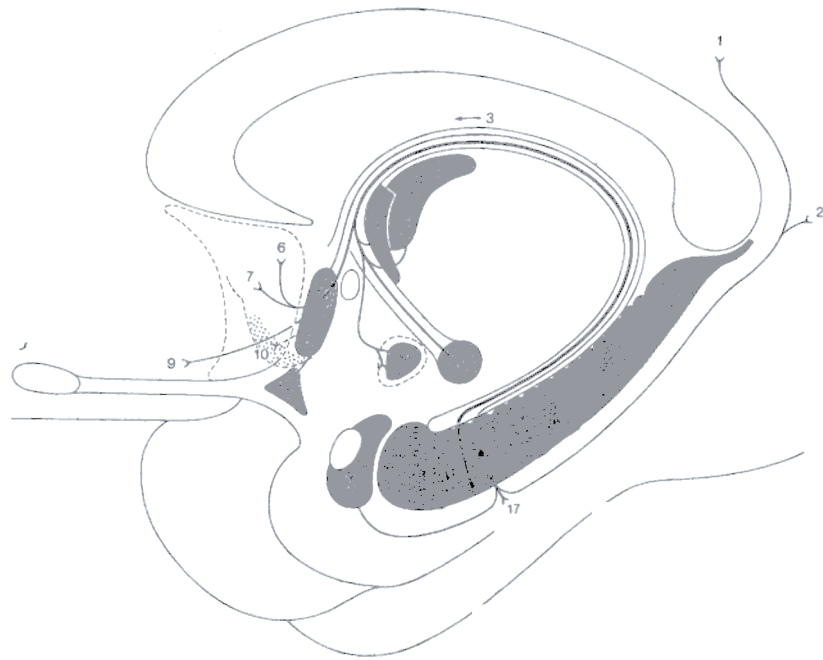
1 Gyrus cinguli (area 23)
2 Cortex retrosplenialis (areae 29, 30)
3 Fornix
4 Nucleus anterior thalami
5 Nucleus interstitialis striae terminalis
6 Hippocampus precommissuralis
7 Cortex frontalis medialis
8 Nuclei septi
9 Gyrus rectus
10 Nucleus accumbens
11 Nucleus olfactorius anterior
12 Nucleus ventromedialis
13 Corpus mamillare
14 Corpus amygdaloideum
15 Cornu ammonis
16 Subiculum
17 Cortex entorhinalis (area 28)

Fig. 205. Efferents of the hippocampus
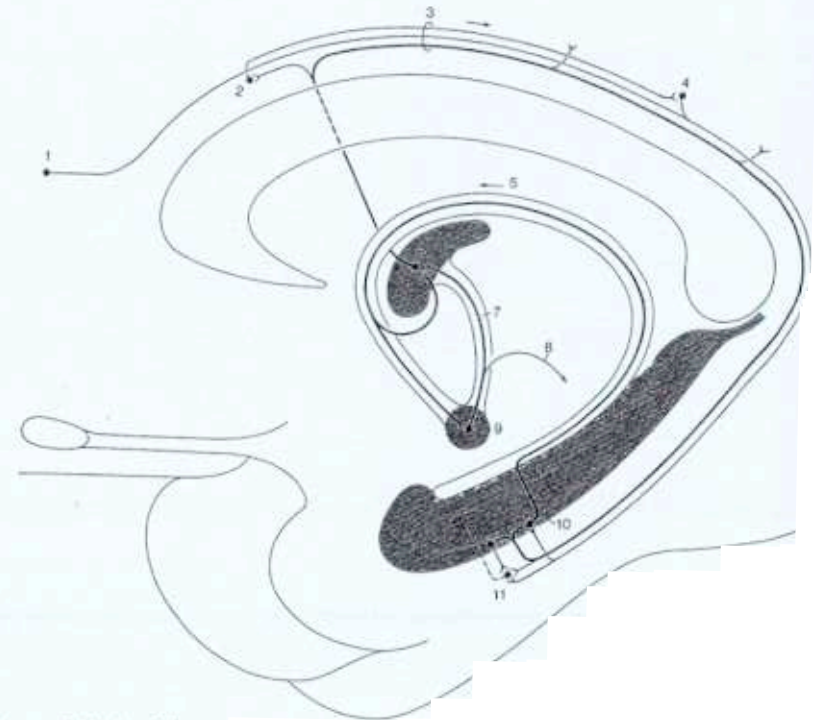
1 Area prelimbica (area 32)
2 Gyrus cinguli (area 24)
3 Cingulum
4 Gyrus cinguli (area 23)
5 Fornix
6 Nucleus anterior thalami
7 Tractus mamillothalamicus
8 Tractus mamillotegmentalis
9 Corpus mamillare
10 Subiculum
11 Cortex entorhinalis (area 28)

Fig. 206. The circuit of Papez

beyond the scope of the present work. A few aspects may be briefly mentioned, however:

1. It has been found that hippocampal afferents travelling with the cingulate bundle terminate in the presubiculum [308, 1241, 1245] and that the latter structure projects massively to the entorhinal area [1241, 1242]. Knowing that the entorhinal area projects to the hippocampal formation by way of the perforant pathway, and unaware that the subicular complex itself gives origin to the postcommissural fornix, Shipley [1241] suggested that projection from the presubiculum to the entorhinal area "closes" the Papez circuit.

2. The indirect hippocampothalamic pathway via the mamillary body is supplemented by a substantial direct pathway [715].

3. The place of the cingulate gyrus in the circuit has been questioned. The anterior thalamic nucleus supplies all parts of the cingulate gyrus [592], but this projection is reportedly not substantial [278]. There is experimental evidence indicating that the most rostral (area 32) and the caudal parts (area 23) of the cingulate gyrus project to the entorhinal cortex and to the subicular complex [89, 1046, 1148]; however, these connections too are considered to be only moderately developed [592]. Moreover, the cingulate gyrus appears to entertain primarily widespread reciprocal connections with various neocortical areas [74, 1046]. The anterior thalamic nucleus, on the other hand, has been found to contribute numerous fibres to the cingulum bundle, many of which project directly to the subicular complex [592, 1241, 1245]. In light of these findings it has been proposed that the cingulate cortex – as opposed to the cingulum bundle – should be considered a component of primarily the neocortex rather than the limbic system [278] and that the "core" of the Papez circuit is constituted by the subicular complex, the mamillary body, the anterior thalamus and their interconnecting fibre systems [592]. Dagi and Poletti [278] recently even went one step further by not including the mamillary body. The circuit of Papez and some related connections are diagrammatically represented in Fig. 206.

The Olfactory System
(Figs. 207, 208)

The central olfactory system or rhinencephalon is entirely confined to the telencephalon, and comprises bilaterally the olfactory bulb, the olfactory tract and the basal olfactory area (Fig. 9). The olfactory bulb represents the primary centre for reception of olfactory impulses. It is a small, flattened, ovoid body that rests on the cribriform plate of the ethmoid bone. Arising from the posterior pole of the bulb, the olfactory tract passes backwards over the basal surface of the frontal lobe to become attached to the hemisphere. At its site of attachment the tract bifurcates into medial and lateral olfactory striae. The initial parts of these striae border, together with the diagonal band of Broca, a territory known as the anterior perforated substance. The medial olfactory stria extends towards the subcallosal area on the medial surface of the frontal lobe; the lateral olfactory stria passes laterally and then bends sharply around the limen insulae to enter the rostromedial part of the temporal lobe (Fig. 196). A small intermediate olfactory stria continues the course of the olfactory tract for a short distance and then fans out in the anterior perforated substance.

The basal olfactory area is formed by those grisea that receive direct projections from the olfactory bulb and includes the anterior olfactory nucleus, the olfactory tubercle, the prepiriform cortex and the cortical nucleus of the amygdala [1150, 1394]. The anterior olfactory nucleus consists of some small groups of neurons located in the caudal part of the olfactory bulb, in the olfactory tract and in the rostral end of the olfactory trigone. The olfactory tubercle (so named because its homologue in macrosmatic mammals is marked by a prominent elevation) is represented by a thin sheet of grey matter, situated in the area of the anterior perforated substance. The prepiriform cortex can be divided into two parts, a medial part overlying the lateral olfactory stria as it travels laterally

across the base of the frontal lobe and a lateral part extending from the limen insulae over a small anteromedial area of the temporal lobe. Caudally, the prepiriform cortex is replaced by the superficial, cortical nucleus of the amygdala. Except for the anterior olfactory nucleus, all grisea that receive direct olfactory afferents exhibit a laminated structure [1394].

The receptive elements of the olfactory apparatus are slender, bipolar cells found in a specialised area of the nasal mucosa. These elements have extremely fine axons that collect as small bundles, penetrate the cribriform plate, and enter the olfactory bulb. Within the olfactory bulb, the primary olfactory fibres synapse with various types of cells, among which the large mitral cells are the most conspicuous. For recent reviews on the microcircuitry of the olfactory bulb, the reader is referred to Macrides and Davis [845] and Nieuwenhuys, [997]. The axons of these olfactory bulb cells pass backwards in the olfactory tract and are distributed to the secondary olfactory areas mentioned above. Experimental studies have conclusively shown that the macroscopic elevation known as the medial olfactory stria does not receive any secondary olfactory fibres [492, 1150, 1394]. After having distributed fibres to the anterior olfactory nucleus and the olfactory tubercle, the entire secondary olfactory projection enters the lateral olfactory stria. Following that stria, the fibres reach the prepiriform and entorhinal cortices, and the cortical and medial amygdaloid nuclei, where they terminate.

The most important tertiary olfactory projections and the various routes along which the rhinencephalon may discharge impulses to the neocortex and the reticulomotor apparatus of the brain stem are diagrammatically represented in Fig. 207. These pathways warrant the following comments:

1. Two regions of the monkey frontal cortex respond to electrical stimulation of the olfactory bulb and to odor stimulation [1355]. One region is the centroposterior orbitofron- tal cortex (CPOF), which corresponds approximately to area 13. The second region is the lateroposterior orbitofrontal cortex (LPOF), which includes the posterior part of area 12. The olfactory projection to the CPOF is transthalamic. The medial, magnocellular portion of the medial thalamic nucleus (Mmc) receives afferents from the prepiriform cortex and the medial part of the amygdala. The thalamopetal fibres emanating from these two destinations of secondary olfactory fibres pass medially, enter the medial forebrain bundle and ascend via the inferior thalamic peduncle to the thalamus [491, 492]. The Mmc projects its fibres to the CPOF [981]. Ethophysiological experiments have shown that the CPOF plays an essential role in olfactory discrimination [1354].

The olfactory pathways to the LPOF are extrathalamic. Electrophysiological experiments suggest that these pathways have their relay neurons primarily in the medial part of the amygdala and in the lateral part of the substantia innominata. The latter area is reported to receive afferents from the medial amygdala as well as from the prepiriform cortex [1355]. In addition, Potter and Nauta [1099] have shown that the monkey prorhinal cortex, which represents a lateral extension of the entorhinal cortex, receives afferents from the prepiriform cortex and projects to the LPOF.

2. Neurophysiological evidence indicates that olfactory impulses reach the lateral hypothalamus. However, there is no unanimity regarding which pathways are involved. The presence of fibres originating from the olfactory tubercle and the primary olfactory cortex which, after having descended with the medial forebrain bundle, terminate in the lateral hypothalamus, has been repeatedly reported [1102, 1225]. It is, however, important to note that Heimer [491, 492] has challenged the existence of a substantial olfactory projection to the lateral hypothalamic area (LHA). According to his observations, the fibres that were supposed to terminate there actually continue to the medial thalamic nucleus. After injecting HRP into the LHA of