FIBRE DEGENERATION FOLLOWING LESIONS OF THE AMYGDALOID COMPLEX IN THE MONKEY

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Of the amygdaloid projection pathways the stria terminalis has traditionally received strong emphasis in anatomical studies, and less attention has customarily been given other fibre systems originating in the amygdaloid complex. It is, however, known that the amygdala is connected with other basal telencephalic structures and with the diencephalon by a massive ventral fibre system which spreads forward and medially through the region underneath the lentiform nucleus. This fibre system appears to have been recognized first by Johnston (1923), who considered it to be an amygdalofugal component of his 'longitudinal association bundle'. Johnston limited his account of this projection system to the statement that such fibres beneath the globus pallidus join 'the general system of precommissural fibres passing up through the parolfactory area'. Later workers, on the basis of experimental-anatomical observations in the cat, described distributions of the ventral amygdalofugal fibre system to the preoptic region and hypothalamus (Lammers & Lohman, 1957; Hall, 1960), the bed nucleus of the stria terminalis (Fox, 1943), the caudate nucleus and the subcallosal gyrus (Lammers & Lohman, 1957).

In Marchi experiments in the monkey, Fox (1949) made the interesting observation that fibres of apparently the same general category join the inferior thalamic peduncle and terminate in the dorso-medial nucleus of the thalamus. In a recent study by the aid of the Nauta–Gygax silver technique the existence of a direct amygdalo-thalamic projection in the monkey was confirmed, whereas other components of the ventral amygdalofugal fibre system were traced to the substantia innominata, the lateral preoptic and hypothalamic regions, the basal septal region, olfactory tubercle, and rostral limbic cortex (Nauta & Valenstein, 1958). These findings have hitherto been published only in the form of an abstract. The present paper will serve to present a more detailed account of the pertinent observations.

MATERIAL AND METHODS

This report is based largely on observations made in six young adult *Macaca mulatta* monkeys in which surgical lesions had been placed in the amygdaloid complex. Several further incidental observations made in other material will be mentioned in the Discussion.

The operative procedure was as follows. With the animal in deep pentobarbital anaesthesia, unilateral lesions of the amygdaloid complex were made, using the subfrontal approach indicated by Scoville & Milner (1957). According to this procedure, a large frontal bone flap was turned, the dura opened widely, and the frontal lobe lifted from the orbital roof, with all exposed cortex thoroughly protected from

mechanical injury by strips of cottonoid soaked in saline. Gentle elevation of the fronto-temporal junction exposed the rostral aspect of the amygdalo-piriform prominence, and a narrow suction tip, fashioned of a suitably curved 20-gauge injection cannula with the cutting tip ground off, was inserted into the amygdalo-piriform complex, using the internal carotid and middle cerebral arteries respectively as medial and dorsal landmarks. Following the aspiration of amygdaloid substance through the small puncture hole, the dura was carefully sutured and the bone flap replaced and fastened.

The animals were killed by an overdose of pentobarbital 9–12 days post-operatively. Fixation of the brain with formalin was initiated by perfusion and extended by storage in the fixative for 6–12 weeks. Frozen sections of the brains were stained following the Laidlaw modification of the Nauta–Gygax silver technique, and axon degeneration, as identified microscopically, was recorded in projection drawings of selected sections.

OBSERVATIONS

As expected, marked variations were encountered in the localization of the lesions. In all cases, the suction tip had penetrated either the piriform cortex or the cortical amygdaloid nucleus, and the lesion extended laterally from this point of entry into at least the basal and accessory basal nuclei. The lateral nucleus was involved in four animals, the medial nucleus in one. In two cases the defect was found to encroach upon the temporal white matter covering the lateral aspect of the amygdala; one of these cases showed additional slight involvement of the ventral edge of the putamen. In all remaining cases the lesion was entirely confined to the amygdalo-piriform complex.

Further variations encountered in this series of experiments concerned the position of the lesion with respect to the dorso-ventral and rostro-caudal coordinates. As concerns the ventral amygdalofugal pathways, such variations appeared to affect the quantity rather than the distribution of the fibre degeneration, more massive degeneration apparently being related to greater involvement of the dorsal amygdaloid regions. The degeneration observed in the stria terminalis appeared to be more strikingly dependent on the localization of the lesion in regard to both quantity and distribution.

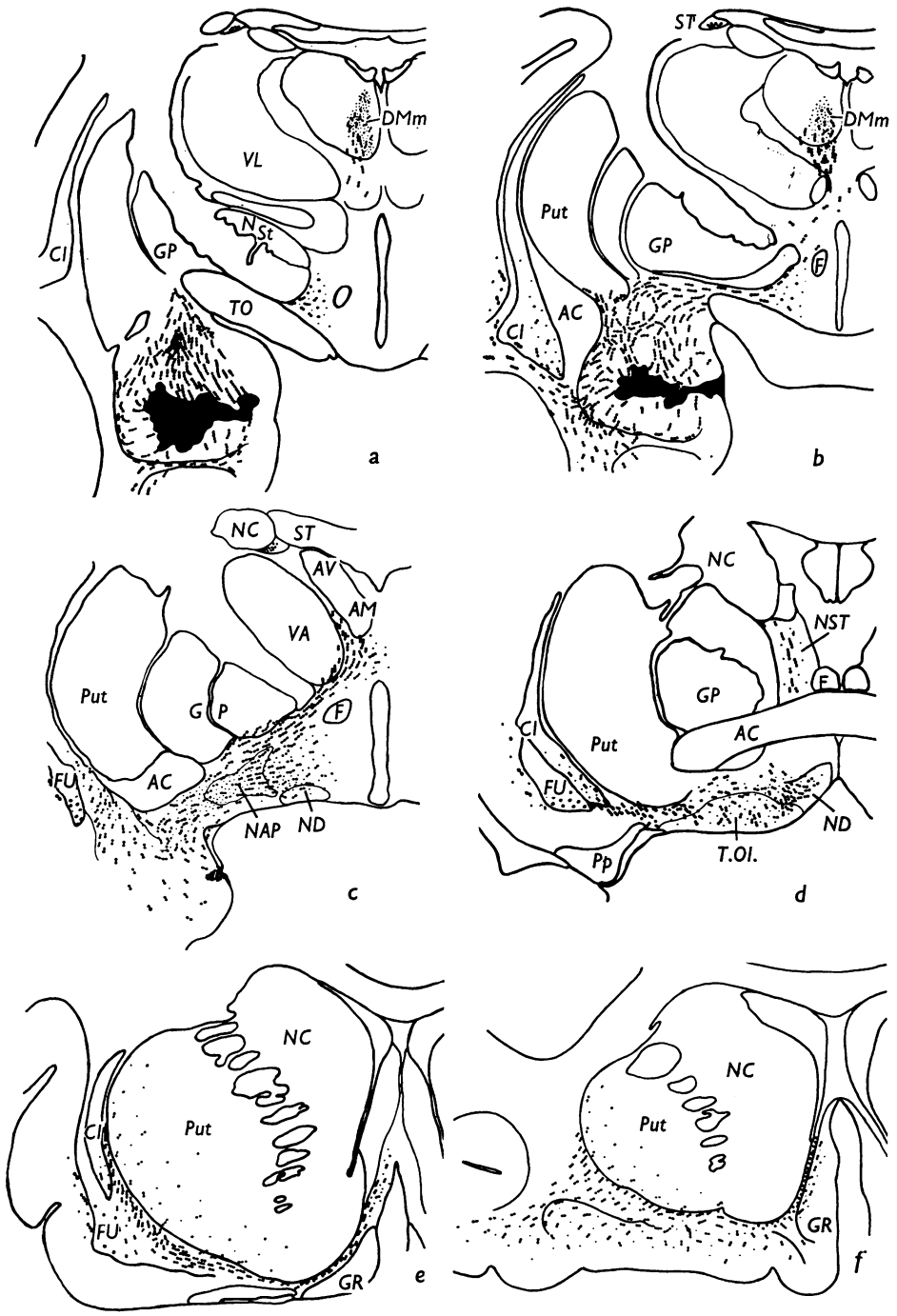
In the following account two of the six cases will be discussed in some detail.

(1) *Case MA* 3 (Text-fig. 1)

The lesion in this case was largely limited to the rostro-ventral quarter of the amygdaloid complex. It involved mainly the basal and accessory basal nuclei, and to a lesser extent the lateral nucleus. The suction tip had caused additional damage to the cortical nucleus and, more rostrally, to the piriform cortex. The lesion was separated from the temporal white matter adjoining the amygdaloid complex laterally by at least a millimeter of apparently normal tissue.

A. *Ventral amygdalofugal pathways*

It is evident even under low magnification that massive fibre degeneration extends from the lesion in the dorsal and rostral directions. Within the amygdaloid complex such degenerated fibres compose a complicated mazework (Text-fig. 1*b*) in which,



Text-fig. 1. Fibre degeneration observed in case MA 3. The amygdaloid lesion is indicated in jet black. Coarse dots indicate degenerating fibres of passage, fine stipple preterminal and terminal degeneration. Abbreviations: see p. 531.

however, at least one more condensed group of relatively fine fibres can be distinguished immediately dorsal to the basal amygdaloid nuclei (Text-fig. 1*a*). This fibre group is tentatively identified as the longitudinal association bundle, but it is noted that the bundle forms part of a more diffuse and widespread fibre system apparently originating mainly from the basolateral group of nuclei. It is of further interest to note the presence of numerous scattered degenerating axons of heavy calibre which, like the finer constituents of the longitudinal association bundle, in general follow dorsal and rostral trajectories through the amygdala.

Substantia innominata. From the level of the caudal border of the chiasma rostralward, large numbers of degenerating fibres curve medially and enter the sublenticular region often labelled substantia innominata. The latter region is pervaded by innumerable disintegrating axons of various calibres (Text-fig. 1*c*; Pl. 1*a*). In the ventral parts of the region fine fibres predominate, whereas coarse axons are more numerous in the dorsal zone adjoining the lentiform nucleus. The occurrence of fine degenerating pericellular fibres indicates that some amygdalofugal fibres actually terminate in the substantia innominata, both in the large-celled dorsal area known as the nucleus ansae peduncularis (Meynert's 'Basalganglion'; Ganser's nucleus basalis) and in the less well defined ventral zones which include a caudal extension of the nucleus of Broca's diagonal band. However, most of the fibres of the ventral amygdalofugal pathway only pass through the substantia innominata *en route* to more distant structures. Somewhat schematically, it can be said that such transit fibres are disposed in fan-tail fashion, with the caudal components oriented medially, the rostral ones rostrally in nearly sagittal planes.

Preoptic region and hypothalamus. The more caudal sublenticular transit fibres are distributed to the lateral preoptic and hypothalamic regions adjoining the substantia innominata (Text-fig. 1*a–c*). They terminate diffusely among cell groups scattered between the longitudinal fibres of the medial forebrain bundle. Only few such fibres accompany the medial forebrain bundle caudalward, and consequently little, if any, degeneration appears in the lateral hypothalamus at infundibular levels or farther caudally.

The most ventral of these amygdalo-hypothalamic fibres course immediately dorsal to the supraoptic nucleus, and a few scattered degenerating elements are seen to enter this cell group. There is, however, no convincing evidence for arborization of such fibres within the nucleus. Signs of fibre termination are, by contrast, abundant in the ventral hypothalamic zone immediately dorsal to the supraoptic nucleus.

Thalamus. The fibre degeneration extending to the lateral preoptic region is accompanied dorsally by a considerable number of degenerating coarse axons which join the inferior thalamic peduncle (Text-fig. 1*c*). Before gaining the peduncle most of these fibres follow dorsal paths in their medial course through the substantia innominata; some of the most dorsal ones even trace weaving trajectories through a ventral zone of the globus pallidus without, however, displaying signs of termination in that structure. In the peduncle the degenerating fibres form a rather scattered group (Pl. 1*b*) which, upon entering the thalamus, issues a few fibres medially to the nucleus reuniens (Text-fig. 1*c*) and laterally to the medial part of the nucleus reticularis thalami. The bundle then breaks up into a number of scattered fascicles

which curve caudalward and follow the medial one-third of the internal medullary lamina to the medial, magnocellular part of the ipsilateral dorso-medial thalamic nucleus (Text-fig. 1*a*, *b*). In this cell group the constituent coarse axons terminate with profuse pericellular arborizations, as indicated by the extremely dense feltwork of disintegrating fine axons which fills the nucleus and sharply delimits it from its surroundings (Pl. 1*c*). A small number of amygdalo-thalamic fibres decussate in the internal medullary lamina and disperse in the medial part of the contralateral dorso-medial nucleus.

Olfactory tubercle, septal region, gyrus subcallosus, rostral limbic cortex. Rostrally the substantia innominata continues into the region of the substantia perforata anterior. This region is characterized by the appearance of the olfactory tubercle, a circumscript cortical formation flanked medially by the nucleus of Broca's diagonal band, and laterally by the prepiriform cortex (Text-fig. 1*d*). In its caudal half the tubercle is separated from the more dorsally situated lentiform nucleus by a rather loosely structured rostral extension of the nucleus ansae peduncularis (n. basalis of Ganser). More rostrally, however, the diagonal band curves dorsally into the septal region, and the nucleus ansae peduncularis tapers to a vague rostral limit, leaving the olfactory tubercle in immediate contact with the ventral aspect of the caudato-putaminal junction. Farther rostrally still the olfactory tubercle reaches its rostral boundary; from here forward the fundus striati is covered by the orbito-frontal cortex.

As shown by Text-fig. 1*d*, numerous fibres of the sublenticular amygdalofugal fibre system extend forward into the region of the olfactory tubercle. In the tubercle proper such fibres appear to terminate in the multiform as well as in the pyramidal cell layers. Other fibres are distributed to the nucleus ansae peduncularis deep to the tubercle, whereas densely packed fine degenerating axons follow a more medial path alongside and in the diagonal band. Undoubtedly many of these more medial fibres terminate in the diagonal nucleus, but this degeneration does not follow the nucleus over more than a short distance into the septal region (Text-fig. 1*e*), and consequently no axon degeneration is detectable in more dorsal parts of the septum.

Fibres of the same medial group that conveys amygdaloid efferents to the nucleus of the diagonal band extend forward beyond the septum, in the white matter of the gyrus rectus (Text-fig. 1*e*). Many of these fibres arborize in the grey matter of the gyrus subcallosus (Text-fig. 1*f*). Other fibres of the same group continue even farther forward, bend around the genu corporis callosi and become dispersed among the fibres of the fasciculus cinguli. Degenerating arborizations of these long amygdalofugal fibres are found scattered in the ventral region of approximately the rostral one-third of the gyrus cinguli.

Temporal cortex, insula, putamen, claustrum, orbito-frontal cortex. As shown by Text-fig. 1*e–f*, the aforementioned degeneration spreading to the septum and rostral regions of the gyrus fornicatus forms only a medial part of a widespread stratum of degenerating fibres that covers the ventral half of the putamen and nucleus accumbens. Approximately the lateral half of this degenerated fibre stratum appears to be made up of fibres closely related to the fasciculus uncinatus and the ventral margins of the outer capsules. It seems likely that these degenerating axons belong to a fibre system which takes a lateral exit from the amygdaloid complex, enters the white

matter of the temporal lobe (Text-fig. 1*b*) and spreads from here in various directions: (*a*) ventralward to a rostral part of the inferior temporal gyrus, (*b*) lateralward to rostral parts of the middle and superior temporal gyri, and (*c*) rostrally to the claustrum (Text-fig. 1*b–e*), the ventral part of the insular cortex (Text-fig. 1*b*, *d*, *e*), the lateral zone of the putamen (Text-fig. 1*e–f*), and the caudal orbito-frontal cortex (Text-fig. 1*f*). It must be remarked, however, that with the exception of the fibres to the inferior temporal gyrus and claustrum, a continuous tracing of the paths followed by the degeneration in question has not been possible. It is especially difficult to establish the connexion of the degeneration in the temporal white matter with that in the fasciculus uncinatus and in the base of the outer capsules. Hence, as will be pointed out more fully in the Discussion, the evidence in regard to some of the amygdalo-cortical connexions indicated above appears to be somewhat less than conclusive.

B. *Stria terminalis*

In this case only a small ventro-lateral part of the stria terminalis is degenerated. The fibres involved extend forward to the bed nucleus of the stria, in which cell groups all appear to terminate (Text-fig. 1*d*). No strial degeneration can be traced ventralward past the anterior commissure.

(2) *Case MA* 11 (Text-figs. 2, 3)

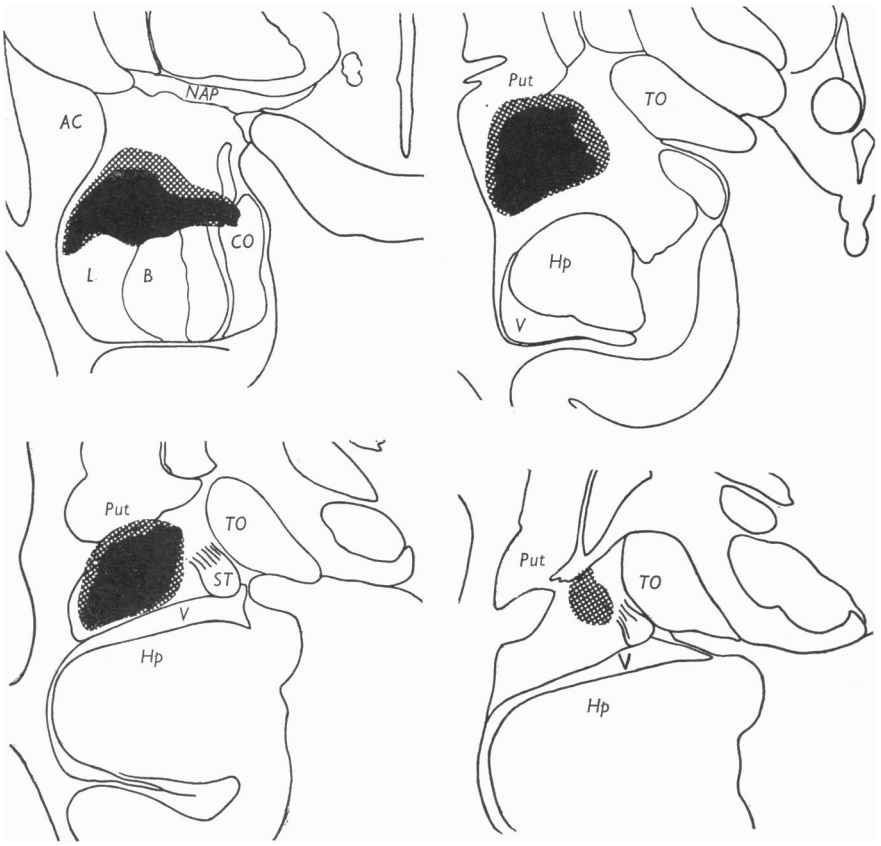
This case is briefly described here for the supplementary information which it furnishes concerning the stria terminalis. The lesion in MA 11 was situated farther caudally in the amygdaloid complex than was the case in MA 3, and it extended into that part of the complex which extends caudally in the roof of the temporal horn of the lateral ventricle (Text-fig. 2). As in MA 3, the lesion involved mostly the basolateral cell groups, but it extended farther dorsally; also it had spared the rostral half of the amygdaloid complex, which was involved to a considerable extent in MA 3.

Stria terminalis

The stria terminalis shows massive degeneration. In contrast to its localization in case MA 3, the degeneration is densest in the dorso-medial half of the stria; it maintains this relative position throughout its course through the bed nucleus of the stria (Text-fig. 3*a*). Few if any of the disintegrating fibres appear to end in the latter nucleus, and virtually all continue around the rostral and caudal aspects of the anterior commissure into the medial preoptic region and beyond it into the hypothalamus (Text-fig. 3*b*, *c*). Most of these hypothalamic stria fibres appear to distribute to the anterior hypothalamic nucleus (Text-fig. 3*b*; Pl. 1*b*). In their course caudalward through this nucleus the degenerating fibres shift progressively farther ventrally, rapidly decreasing in number. In frontal sections involving the caudal one-third of the optic chiasma only a small number have remained. These strial components are here found scattered in regions ventral and somewhat lateral to the rostral pole of the ventro-medial nucleus (Text-fig. 3*c*). Only a few isolated degenerating fibres can be traced some distance beyond the caudal border of the

chiasma; their distribution area appears to be ventral to the ventro-medial nucleus and possibly involves a small lateral part of the arcuate nucleus. No degenerating fibres can be traced into the ventro-medial nucleus proper.

The only further component of the stria terminalis which is recognizable in this case appears in the form of a small number of degenerating fibres which join the dorsal stratum of the anterior commissure (Text-fig. 3*a*). Although these few fibres can be followed across the midline, it is not possible to establish their ultimate



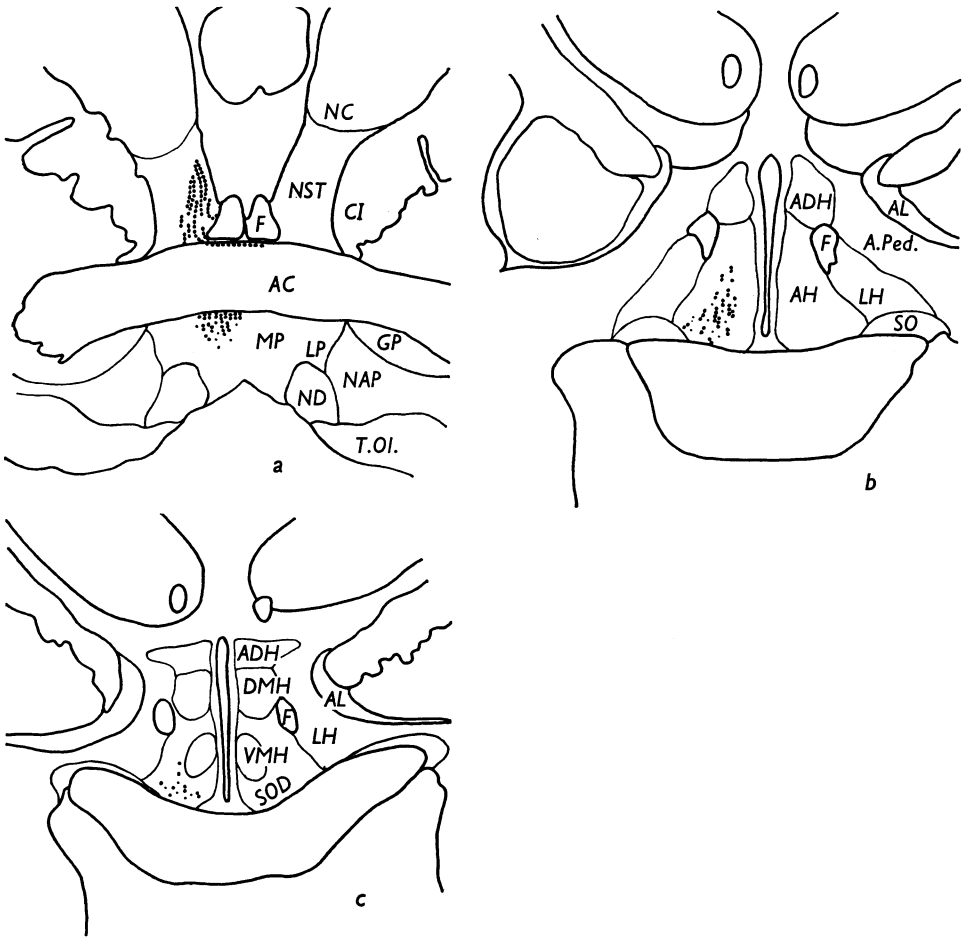
Text-fig. 2. Four drawings of transverse sections showing the extent of the amygdaloid lesions in case MA 11. Complete tissue loss is indicated in jet black, heavy gliosis with loss of cell bodies by cross-hatching. Abbreviations: see p. 531.

distribution. It is likely that this scant degeneration corresponds to the much more massive pars commissuralis striae terminalis described in the opossum by Johnston (1923), and in several subprimate mammalian forms by others.

Ventral projection pathways

The degenerating ventral amygdalofugal system charted in this case appears similar to that observed in MA 3, with the exception that the degeneration in several of the rostral components of the system is considerably less massive than in MA 3.

This is especially true of the degenerations traceable to the orbito-frontal cortex, putamen, claustrum, and olfactory tubercle. By contrast, the degeneration distributing to the nucleus of Broca's diagonal band, as well as to the gyrus subcallosus and rostral limbic cortex appears comparable in volume to that observed in MA 3.



Text-fig. 3. Degeneration of the stria terminalis as observed in case MA 11. Symbols as in Text-fig. 1. Abbreviations: see p. 531.

DISCUSSION

The amygdaloid complex, as is well known, consists of several cell groups of various architecture, and it is unlikely that all these nuclei contribute in the same manner to the pathways described in the foregoing account. Unfortunately, even small surgical lesions in heterogeneous structures such as the amygdala destroy not only the cell bodies which fall within their boundaries, but also fibres of passage originating outside the area of the lesion proper. Only gross impressions of the mosaic of origin can therefore be expected from studies involving the surgical production of amygdaloid lesions. Apart from this restriction, the particular surgical procedure followed

in the present study has the advantage of obviating the track-damage to other structures which unavoidably complicates stereotactic lesions and which would have vitiated several of the present observations by involving either the internal capsule or the temporal white matter lateral to the amygdala.

There remains, none the less, reason for caution in the interpretation of fibre degenerations following amygdaloid lesions: such lesions almost certainly involve transit projection fibres from the piriform cortex. The production of selective defects of the monkey's periamygdaloid cortex, which could have helped to clarify this point, has so far been unsuccessful in our hands. No attempt can consequently be made at this time to distinguish between paleocortical fibres passing through the amygdala, and projection fibres from the amygdaloid cell groups proper. Hence, although the term 'amygdalofugal pathways' is used here, the connexions in question are perhaps more cautiously interpreted as projections from the amygdalo-piriform complex as a whole.

The observations reported above have confirmed the existence of two main amygdalo-subcortical projection pathways in the macaque, namely the relatively compact stria terminalis, and a much more diffuse and widespread ventral amygdalofugal fibre system. Furthermore, the present findings suggest the existence of a third efferent pathway which connects the amygdala with several cortical regions.

As the literature pertaining to the fibre connexions of the amygdala has recently been reviewed succinctly by Gloor (1955, 1959), a detailed bibliographical survey would seem superfluous at this time. In the following account references will therefore be limited mostly to those previous experimental observations which seem immediately pertinent to the findings described in the foregoing account.

A. *Ventral amygdalofugal pathways*

The present findings emphasize the great volume of the ventral amygdalo-subcortical pathways, as well as the multiplicity of their connexions. As pointed out in the description of case MA 3, this fibre system, corresponding in part at least to Johnston's (1923) longitudinal association bundle, emerges from the amygdala in the dorso-medial direction. It spreads medially and forward underneath the lentiform nucleus, distributing fibres to (*a*) basal forebrain structures, namely, the substantia innominata, the lateral preoptic and hypothalamic areas, the substantia perforata anterior including the olfactory tubercle, and the nucleus of the diagonal band; (*b*) rostral parts of the gyrus fornicatus: subcallosal gyrus and anterior cingulate cortex; and (*c*) the magnocellular element of the dorso-medial thalamic nucleus, via the ansa peduncularis.

Amygdaloid projections to the septal-lateral preoptic-lateral hypothalamic region can presumably serve to lead impulses of amygdaloid origin into the paths of both the medial forebrain bundle and stria medullaris-fasciculus retroflexus. The same would appear to hold for the amygdaloid pathways to the substantia innominata, for there is evidence that this structure also contributes a large number of fibres to the medial forebrain bundle (Mehler & Nauta, unpublished observations in the monkey). By virtue of these synaptic relationships with several sources of origin of the medial forebrain bundle and related fibre trajectories such as the stria medullaris, the ventral amygdalo-subcortical pathway appears comparable to the fornix system. Much

like the latter, it appears to furnish a first link in a multi-synaptic chain of conduction which, partly through the intermediary of the lateral hypothalamus, reciprocally connects the limbic forebrain region with an extensive medial area of the midbrain tegmentum and central grey midbrain substance. As indicated previously (Nauta, 1958), this 'limbic system–midbrain circuit' is connected by massive escape pathways with the more laterally located central mesencephalic and subthalamic reticular formation, connexions by which the limbic forebrain structures could conceivably affect a diversity of reticular mechanisms in addition to the autonomic and endocrine functions represented in the midbrain and hypothalamus. It seems possible, for example, that such complex motor stereotypes as the licking, sniffing and chewing movements which have been observed in the course of amygdaloid stimulation experiments (see Gloor, 1959) were elicited by the medium of such indirect amygdalo-reticular connexions.

It is interesting to compare the foregoing anatomical considerations with the results of Gloor's (1955) electrophysiological study in the cat. The distribution of responses of shortest latency (less than 7 msec.) recorded by Gloor in the septum, preoptic region and anterior hypothalamus agrees well with the spread of the ventral amygdalo-subcortical system observed in the present study. Responses of longer latency, presumably denoting indirect connexions, were recorded from more caudal hypothalamic areas, as well as from a large expanse of mesencephalic reticular formation. Although Gloor's observations in general corroborate the anatomical evidence of widespread, if indirect, amygdalo-reticular pathways, it is only fair to point out that his results do not support the notion that such connexions are established mainly by the medial forebrain bundle or via the stria medullaris-fasciculus retroflexus trajectory. Widely scattered responses to amygdaloid stimulation were, for example, recorded from the mesencephalic tegmentum with delays considerably shorter than those registered in caudal regions of the lateral hypothalamus, i.e. along the more caudal part of the hypothalamic trajectory of the medial forebrain bundle. Actually, Gloor's electrophysiological evidence appears to point to extremely medially placed pathways, spreading caudalward through the periventricular hypothalamic region, as the more direct amygdalo-mesencephalic conductors. Conceivably, one such pathway could be furnished by amygdalo-hypothalamic fibres articulating with descending components of Schütz's periventricular fibre system. However, even the relatively fast potentials recorded along this medial route fail to match the surprisingly short latency of some widespread responses obtained in Gloor's experiments from the rostral midbrain tegmentum. In commenting on these findings, Gloor himself suggests the possible existence of a direct or at most oligosynaptic amygdalo-tegmental pathway by-passing the hypothalamus. If such a connexion indeed exists, it appears likely that it would follow the internal capsule and cerebral peduncle. At this time, however, one is forced to conclude that no data are available which could explain all the details of Gloor's observations in terms of known anatomical pathways.

Amygdalo-hippocampal connexions. The present study has failed to produce evidence of the direct amygdalo-hippocampal connexions which have been described on the basis of observations in normal material (Hilpert, 1928, and others). However, the existence of alternate pathways subserving amygdalo-hippocampal interaction

is made likely by the conspicuous amygdaloid projection to the nucleus of the diagonal band, a cell group which is believed to project to the hippocampus either directly (Daitz & Powell, 1954) or via the presubiculum (Cragg & Hamlyn, 1957). The pathway in question probably conducts in both directions: the hippocampal formation is known to project to the entire septal region, and from the latter fibres can be followed along the diagonal band to the immediate vicinity of the amygdala, in the monkey even directly into the medial amygdaloid region (Valenstein & Nauta, 1959). Amygdalo-hippocampal conduction via the entorhinal area as suggested by Gloor (1955) seems conceivable also, although the evidence regarding this pathway is controversial. Adey & Meyer (1952) failed to obtain anatomical evidence of connexions from the amygdalo-piriform complex to the entorhinal area. On the other hand, the spread of strychnine spikes from the periamygdaloid cortex to caudal regions of the hippocampal gyrus, observed by Pribram & MacLean (1952), tends to support Gloor's suggestion.

Amygdalo-thalamic connexions. In agreement with Fox's (1949) observations in Marchi experiments in the monkey, a quite massive amygdaloid projection could be traced via the inferior thalamic peduncle to the dorso-medial nucleus of the thalamus. As degeneration was found in this pathway in all of the six cases of amygdaloid lesion, it is not possible to identify the contributing amygdaloid cell groups with certainty. It is, however, of interest that the lesions produced in the present study all involved the cortical nucleus, the accessory basal nucleus, and the basal nucleus proper. The heavy calibre of most of the constituent axons tends to suggest the basal and lateral nuclei as the most likely sources of origin of the amygdalo-thalamic connexion.

Although not specifically mentioned by Fox, it is clear from the present findings that the amygdalo-thalamic pathway terminates almost exclusively in the medial, magnocellular division of the dorso-medial nucleus. Some further sparse termination seems to take place in the rostral midline region and in the paracentral intralaminar nucleus. No fibres of the connexion could, however, be identified in the lateral part of the dorso-medial nucleus.

The detailed analysis of the dorso-medial thalamo-cortical projection by Pribram, Chow & Semmes (1948) has shown that the medial, magnocellular component of the dorso-medial nucleus projects specifically upon the orbito-frontal cortex. The present findings thus suggest that Fox's amygdalo-thalamic tract represents the first link in a major transthalamic amygdalo-orbito-frontal connexion. The extremely dense arborization of the amygdaloid projection fibres in the nucleus suggests furthermore that fibres of amygdaloid origin furnish the major afferent supply to the medial element of the dorso-medial thalamic nucleus. It must, however, be noted that other, apparently less massive pathways to the pars medialis of the dorso-medial nucleus, have been traced from the septal region (Guillery (1959) in the cat; Valenstein & Nauta (1959) in the monkey), and from the inferior temporal gyrus (Whitlock & Nauta (1956) in the monkey). The temporal cortical projection to the dorso-medial nucleus, like that from the amygdala, follows the inferior thalamic peduncle, but it is unlikely that it was involved in the present experiments as it courses lateral to the amygdala in the white matter of the temporal lobe.

It is noteworthy that in the cat no amygdalo-thalamic projections have been

identified by either experimental-anatomical (Fox, 1943; Lammers & Lohman, 1957; Hall, 1960) or electrophysiological (Gloor, 1955) methods. However, thalamopetal fibre degeneration entirely comparable to the present findings in the monkey has been produced in the cat by lesions in the preoptic region (Nauta, 1958) and substantia innominata, structures that both receive numerous fibres from the amygdala. It thus appears that, despite the apparent absence of a direct connexion, an anatomical pathway for amygdalo-thalamic conduction is present in the cat also. Comparable interspecific variations in neuronal organization have been noted in various other connexions related to the limbic system (Valenstein & Nauta, 1959). It is tempting to speculate that such anatomical differences between species could reflect important functional variations in the neural mechanisms concerned.

Amygdaloid projections to the pulvinar as mentioned by Fox (1949) could not be identified in the present study. Projections apparently comparable to that observed by Fox have, however, been traced from a large extent of the temporal cortex (Whitlock & Nauta, 1956). As Fox's observations were reported only in the form of an abstract it is not possible to say to what extent degeneration of fibres to the pulvinar could have been caused in his experiments by surgical involvement of such cortico-thalamic connexions.

Amygdalo-cortical connexions. In several of the cases of amygdaloid lesion here studied axon degeneration could be traced in continuity from the lesion to (*a*) the gyrus subcallosus and rostral cingulate cortex, and (*b*) the rostral half of the inferior temporal gyrus. The former connexion, established by a moderate number of axons which accompany the fibre pathway to the nucleus of the diagonal band, would seem to correspond to the amygdaloid projection to the gyrus subcallosus observed in the cat by Lammers & Lohman (1957). As regards the fibres to the inferior temporal gyrus, there is little reason to suspect that their degeneration could have been caused by non-specific factors, for besides the uncus no part of the temporal lobe was actually touched during surgery. It would thus seem justified to accept the existence of a rather sparse and diffuse projection of the amygdaloid complex to the inferior temporal gyrus, a connexion which reciprocates an apparently somewhat more massive cortico-amygdaloid projection arising in the same general region of the temporal cortex (Whitlock & Nauta, 1956).

Less unequivocal are the present data regarding amygdaloid pathways to rostral parts of the middle and superior temporal gyri, to the ventral insular region, and to the caudal orbito-frontal cortex. In all of the present cases fibre degeneration was observed to spread to these cortical regions, apparently largely via the uncinate fasciculus, but it was impossible to trace it in continuity from the amygdaloid lesion. Naturally, this failure could have resulted from a peculiar (e.g. recurrent and diffuse) mode of junction of amygdalofugal fibres with components of the uncinate bundle. On the other hand, however, the possibility must be considered that the degeneration in question was caused by inadvertent damage to the orbito-frontal cortex inflicted during the surgical procedure. Such damage could have caused the degeneration of temporopetal fibres in the uncinate fasciculus, and could at the same time have mirrored the amygdaloid projection to the orbito-frontal cortex suggested by the present findings. The circumstance that microscopic evidence of punctate lesions in the orbito-frontal cortex could be found in only one of the cases does not

entirely preclude this possibility.* On the other hand again, the suspicion of orbito-frontal lesion is contradicted on one important point: whereas surgically produced lesions of the orbito-frontal cortex are followed by conspicuous fibre degeneration in the internal capsule, capsular degeneration was absent in all but one of the present cases. It is difficult to conceive of orbito-frontal lesions which could have caused substantial degeneration of associated cortical efferents without concomitant disintegration of subcortical projection fibres. Furthermore, in the present experiments the amount of degeneration in the orbito-frontal cortex appeared to be dependent on the extent of damage inflicted to the rostral half of the amygdaloid complex. It was, for example, notably larger in case MA 3 than in MA 11 in which the lesion was confined to the caudal half of the complex. The surgical procedure being the same in all cases, this observation suggests the existence of a true amygdaloid projection to the orbito-frontal cortex, arising largely in the rostral half of the amygdaloid complex.

In conclusion, the weight of evidence appears to favour the actual existence of amygdaloid projections to (*a*) rostral parts of the middle and superior temporal gyri, (*b*) a ventral region of the insular cortex, and (*c*) a large extent of the caudal orbito-frontal cortex. Some reserve in accepting the present evidence of these amygdalo-cortical connexions remains necessary, especially because it has not been possible to trace the pathways in question in continuity. However, even if the presence of the direct amygdalo-cortical connexions in question be discounted there can be little doubt that the amygdaloid complex can influence the neural mechanisms of at least the orbito-frontal cortex through the intermediary of the dorso-medial thalamic nucleus.†

B. *Stria terminalis*

For detailed normal anatomical descriptions of the various components of the stria terminalis in several subprimate forms especial reference is made to the publications of Johnston (1923), Berkelbach v. d. Sprenkel (1926), Humphrey (1936), and Ariens Kappers, Huber & Crosby (1936).

From a comparison of cases MA 3 and MA 11 it is apparent that the stria terminalis originates largely in the caudal half of the amygdaloid complex, a finding which agrees well with Fox's (1943) and Adey & Meyer's (1952) conclusions from previous experimental studies. The present observations suggest further that some stria fibres, originating in the rostral half of the complex, do not extend beyond the bed nucleus of the stria and hence do not contribute to the preoptic and hypothalamic components of the system. Conversely, the findings in MA 11 indicate that stria

* This statement is based on our experience that strong elevation of the occipitotemporal cortex in the cat, even if carried out extradurally, can cause massive intracortical and corticofugal fibre degeneration despite the absence of identifiable gross or histological lesions of the cortex.

† After this discussion was written, Drs J. Klingler and P. Gloor kindly sent us the typescript of a gross-anatomical study of temporal lobe connexions in man, performed by the aid of Klingler's dissection technique. In this study fibre tracts were dissected which extend between the amygdala on the one hand, the tip of the temporal lobe, the insula and the orbito-frontal cortex on the other hand. The pathways in question emerge from the lateral side of the amygdala and follow curved trajectories in close relationship to the uncinate fasciculus. Drs Klingler and Gloor point out that the gross dissection technique can offer little information regarding the polarity of fibre connexions. However, the appearance of the fibre tracts demonstrated by their analysis is in several respects consistent with the experimental evidence of amygdalo-cortical pathways discussed above.

fibres of more caudal origin by-pass the bed nucleus and make up the bulk of the preoptic and hypothalamic components.

This study has failed to confirm the existence of supracommissural fibres of the stria terminalis to the septal region. The possibility cannot be excluded that such fibres originate in amygdaloid regions not involved in the present experiments. In a case of complete surgical interruption of the stria several millimetres caudal to the anterior commissure (case MF13), fibre degeneration was found in the septal region, but this finding was considered inconclusive for the reason that the fimbria fornicis was to some extent involved in the lesion.

The commissural component of the stria terminalis would seem to be of minimal volume in the monkey. Both in case MA11 and in the case of stria terminalis section (MF13) mentioned above, only a few degenerating fibres could be followed across the midline in the dorsal stratum of the anterior commissure. As in previous Marchi studies in the cat (Fox, 1943; Ban & Omukai, 1959), the termination of these commissural fibres could not be determined.

Stria terminalis fibres to the preoptic region and hypothalamus appear to form by far the largest component of the stria in the monkey. According to the present findings, such fibres distribute largely, if not exclusively, to the medial zone of the preoptic and hypothalamic regions. The stria terminalis differs in this respect from the ventral amygdalo-hypothalamic pathway which appears to connect primarily with more lateral preoptico-hypothalamic areas, and specifically with the region interstitial to the medial forebrain bundle. Within the medial zone most of the stria terminalis fibres appear to terminate among the cells of the medial preoptic and anterior hypothalamic nuclei. Only few fibres could be followed farther caudalward, and all of these appeared to terminate at and only slightly behind the caudal border of the optic chiasma, in the extreme ventral hypothalamic region containing the scattered cells of the so-called nucleus supraopticus diffusus (Rioch, Wislocki & O'Leary, 1940). Some of the longest stria fibres may end in contact with the arcuate nucleus of the infundibulum.

From an experimental study by the Glees technique in the monkey, Adey & Meyer (1952) concluded that amygdalo-hypothalamic fibres are distributed in large part to the ventro-medial hypothalamic nucleus. The same study furthermore indicated a virtually symmetrical bilateral distribution of the amygdalo-hypothalamic projection. The present observations differ from these conclusions in major respects. Naturally, in comparing the present findings with those of Adey & Meyer the possibility must be considered that certain amygdalofugal fibre contingents had escaped degeneration in all of the present cases of amygdaloid lesion. However, incidental findings made in three further cases likewise failed to confirm the existence of bilateral amygdaloid projections to the ventro-medial hypothalamic nucleus. In one of these supplementary cases (MF13 mentioned before in this Discussion) complete unilateral interruption of the stria terminalis resulted in exclusively ipsilateral degeneration of hypothalamic stria fibres in a distribution comparable to that found in MA11. Two other cases, in which the lateral half of the substantia innominata had been extensively damaged in an unsuccessful attempt to produce stereotactic lesions of the globus pallidus, again showed absence of any but ipsilateral hypothalamic degeneration; in neither case was fibre degeneration observed in the

ventro-medial nucleus. The lesions in the two latter cases had undoubtedly severed most of the ventral amygdalo-hypothalamic fibres in their sublenticular passage medialward. Thus, in the present experiments neither a variety of amygdaloid lesions nor the massive interruption of the two known amygdalo-hypothalamic pathways was followed by contralateral hypothalamic fibre degeneration or degeneration of preterminal fibres in the ventro-medial nucleus of either side. Even when allowance is made for the greater ease with which details of terminal degeneration can be identified with the Glees method than by the Nauta–Gygax technique (Bowsher, Brodal & Walberg, 1960), the very small number of the degenerated fibres of passage which in the present study could be followed into the medial hypothalamic zone caudal to the optic chiasma appears to contradict the existence of a significant direct amygdaloid projection to the ventro-medial hypothalamic nucleus.

SUMMARY

The fibre degenerations resulting from lesions in the amygdaloid complex in the monkey were studied by means of the Nauta–Gygax technique. The results confirm the existence of two major amygdalo-subcortical fibre systems, namely, a relatively diffuse ventral amygdalofugal pathway, and the compact stria terminalis.

1. The ventral amygdalofugal pathway, apparently the most massive amygdaloid projection system, spreads medially and forward ventral to the lentiform nucleus and connects with the substantia innominata, lateral preoptic and hypothalamic regions, nucleus of Broca's diagonal band, and the olfactory tubercle. A prominent further component of the system by-passes the preoptic region and follows the inferior thalamic peduncle to terminate in the medial, magnocellular division of the dorsomedial thalamic nucleus. Furthermore, the ventral amygdalofugal pathway contains an amygdalo-cortical component which accompanies the pathway to the nucleus of Broca's diagonal band and terminates in rostral parts of the gyrus fornicatus (gyrus subcallosus and rostral cingulate cortex).

2. The stria terminalis originates mostly in the caudal half of the amygdaloid complex. Fibres arising most rostrally in the complex appear to terminate largely in the bed nucleus of the stria terminalis. Other fibres of more caudal origin form a prominent preoptico-hypothalamic component distributing fibres to the medial preoptic nucleus, anterior hypothalamic nucleus, and the region of the nucleus supraopticus diffusus. No stria terminalis fibres could be followed to the ventro-medial hypothalamic nucleus. Only ipsilateral amygdalo-hypothalamic fibres could be identified.

3. Evidence was obtained of an additional amygdalofugal fibre system which emerges through the lateral and ventral sides of the amygdala and distributes fibres to rostral parts of the superior, middle and inferior temporal gyri, ventral insular cortex, claustrum, rostral putamen, and caudal orbito-frontal cortex. As most of these connexions could not be followed in continuity, the present evidence of their existence cannot by itself be considered conclusive.

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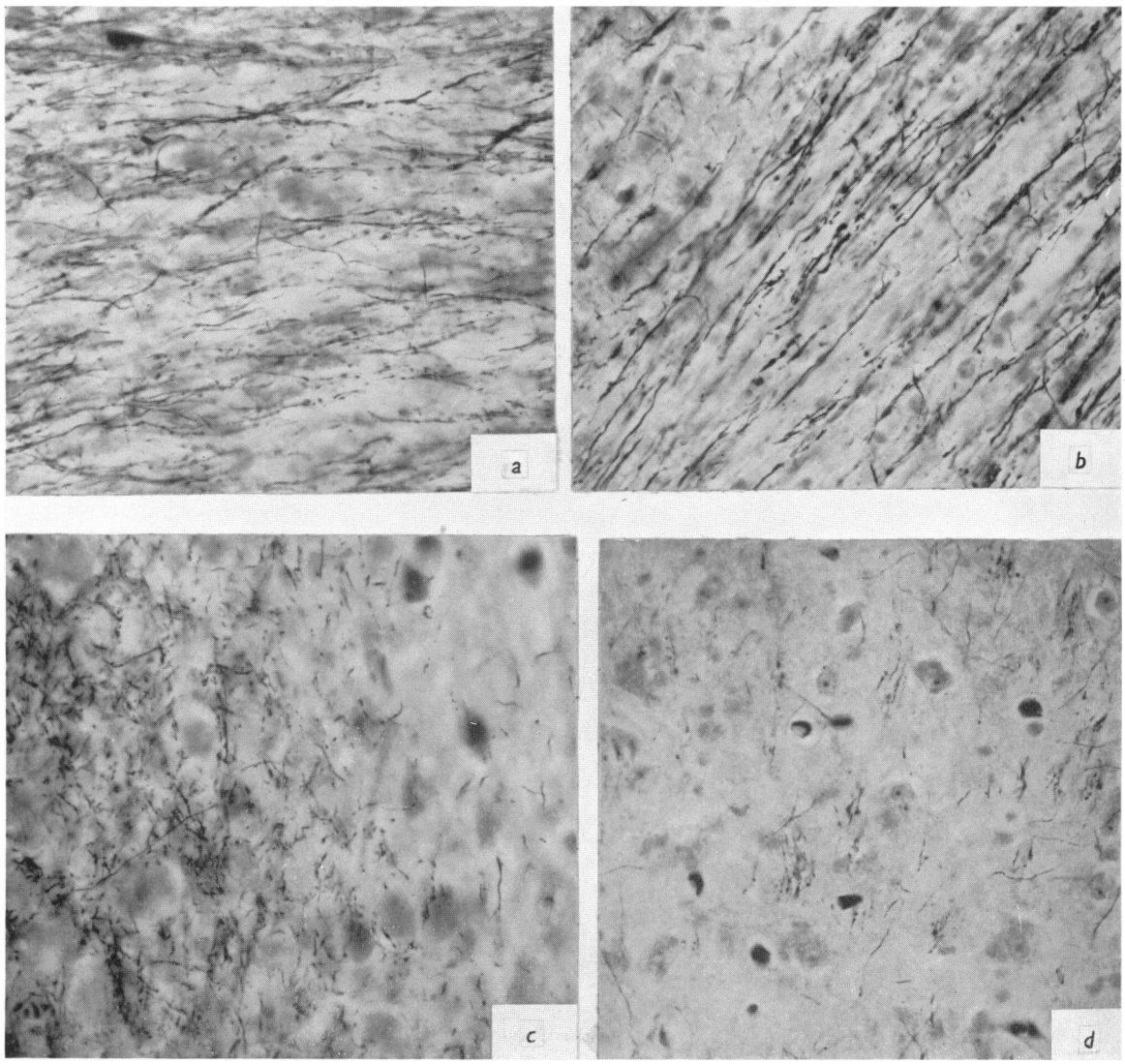

NAUTA—AMYGDALOID PROJECTIONS IN THE MONKEY

(*Facing p.* 531)

EXPLANATION OF PLATE

Photomicrographs (× 230) of fibre degeneration following lesion of the amygdaloid complex.

a, degenerating axons of various calibre traversing the substantia innominata. Case MA 3.

b, degenerating coarse axons in the inferior thalamic peduncle. Case MA 3.

c, dense pericellular and intercellular axon degeneration in a circumscript region (pars medialis) of the n. dorsomedialis thalami. The nucleus periventricularis anterior thalami appears near the right margin of the picture. Case MA 3.

d, degenerating fascicles of the stria terminalis passing through the anterior hypothalamic nucleus. Case MA 11.

KEY TO ABBREVIATIONS USED IN FIGURES

AC, anterior commissure; *ADH*, area dorsalis hypothalami; *AH*, nucleus anterior hypothalami; *AL*, ansa lenticularis; *AM*, nucleus anterior medialis thalami; *A.Ped.*, ansa peduncularis; *AV*, nucleus anterior ventralis thalami; *B*, basal amygdaloid nucleus; *CI*, capsula interna; *Cl*, claustrum; *DMH*, nucleus dorsomedialis hypothalami; *CO*, cortical amygdaloid nucleus; *DMm*, nucleus dorsomedialis thalami, pars medialis; *F*, fornix; *FU*, fasciculus uncinatus, *GP*, globus pallidus; *GR*, gyrus rectus; *Hp*, hippocampus; *L*, lateral amygdaloid nucleus; *LH*, nucleus lateralis hypothalami; *LP*, nucleus preopticus lateralis; *MP*, nucleus preopticus medialis; *NAP*, nucleus ansae peduncularis; *NC*, nucleus caudatus; *ND*, nucleus of the diagonal band of Broca; *NST*, nucleus striae terminalis; *NSt*, nucleus subthalamicus; *Pp*, cortex prepiriformis; *Put*, putamen; *SO*, nucleus supraopticus; *SOD*, nucleus supraopticus diffusus; *ST*, stria terminalis; *TO*, tractus opticus; *T.Ol.*, tuberculum olfactorium; *V*, lateral ventricle; *VA*, nucleus ventralis anterior thalami; *VL*, nucleus ventralis lateralis thalami; *VMH*, nucleus ventromedialis hypothalami.