CORTICOFUGAL FIBRES TO THE BRAIN-STEM RETICULAR FORMATION. AN EXPERIMENTAL STUDY IN THE CAT

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INTRODUCTION

In recent years the reticular formation of the brain stem has been intensively studied by physiological methods. Fairly circumscribed areas have been identified as 'centres' for inhibition and facilitation of cortically and reflexly elicited movements, and the centres have been shown to be subject to influences from the cerebellum, the spinal cord and the cerebral cortex. Respiratory and cardio-vascular 'centres' appear to be closely related topographically to those mentioned above. The demonstration within the brain-stem reticular formation of a 'reticular activating system', exerting its effect on higher levels of the brain, including the cerebral cortex (Moruzzi & Magoun, 1949), adds to the complexity of the functional organization of this part of the central nervous system.

Knowledge of the minute structure of the reticular formation is still insufficient to permit satisfactory correlations with the many new physiological discoveries. The present study represents an attempt to fill one of the gaps in our knowledge of the fibre connexions of the reticular formation. It was undertaken in order to decide whether there are fibres passing from the cerebral cortex directly to those areas of the brain-stem reticular formation in which the 'centres' mentioned have been located by physiological studies.

Several investigators have shown that electrical stimulation of various parts of the cerebral cortex may either inhibit or facilitate functions that are under the influence of the 'centres' of the reticular formation (for references see Kaada, 1951). To what extent these effects are mediated via fibres passing directly from the cerebral cortex to the reticular formation is still a matter of debate. McCulloch, Graf & Magoun (1946), using the strychnine method, have demonstrated a cortico-bulbo-reticular pathway from area 4*s*, and have brought forward evidence that the impulses, at least in part, follow the course of the pyramidal tract fibres. However, although their experiments are highly suggestive that this is a one-neuron pathway, the findings are not decisive. Also the recording of single-unit activity in the reticular formation following stimulation of the cerebral cortex (Baumgarten, Mollica & Moruzzi, 1954) fails to show decisively if the effects are mediated via direct cortico-bulbar fibres, although the short latencies observed by Amassian & DeVito (1954) and French, Hernández-Péon & Livingston (1955) make this appear likely.

While numerous authors (vide infra) have studied by anatomical methods the efferent fibres descending from the cerebral cortex to the pons, medulla and spinal

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cord, most of them were not interested in the possible termination of cortico-fugal fibres in the reticular formation. Others who have observed fibres of this kind mention them only in passing and give no precise information on where in the reticular formation they end. Since these workers all used the Marchi or cruder methods, comment could not, in any case, have been convincing. However, in the light of present-day knowledge of the functional organization of the brain-stem reticular formation, it is now of interest to know, not only where cortico-reticular fibres take their origin, but also to possess as exact information as possible on their terminal distribution within the reticular formation. This can be achieved only if the fibres degenerating as a consequence of cortical lesions are studied by silver impregnation methods, which allow the tracing of fibres to their ultimate termination.

The present study represents an attempt to investigate the problems of the cortico-reticular projection in this way. It was hoped that it would be possible to determine not only from which cortical regions such fibres take origin and in which areas of the reticular formation they end, but also to see if fibres from different sources have different terminal areas within the reticular formation. Even if decisive answers have not been obtained to all these questions, the results appear to be of sufficient interest to merit publication.

Only the pontine and medullary reticular formation have been studied. The cell groups of the reticular formation projecting on to the cerebellum, namely, the nucleus reticularis tegmenti pontis of Bechterew, the lateral reticular nucleus or nucleus of the lateral funiculus, and the nucleus reticularis paramedianus (Brodal, 1953) will not be considered here.

HISTORICAL

The literature dealing with fibres descending from the cerebral cortex to the brain stem and spinal cord is overwhelming. No attempt has been made to review it completely. Following a scrutiny of a fair proportion of the writings on this subject, those papers have been selected for consideration which make specific reference to fibres passing to the reticular formation. Most of the studies have been made in monkeys, but there are also some relevant observations on human material. In the brief survey to be given below, the data will be grouped according to the origin of cortico-reticular fibres from the four cerebral lobes.

(1) *The frontal lobe*

(*a*) *Area* 4. Frontal cortico-reticular fibres, more particularly alleged to come from the area 4 of Brodmann, have been described in human material (Marchi method) by Hoche (1898), Dejerine (1901), Sand (1903) and some other authors. Among the first experimental studies relevant to this subject are those of Simpson & Jolly (1907) in the monkey. In Marchi preparations these workers found degenerating fibres leaving the pyramid and entering the contralateral bulbar reticular formation after crossing in the raphe. The fibres are given off along the entire extent of the medullary pyramid. Probst (1899) also described fibres leaving the pyramid and entering the pontine reticular formation. Mettler (1935*b*, 1947), in the monkey, found many fibres from the precentral gyrus passing through the reticular formation to reach the facial, ambiguus and hypoglossal nuclei. Levin (1936) reported similar findings and emphasized the bilateral distribution, with predominance contralaterally. Verhaart & Kennard (1940) also subscribe to these fibres, but maintain that the cortico-bulbar fibres are very scarce. Minckler, Klemme & Minckler (1944), in a study of human and monkey material with the Marchi and Weigert methods, comment upon the reduction in the number of descending degenerating fibres at levels between the midbrain and the spinal cord. In Marchi and Weil sections from hemidecorticated rats Combs (1949) describes degenerating fibres passing from the pyramid to the bulbar and pontine tegmentum, and Escolar (1950) in the cat finds degenerating fibres leaving the pyramid and passing to the medial reticular formation of both sides. Finally, Krieg (1954) distinguishes different contingents of fibres, passing from the area 4 to the reticular formation of the lower brain stem.

(*b*) *Area* 4*s*. Verhaart & Kennard (1940) deny the existence of fibres from area 4*s* to levels caudal to the pons, while Marion Hines (1943) finds such fibres in the tegmentum of the bulbar reticular formation. Mettler (1947), while describing fibres to the inferior olive and the hypoglossal nucleus, does not mention fibres to the reticular formation. Ward (1948) claims that fibres from area 4*s* pass to the caudal pontine reticular formation and from area 24 to its rostral part. All these studies were made by the Marchi method in the monkey.

(*c*) *Area* 6. A small number of fibres has been traced from this part of the frontal lobe to the bulbar reticular formation by Mettler (1935*b*) and Levin (1936), while Verhaart & Kennard (1940) and Krieg (1954) in the monkey and Escolar (1950) in the cat are inclined to deny their existence.

(2) *The parietal lobe*

Only few reports are available on parieto-reticular fibres. They have been described by Mettler (1935*c*) in the monkey, more particularly from the postcentral gyrus, and in the cat by Escolar (1950). Peele (1942) and Gobbel & Liles (1945) in monkey and cat, respectively, did not observe such fibres.

(3) *The temporal lobe*

Mettler (1935*d*) found temporo-reticular fibres to the medulla, possibly running in the pyramid, in the monkey, while Rundles & Papez (1938) in this animal and Poljak (1927) in the cat deny the existence of temporo-fugal fibres below the pons.

(4) *The occipital lobe*

Mention of fibres to the reticular formation from the occipital lobe is not made by Poljak (1927) and Escolar (1950) studying the occipital fibres in the cat, nor by Mettler (1935*a*) and Nyby & Jansen (1951) in the monkey.

From this review of the literature, although incomplete, it appears that the great majority of cortico-reticular fibres come from the frontal lobe, particularly the 'motor areas', while the existence of such fibres from the other lobes is more equivocal. The available literature on the whole does not give indications that the cortico-reticular fibres are distributed to particular areas or levels of the reticular formation.

MATERIAL AND METHODS

The cats used as experimental animals in the present study are some of those used previously for the study of pyramidal tract fibres from the temporal and occipital lobes by Walberg & Brodal (1953) and for the study of descending fibres to the inferior olive by Walberg (1954, 1955).

Adult cats were subjected to surgical removals of different parts of the cerebral cortex under intraperitoneal nembutal (pentobarbital) anaesthesia. The surgical procedures were performed under sterile conditions, and, as far as possible, the excisions were limited to the cortex, although usually some of the subcortical white matter was involved in the lesion. Brains of several normal animals served as controls.

The animals were killed 5–8 days after the operation by exsanguination under chloroform or nembutal anaesthesia. The brain and spinal cord were then immediately dissected free and immersed into 10 % formalin for fixation. The area of the cortex containing the lesion was in some of the cases cut away 1 or 2 days later, transferred to 96 % alcohol, embedded in paraffin and cut in serial sections. Every 10th–20th of these was stained with thionine to permit exact identification of the parts damaged by the lesion. In other cases the extent of the lesion was studied in Nissl stained sections from the blocks prepared for silver impregnation (vide infra). After fixation for some weeks, the cerebral hemispheres, or what was left of them when the part containing the lesion had been removed, were cut in transverse slices 3–4 mm. thick. From each of these slices several frozen sections 15 μ. thick, were usually cut. The slice itself was preserved so that when the different slices were assembled it was possible to decide exactly which parts of the cortex had been studied.

The brain stems of the cats were cut serially at 15 μ. in horizontal, frozen sections. The sections were collected in groups of fifteen consecutive ones, and of each group two or three were stained according to the Glees (1946) method. In some cases the method of Nauta & Gygax (1951) was employed. The sections were searched for the occurrence of degenerating nerve fibres and terminal boutons.

RESULTS

The normal reticular formation of the brain stem as seen in silver impregnated sections

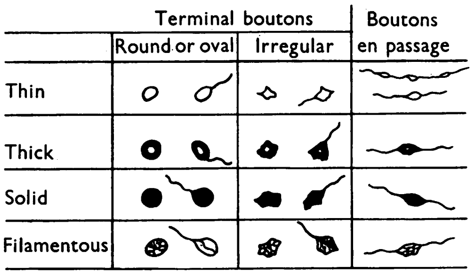
As is well known the bulbar and pontine reticular formation contains cells of very varying types and sizes, separated by fibre bundles coursing in virtually all directions. Several attempts have been made to subdivide the reticular formation into particular cell groups or nuclei, the most recent and most detailed being the studies of Meessen & Olszewski (1949), Olszewski & Baxter (1954) and Olszewski (1954). Since, however, the borders between the different groups distinguished on a cytoarchitectonic basis are in many places somewhat arbitrary, we have chosen to present our findings concerning the distribution of cortico-reticular fibres with reference to drawings of the brain stem only. To what extent there is any correlation with particular nuclei will be considered in the discussion.

For an evaluation of degenerating terminal fibres and boutons in the reticular formation, a knowledge of the normal appearance of these structures is essential. Text-fig. 1 shows in a semidiagrammatic way the types of terminal boutons which may be seen in Glees-impregnated sections from the reticular formation of the normal adult cat's brain stem. As will be seen, there are wide variations. The boutons vary from regular, circular ring-shaped ones, to heavily impregnated, dark and irregular bodies. The most frequent type are the light round or oval rings. Some of the terminal boutons of all types can be seen to be connected with a delicate terminal fibre. Similar variations as in the terminal boutons occur in the so-called *boutons en passage*. From the photomicrographs on Pl. 1, figs. 1–3, it will be seen that the boutons may vary considerably in size. Furthermore, it is common to find boutons of different sizes as well as boutons of different types on the same cell (Pl. 1, figs. 1, 3). Quite frequently, however, the relations of the boutons to nerve cells or their processes cannot be ascertained, since the boutons may be seen lying apparently free in the spaces between nerve cells and fibres. Whether the wide variations in the appearance of the terminal boutons and *boutons en passage* in normal preparations are due only to technical factors cannot be decided.

Terminal degeneration in the reticular formation and its evaluation

The term 'terminal degeneration' is taken here to denote the degenerative changes occurring in terminal boutons and the terminal fibres leading up to them (or possibly also ending freely), following transection of axons or destruction of their perikarya. The determination of terminal degeneration in the reticular formation meets, however, with greater difficulties than in most other regions of the central nervous system.

It is obvious from the variations in the normal appearance of terminal boutons, described above, that identification of truly degenerating boutons in the reticular formation will be practically impossible. Some of the types occurring normally resemble very much the picture usually seen when degenerating boutons occur, for example, in the lateral reticular nucleus (Brodal, 1949) or the lateral cervical nucleus (Brodal & Rexed, 1953). As a rule such boutons, in addition to becoming irregular, swell. On account of the normal presence of rather large boutons, size is, however, no reliable criterion, since, for example, a normal large and irregular bouton cannot be distinguished from a degenerating medium-sized one. Only when an unusually large and irregular bouton is seen, may it, with some confidence, be taken as a degenerating specimen of the largest type. To avoid possible errors due to misinterpretations of terminal boutons, we have discarded them in the recordings of changes. Occasionally, an extremely large, compact and irregular bouton has been taken into account.



Text-fig. 1. Drawings of the different types of boutons, terminal and *en passage*, which may be seen in the brain stem reticular formation of the normal cat in Glees sections. The most common types are the round or oval terminal boutons, and among these the thin type is most common, followed by the thick and solid type. The solid irregular boutons may be mistaken for degenerating specimens.

The exclusion of changes in boutons as criteria of terminal degeneration leaves us with the degenerating fine terminal fibres as evidence of termination of injured cortico-reticular fibres. The changes in the terminal fibres are considered as indications of degeneration when the fibres appear as rows of fine black dots of circular or somewhat irregular shape. Examples are shown in Pl. 1, figs. 5–14.

The structure of the reticular formation makes the recognition of such fine degenerating fibres a difficult and time-consuming procedure. The wealth of fibres of all sizes found everywhere in the reticular formation, even within those areas which have been outlined as particular nuclear groups, gives a background little suited for the identification of fine degenerating fibres. Further, as they course in all directions, only a certain proportion of them, lying approximately in the plane of the sections, can be recognized. In some places, where the cells are more closely grouped, the yellow background is more favourable, but an apparent greater concentration of terminal degenerating fibres in such places may not be real.

Quantitative estimates of degenerating terminal fibres in silver-impregnated preparations are difficult. Only when there are very marked regional differences in their number can comparisons be made on a secure basis. Our experimental animals have been killed 5–8 days after the lesion was made. It is possible that more marked degenerative changes might have been seen with other survival times, but greater differences could scarcely be expected.

Having used the strict criteria outlined above, we feel certain that our findings are reliable. However, it is clear that the changes recorded will represent a minimum of those possibly present. Furthermore, only few quantitative data can be given. The exclusion of degenerating boutons from study also prevents conclusions concerning the mode of termination of the cortico-reticular fibres.

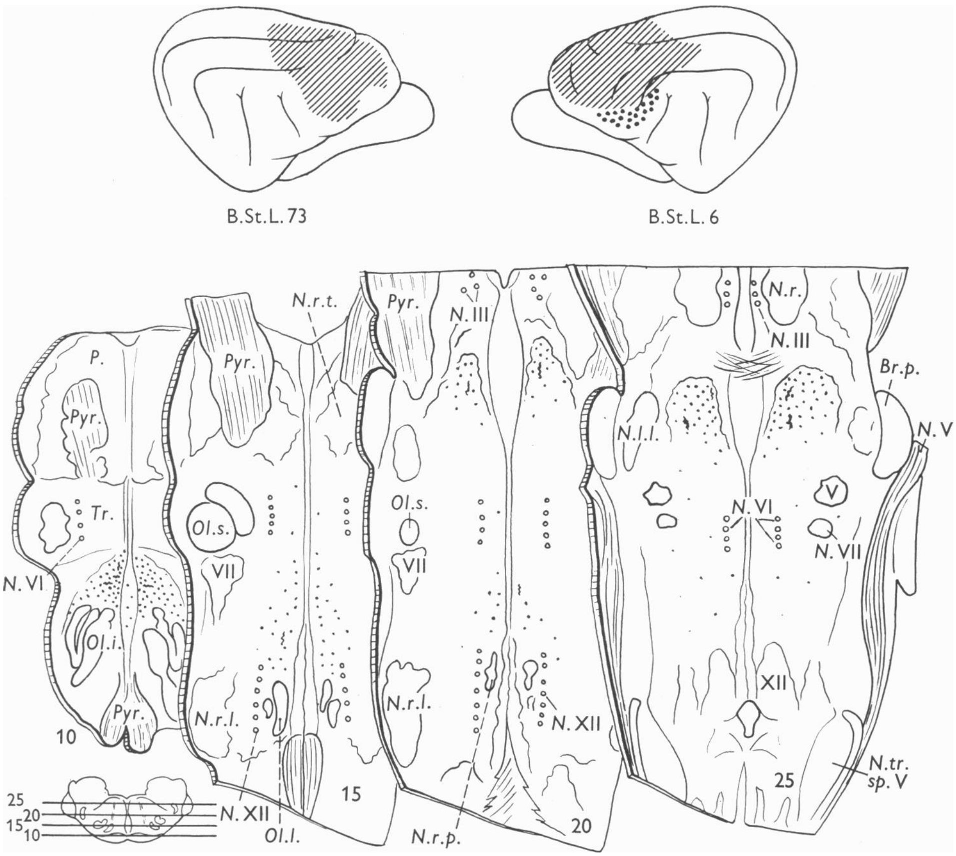
Origin and termination of cortico-reticular fibres

Since the regional distribution of terminal degenerating fibres in the reticular formation was found to be largely identical in cases with lesions in different parts of the cerebral cortex, it will be sufficient to describe their distribution more closely with reference to a few particular experiments. Most intense changes were seen following large fronto-parietal lesions. A case of this type will, therefore, be presented first.

Cat Sp.C.L. 73. *Killed after 7 days* (Text-fig. 2, and Pl. 1, figs. 4–8). The lesion comprises a considerable part of the cortex in front of and behind the right cruciate sulcus, destroying the entire 'motor area'. In sections through the lesion it is seen that it extends somewhat into the white subcortical matter, but it does not reach the ventricle.

In the horizontal silver-stained sections through the brain stem, scattered degenerating terminal fibres are found almost throughout the reticular formation on both sides, but larger numbers occur only in two fairly circumscribed areas, as shown by the dots in the drawings of Text-fig. 2. On the whole the degeneration is rather scanty also in these areas, and in no place is it of an intensity which can in any way be compared with that seen, for example, in the lateral reticular nucleus following transection of its spinal afferents (Brodal, 1949) or in the gracile and cuneate nuclei following transection of the dorsal columns (Glees & Soler, 1951). Photomicrographs of degenerating terminal and preterminal fibres in this case are shown in Pl. 1, figs. 4–8. On account of the small depth of focus with oil immersion it is seldom possible to get more than one or very few degenerating fibres on the same photograph, but this fact may serve to convey an idea also of the relatively scarce degeneration present. In the drawings of Text-fig. 2 each dot does not represent a certain number of degenerating fibres, but the spacing of dots indicates approximately the relative density of such fibres in different regions.

It will be seen from Text-fig. 2 that of the two regions which contain very many degenerating terminal fibres, most intense degeneration is found in the area of the reticular



Text-fig. 2. Diagram showing the distribution of terminal degenerating fibres in the reticular formation in two cases with large fronto-parietal lesions (cats B.St.L. 73 and 6). The density of the dots gives an impression of the relative number of degenerating terminal fibres in different parts of the reticular formation. Degenerating coarser fibres are shown as wavy lines. Degeneration occurring in other areas than the reticular formation (e.g. the pontine nuclei) is not shown. The numbers of the drawings refer to their order in the series of cat B.St.L. 73. The coarse dots in the diagram of the lesion in cat B.St.L. 6 indicate areas the fibres from which have been damaged.

Abbreviations employed in Text-figs. 2, 4, 6 *and* 8

B.	Nucleus of Bechterew
B.c.	Brachium conjunctivum
Br.p.	Brachium pontis
C.i.	Inferior colliculus
D.	Nucleus of Deiters
N.c.e.	External cuneate nucleus
N.f.c.	Cuneate nucleus
N.f.g.	Gracile nucleus
N.l.l.	Nucleus of lateral lemniscus
N.r.	Red nucleus
N.r.l.	Lateral reticular nucleus (Nucleus funiculi lateralis)
N.r.p.	Paramedian reticular nucleus of medulla oblongata
N.r.t.	Nucleus reticularis tegmenti pontis of Bechterew
N.tr.sp.V.	Nucleus of spinal trigeminal tract
N. III, V, VI, VII, XII	Root fibres of cranial nerves III, V, VI, VII and XII.
Ol.i.	Inferior olive
Ol.s.	Superior olive
P.	Pontine gray
Pyr.	Pyramidal tract fibres
S.n.	Substantia nigra
Tr.	Trapezoid body
Tr.sp.V.	Spinal tract of trigeminal nerve
III, V, VI, VII, XII.	Motor cranial nerve nuclei

formation situated immediately dorsal to the rostral half of the inferior olive and a little more rostrally. From this area the degeneration decreases in all directions. The rostralmost medulla shows only slight changes. The same is the case at lower pontine levels, but in the upper pons, dorsal to the pontine nuclei proper, there is an area which is almost as much changed as the area in the lower medulla described above. This pontine area is found caudal to the fibres of the ventral tegmental decussation and is seen in the drawing of sections 20 and 25 in Text-fig. 2. It is also seen in sections farther dorsally, but the degeneration decreases by and by. Ventral to the plane of the abducent nucleus there is, however, still a fair number of degenerating terminal fibres (section 30, not shown in the diagram).

Somewhat coarser, presumably in part preterminal, degenerating fibres are also seen in the same areas. Some of them run horizontally and appear to enter the reticular formation from the raphe, which also contains some degenerating terminal fibres (see Pl. 1, fig. 8). Others have a longitudinal course. The pyramidal tract contains numerous degenerating fibres of different sizes, considerably more on the right than on the left, but owing to the direction of the sections it is not possible to trace degenerating fibres from the pyramids into the reticular formation.

Cat. B.St.L. 6. *Killed after* 5 *days* (Text-fig. 2, Pl. 1, fig. 9). The lesion in this case is similar to that in cat B.St.L. 73, described above, but a little more extensive, and encroaches a little on the caudate nucleus. The ensuing terminal degeneration has the same distribution as that mapped in the drawings from the reticular formation in Text-fig. 2, which have been made by means of a projection apparatus from sections in cat B.St.L. 73.

The findings in these two cases show that fibres arising in the fronto-parietal region of the cortex reach the reticular formation of the pons and medulla. The fibres are distributed bilaterally, but whether there is any quantitative difference between the two sides cannot be decided.

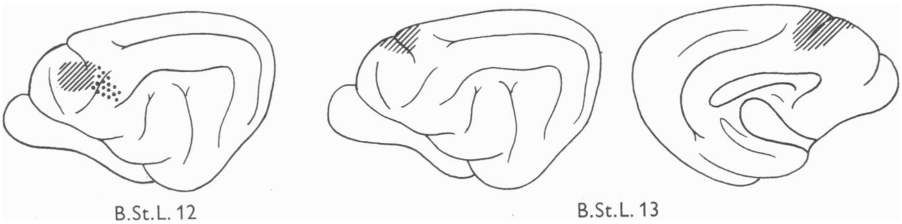
In spite of the occurrence of scattered degenerating terminal fibres over almost the entire reticular formation, there are two areas which can clearly be recognized as the chief terminal stations for the cortico-fugal fibres. Thus there is an area of more intense degeneration in the reticular formation immediately dorsal to the rostral half of the inferior olive, and extending from here more rostrally. Another area of more marked changes is found in the rostral pons. This area extends dorsally to a horizontal level passing just in front of the abducent nerve. The changes in the pontine area appear to be a little less intense than in the medullary area. If there are other regional variations, they are too fine to be evaluated.

The lesions in the two cases described above are rather large. However, a considerable proportion of the degenerating fibres in these cases must come from the 'motor area' as outlined by Garol (1942). This is learnt from two cases in which lesions were made in this part of the cortex. Following electro-physiological determination (by stimulation) of the fore-limb and hind-limb area, respectively, these were extirpated (cats B.St.L. 12 and 13). Both animals were killed after 8 days. The lesions are seen in Text-fig. 3. There was only little affection of the underlying white matter.

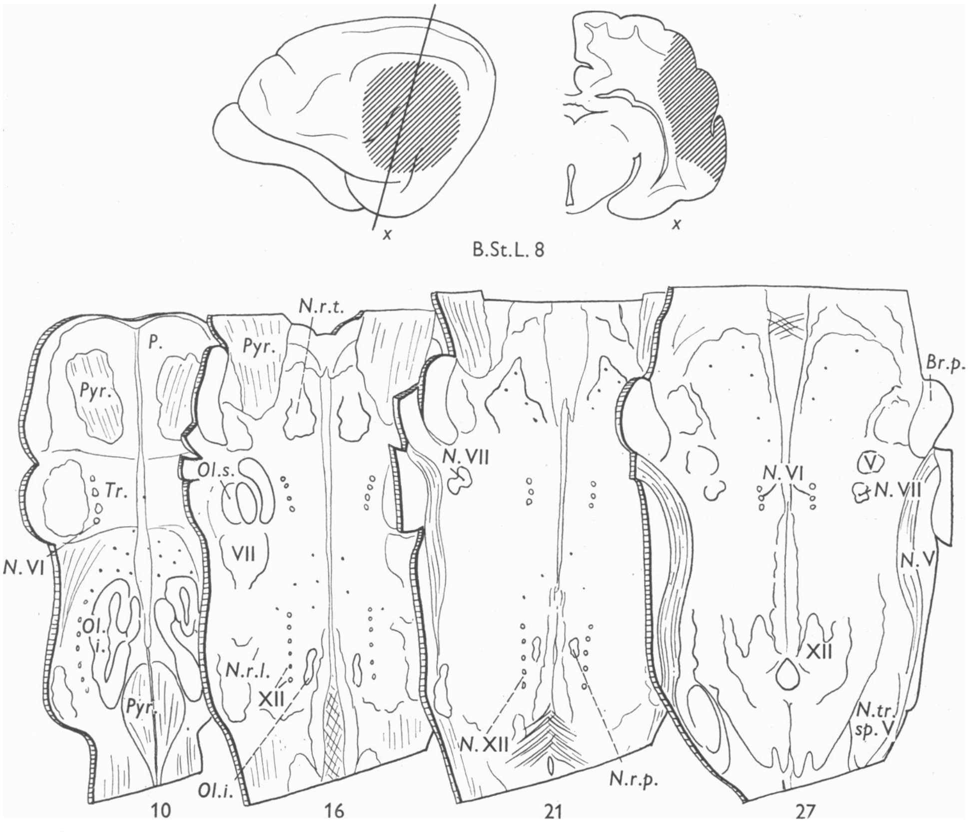
In the brain-stem reticular formation the distribution of terminal degeneration is essentially as in the animals with larger fronto-parietal lesions, but is somewhat less intense. It is not possible to detect any difference between these two cases with regard to regional distribution of degeneration, which might indicate a somatotopical arrangement of termination of the cortico-reticular fibres.

Lesions in the temporal or occipital lobes are also followed by terminal degeneration in the reticular formation, but the degeneration is much less impressive than in the cases described above. Since the findings are practically similar in the four cases studied only one of them will be described more fully.

Cat B.St.L. **8.** ***Killed after*** **8** ***days*** **(Text-fig. 4, and Pl. 1, fig. 13). The lesion involves the left temporal region, destroying part of the middle and posterior ectosylvian gyri and of the**



Text-fig. 3. Drawings showing the extent of the lesions in two cases with cortical damage to the motor region (cats B.St.L. 12 and 13). Hatchings indicate parts destroyed, coarse dots areas the fibres from which have been interrupted. The distribution of the ensuing terminal degeneration in the reticular formation is essentially as in the cases shown in Text-fig. 2, but somewhat less marked.

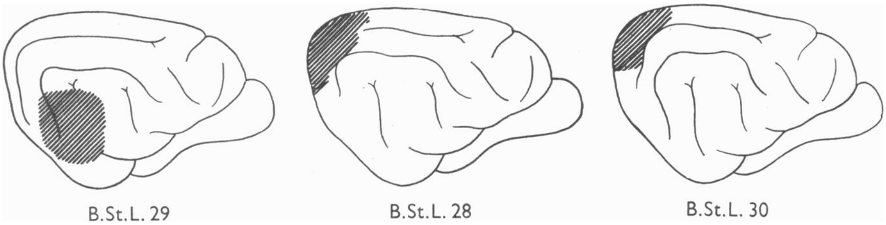


Text-fig. 4. Diagram of the findings in cat B.St.L. 8 after the same principle as in Text-fig. 2. The section to the right (x) shows the depth of the lesion. Abbreviations as in the legend to Text-fig. 2.

anterior sylvian gyrus. In its central, deepest part the lesion approaches the lateral ventricle, but there is a zone of intact white matter left.

In the reticular formation of the brain stem scattered degenerating terminal fibres are seen on both sides, but their number is much smaller than in any of the cases described above. However, as in those cases there is a definite overweight of degeneration in the area dorsal and rostral to the inferior olive, and in the rostral part of the pontine reticular formation. Here a preterminal degenerating fibre is also occasionally seen.

In the cat B.St.L. 29 (killed after 6 days) the temporal lobe lesion (Text-fig. 5) was a little smaller than in the case described above. The distribution of the terminal degeneration in the reticular formation (Pl. 1, figs. 11–12) is, however, the same. Also following lesions of the occipital lobe, comprising chiefly the striate area (cats B.St.L. 28 and 30, both killed after 6 days, Text-fig. 5), the distribution of terminal degeneration is the same. The intensity in all these cases is clearly less than following motor area lesions of a similar size and also less than in cat B.St.L. 8.



Text-fig. 5. Diagram of the lesion in one case with a lesion of the temporal lobe and two cases with lesions of the occipital lobe. The terminal distribution is in all cases essentially as in cat B.St.L. 8, shown in Text-fig. 4.

The cases described above demonstrate that there are cortico-reticular fibres from the occipital and temporal lobes. Like those from the fronto-parietal areas they are distributed bilaterally to the pontine and medullary reticular formation, but they are much more scarce. Only in the area dorsal and rostral to the inferior olive and in the upper pons is there some concentration of degenerating terminal fibres.

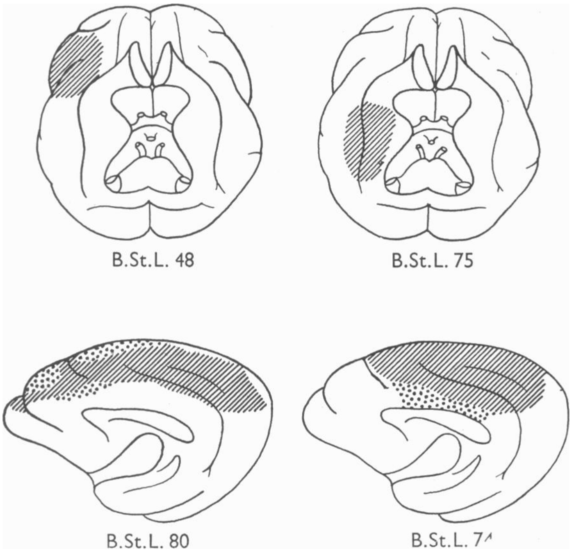
More important contributions of cortico-reticular fibres come from the basal and medial surfaces of the brain. Text-fig. 6 shows the findings in a relevant case, cat B.St.L. 79 (killed after 7 days). While a few terminal degenerating fibres are found scattered throughout the reticular formation, larger numbers occur bilaterally in the same pontine and medullary areas which show most changes following lesions of other parts of the cortex.

In cat B.St.L. 79 (Text-fig. 6) the lesion of the basal surface was rather extensive, and included parts of the orbital surface and posteriorly the greater part of the pyriform lobe, as well as smaller parts of the lateral and posterior suprasylvian gyri. In another animal with a basal lesion, cat B.St.L. 48 (Text-fig. 7), a thermocautery lesion damaged the right orbital and anterior ectosylvian gyri, and in a third (cat B.St.L. 75) the lateral part of the pyriform lobe and adjacent parts of the anterior and posterior sylvian gyri were damaged. In both cases the distribution of terminal degeneration is as in cat B.St.L. 79, but the degeneration is considerably less intense. Since the lesion in cat B.St.L. 75 involves parts of the pyriform lobe as well as neocortical parts it is not possible to decide whether the lesion of the palaeo-cortex is responsible for the terminal degeneration. However, it can at least be concluded that fibres to the reticular formation take origin from anterior as well as posterior regions of the basal cortex of the cerebrum.

In Text-fig. 7 are also shown the lesions in two cats, in which the medial cortex was damaged. In both cases the distribution of the terminal degeneration is similar

Text-fig. 6. Diagram of the findings in cat B.St.L. 79, having an extensive lesion of the basal surface. The distribution of terminal degeneration is shown as in the diagram in Text-fig. 2.

to that found following lesions of other parts of the cortex. The intensity of degeneration is almost the same as that following a large basal lesion (cat B.St.L. 79, Text-fig. 6). In cat B.St.L. 80 the lesion extends so far in an anterior direction that it has destroyed the cortex surrounding the cruciate sulcus, i.e. presumably part of the cortex belonging to the 'motor area'. Since, however, degeneration is not more, but rather less, marked in this case than in cat B.St.L. 74, it may be assumed that cortico-reticular fibres take origin from the medial surface posterior to the cruciate sulcus, i.e. from the cingulate and/or the splenial and suprasplenial gyri.



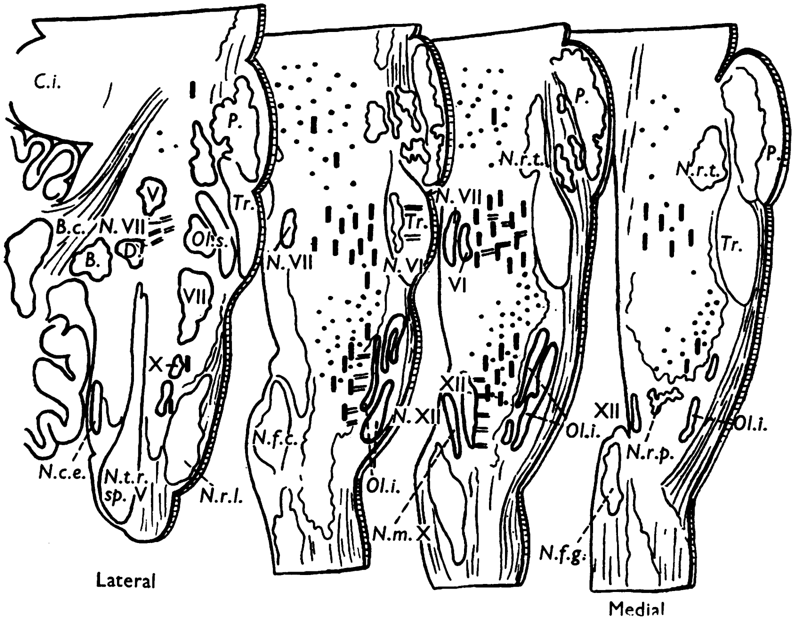
Text-fig. 7. Diagram showing the lesions in four animals, B.St.L. 48, 75, 80 and 74—killed after 6, 7, 6, and 7 days respectively. Coarse dots indicate areas the fibres from which have been cut. Terminal degeneration in all cases in the same areas as shown for cat B.St.L. 79 in Text-fig. 6. The intensity of degeneration is described in the text.

It appears from our findings that cortico-fugal fibres from all regions of the cortex studied have two common terminal areas in the reticular formation, one in the pons, another in the medulla.* In Text-fig. 8 these two chief terminal areas are shown as projected on a series of sagittal drawings. For comparison the distribution of reticular neurons having long ascending axons (Brodal & Rossi, 1955) is also shown. It will be seen that there is relatively little overlap. The possible significance of this will be considered in the discussion.

*** It should again be emphasized that in this study we have left out of account those parts of the reticular formation which project on to the cerebellum. To avoid misunderstandings, however, it may be mentioned that cortical fibres reach also these nuclei (the nucleus reticularis tegmenti pontis of Bechterew, the nucleus reticularis lateralis or funiculi lateralis, and the nucleus reticularis paramedianus medullae oblongatae). A detailed analysis of these subdivisions of the cortico-reticular projection remains to be done.**

DISCUSSION

As mentioned above, degenerating terminal boutons in the reticular formation cannot always be distinguished from normal ones, since the latter show wide normal variations (see Text-fig. 1). We have, therefore, restricted our recordings of degenerative changes to those occurring in the terminal fibres. Their characteristic appearance in the experimental animals and the absence of similar fibres in normal controls leave no doubt that we are dealing with truly degenerating terminal and preterminal fibres.



Text-fig. 8. A series of sagittal sections through the cat's brain stem, showing the chief terminal areas of cortico-reticular fibres (dots) as determined in the present study and the sites of reticular neurons having long ascending axons (vertical bars) as determined previously (Brodal & Rossi, 1955).

It is clear from our findings that the number of fibres in the reticular formation of the cat, degenerating as a consequence of cortical lesions, is not very large. This agrees with the opinions expressed by Verhaart & Kennard (1940) and others on the basis of Marchi studies in the monkey. However, different parts of the cerebral cortex send varying numbers of fibres to the reticular formation of the brain stem. Since most lesions were not limited to particular cytoarchitectonic areas, the origin of the fibres cannot be given with reference to specific areas except for the 'motor area'. This, without doubt, is an important source of cortico-reticular fibres and appears to give origin to a great proportion of all fibres from the fronto-parietal cortex to the reticular formation. Basal areas of the brain, as well as parts of the medial surface, also contribute considerably to the cortico-reticular projection. In experimental lesions involving the sensory acoustic and particularly the optic areas, on the other hand, very little degeneration of cortico-reticular fibres is found.

The relative contributions determined here agree fairly well with the findings made in Marchi material by previous students, particularly concerning the predominance of fronto-reticular fibres (see p. 43). Our findings make clear that the disputed fibres from the temporal and occipital lobes do exist, even if their number is very modest. That such fibres may be more abundant to the mesencephalic reticular formation may be surmised, since, by physiological methods, Jasper, Ajmone-Marsan & Stoll (1952), Bremer & Terzuolo (1954) and French *et al.* (1955) found evidence for ample projections to this region from various parts of the cerebral cortex. Further, and in agreement with our anatomical findings, Scheibel, Scheibel, Mollica & Moruzzi (1955) report that electrical or strychnine stimulation of the acoustic cortex was quite ineffective in producing micro-electrode responses from the lower medulla. Our findings confirm Ward's (1948) concerning fibres from area 24 to the pontine reticular formation and to the medulla oblongata.

It is interesting to note that with regard to their sites of origin the cortico-reticular fibres show a parallelism with certain other cortico-fugal systems, for example, the pyramidal tract. In addition to fibres from the 'motor' and 'premotor' areas, this tract contains smaller contingents from the occipital and temporal lobes (Walberg & Brodal, 1953), and it appears that there are also cortico-spinal fibres from the medial and basal surface of the cerebrum (unpublished observations). There is also a correspondence between the sources of cortical fibres to the inferior olive (Walberg, 1954, 1955) and to the reticular formation.

The method used in this study is not well suited to determine the course taken by the cortico-reticular fibres. If they descend intermingled with, or are collaterals from, the fibres of the pyramidal tract, as appears likely (see Cajal, 1909), they might be recognized where they take off from the main bundle. Although we have frequently seen degenerating preterminal fibres in the changed areas of the reticular formation, coursing longitudinally or transversely, we have never been able to follow fibres of this type from the bundles of the pyramidal tract. This inability may in part be due to the direction of sectioning which is little favourable for such study. However, our findings do not contradict the observations of several previous authors that the cortico-reticular fibres descend among those of the pyramidal tract or are collaterals from such fibres.

The advantage of the method employed in this study is that it makes it possible to establish the areas of termination of the cortico-reticular fibres, a problem which could not be solved by the Marchi method used by previous authors. As has been seen, fibres from widely different parts of the cerebral cortex terminate in identical areas of the reticular formation. These areas, therefore, may be considered as sites of convergence of impulses from various cortical regions. That convergence of this type actually occurs in the reticular formation has been shown by Bremer & Terzuolo (1954) and Scheibel *et al.* (1955). The findings concerning the fibres from the motor area, furthermore, indicate that there is no somatotopical subdivision within the terminal areas. However, these conclusions must be made with certain qualifications, since it is impossible to make exact quantitative estimates of degenerating terminal fibres. For this reason there may be within the total terminal areas determined in our experiments, smaller regional differences which betray a certain differential distribution, but which have escaped recognition. For the same reason our finding of an approximately equal number of degenerating fibres on both sides of the reticular formation, following a unilateral cerebral lesion, probably requires qualifications.

Although scattered cortico-reticular fibres appear to reach almost all parts of the pontine and medullary reticular formation, it is clear from our findings that the bulk of the fibres reach two terminal areas, one in the medulla, another in the pons. Their situation is seen in Text-figs. 2, 4, 6 and 8. They are separated by areas of the reticular formation receiving very few or practically no cortico-fugal fibres. The two areas appear to be almost equally important with regard to the number of fibres they receive.

The demonstration of two fairly well circumscribed terminal areas for the cortico-reticular fibres raises the question whether these areas correspond to definite structurally characterized parts of the reticular formation, and whether there is any correlation between them and the areas outlined by physiological methods as 'centres' for different functions. A comparison with Meessen & Olszewski's (1949) atlas of the rabbit's brain stem shows that the pontine area determined here as a terminal station for cortico-reticular fibres coincides almost completely with the part of the reticular formation outlined by these authors as the 'nucleus pontis oralis' which can be recognized also in the horizontal silver sections. Degeneration appears to be a little more marked in its rostral part than caudally, but there is also clear-cut but scanty degeneration in the rostral-most part of the nucleus reticularis pontis caudalis. The medullary terminal area corresponds to Meessen & Olszewski's 'nucleus gigantocellularis medullae oblongata', but the dorsal regions of this are certainly less changed than the ventral parts, situated just dorsal to the inferior olive. Furthermore, it appears that degeneration is more abundant in the rostral part of the nucleus than in the caudal.

These findings tend to support the assumption that the subdivisions of the brain-stem reticular formation which can be made on a cytoarchitectonic basis have functional significance. For an understanding of the functional importance of the cortico-reticular fibres, it is necessary to know the destination of the efferent fibres from their two terminal areas. It appears from preliminary studies of the origin of descending fibres from the reticular formation (unpublished) that following transection of the spinal cord at high cervical levels, large numbers of altered nerve cells are found in those parts of the reticular formation which according to the present study are the chief end-stations for the cortico-reticular fibres. The medullary terminal area appears to correspond also to the area determined by Pitts (1940) as the site of origin of reticulo-spinal fibres. Finally, Papez (1926) in his Marchi experiments found evidence that reticulo-spinal fibres from the medulla come from 'large reticular cells of the upper oblongata' and from 'large reticular elements of the pons and isthmus'. When taken together the data given here thus make it appear likely that the cortico-reticular fibres terminate chiefly in areas of the reticular formation, from which a large proportion of reticulo-spinal fibres take origin, i.e. that the cortico-reticular projection system is a link in pathways capable of transmitting impulses of cortical origin to cells in the spinal cord.

It would, however, be an undue over-simplification to assume that this should be their only task. A comparison of the terminal areas of the cortico-reticular fibres with the regional distribution of reticular neurons sending their axons in a rostral direction is illuminating in this respect. In a recent study (Brodal & Rossi, 1955) it has been shown that scattered cells sending their axon rostrally beyond the mesencephalon occur over large areas of the reticular formation, but they are collected in greater numbers in certain places only. One of these areas is that surrounding the root fibres of the abducent nerve, corresponding to a large part of Meessen & Olszewski's 'nucleus reticularis pontis caudalis'. Another such area is found in the medulla dorsal to the inferior olive and comprises most of the nucleus reticularis giganto-cellularis, but also the ventral parts of the nucleus reticularis lateralis of Meessen & Olszewski and the medial parts of their ventral reticular nucleus. (In addition, a certain number of ascending fibres take origin in the mesencephalon.) From Text-fig. 8 where the distribution of rostrally projecting cells is shown as contrasted with the sites of termination of cortico-reticular fibres, it will be seen that the majority of ascending reticular fibres take origin from other parts of the reticular formation than those in which the cortico-reticular fibres terminate. This is particularly evident in the pons. However, dorsal to the inferior olive, i.e. in the nucleus reticularis giganto-cellularis, there is a common area (even if the rostral part of this nucleus contains few ascending neurons but many terminations of cortico-fugal fibres, and the adjoining areas, rich in rostrally projecting cells are almost free from terminations of cortico-reticular fibres). Thus we have here apparently a mechanism whereby impulses from the cerebral cortex may influence the activity of the rostrally projecting reticular system.*

It is remarkable that with the exception of the region just mentioned, the areas of the reticular formation particularly rich in rostrally projecting neurons, are other than those receiving cortico-reticular fibres (and probably containing chiefly caudally projecting neurons, vide supra). The findings so far available, therefore, cast considerable doubt on the common assumption that the brain-stem reticular formation is entirely diffusely organized. However, the segregation into regions having different fibre connexions and presumably different functions is certainly not sharp, as appears from the termination of scattered cortico-reticular fibres outside their chief terminal areas and from the wide distribution of neurons projecting rostrally. Other features point in the same direction, as, for example, the presence within the reticular formation of numerous cells having an axon which dichotomizes into an ascending and a descending branch.

It is a question of considerable interest whether the cortico-reticular fibres establish synaptic contact with cells of all types or with cells of one or a few types only. Since we have left out of consideration the alterations occurring in the terminal boutons in our experimental animals, no answer can be given to this question.

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* That this is not a unique example of cortico-fugal fibres passing to rostrally projecting nuclei is learnt from our observation (not mentioned in the descriptions given above) that a fair number of cortico-fugal fibres terminate in the spinal trigeminal nucleus and the nucleus of the solitary tract. There appears to be also some degeneration in the immediately adjoining areas of the reticular formation, but with the direction of sectioning used, this is difficult to decide. These anatomical findings are of particular interest in connexion with Hagbarth & Kerr's (1954) recent physiological observations of central inhibitory influences on afferent conduction in the spinal cord.

Functional correlations

While concerned primarily with structural features the considerations made above also have important bearings on problems of the physiology of the reticular formation. It would take us too far to discuss the anatomico-physiological correlations fully, but it will be appropriate to mention some relevant points.

As is well known, respiratory movements, cardio-vascular functions and the activity of skeletal muscles can be influenced by stimulation of various parts of the cerebral cortex. However, concerning the pathways which mediate these effects there is still considerable doubt. While there is evidence that some of them may be mediated at least in part through pathways involving various subcortical structures, it is possible that a certain role is also played by direct corticofugal fibres to 'centres' of the brain stem which have been identified as subserving the regulation of the functions in question. The observations of McCulloch *et al.* (1946), Ward (1948) and McCulloch and Henneman (1948) who recorded spikes in the reticular formation following strychninization of areas 4*s*, 24 and 19, respectively, have been taken to support this view, as have also the single unit recordings of Baumgarten *et al.* (1954).

In discussing whether our findings are in agreement with this concept, it is essential to consider whether the terminal areas of cortico-reticular fibres determined here coincide with those parts of the reticular formation which have been found by physiological methods to subserve the various functions. Such a comparison, however, meets with certain difficulties. Points and areas stimulated or recorded from are not always given with sufficiently detailed reference to anatomical features. Furthermore, there is always the possibility that the structures stimulated or recorded from have been not perikarya but afferent or efferent fibres of the structures in question. In spite of these factors of incertitude a comparison shows that, on many points, there is a remarkable correspondence between the anatomical and physiological findings.

Thus the cortico-fugal terminal area in the nucleus reticularis giganto-cellularis of the medulla (see Text-figs. 2, 4, 6 and 8) covers most of the field indicated by Maguon & Rhines (1946) and also by later authors as the area harbouring an inhibitory mechanism for motor activities. The cardio-vascular depressor centre of Alexander (1946) appears to be almost coincident with the same area as does also the inspiratory centre of Pitts (1940). The cell group labelled NR IV in Pitts's drawings appears to be the nucleus reticularis gigantocellularis of Meessen & Olszewski (1949).

The spatial correspondence between the terminal area of cortico-reticular fibres and the area allotted to the various 'centres' in the medulla seems to be sufficiently close to warrant the conclusion that the cortico-reticular fibre system described here may be concerned in the inhibition of muscular activity, inspiratory effects and cardio-vascular depressor effects obtainable from stimulation of various parts of the cortex. The fact that the areas in the medulla subserving these diverse functions appear to be practically the same is paralleled by the fact that all three types of effects may be obtained from some of the regions considered here (see Kaada, 1951). Furthermore, it is of interest that effects of one type or the other have been obtained from stimulation of all regions shown to project on to the medullary reticular formation.

Concerning the pontine cortico-reticular terminal area correlation with the physiological findings is less clear. It appears, however, that this area (comprising chiefly the nucleus pontis oralis) is part of the region of the brain-stem reticular formation shown by Rhines & Magoun (1946) and others to exert a facilitatory effect on motor activities, even if this area appears to extend also a little more caudally, as well as rostrally, into the mesencephalon (the possible cortico-reticular fibres to this have, however, not been included in our study). Pitts's (1940) expiratory centre, however, seems to be limited to the dorsal parts of the medullary reticular formation, and Alexander's (1946) pressor centre appears to be situated largely caudal to the chief cortico-reticular terminal area in the pons. However, this may be due to the fact that. in part, descending fibres as well as nerve cells have been stimulated in the physiological experiments.

On the whole, it appears likely that the cortico-fugal fibres to the pontine reticular formation (and possibly to the mesencephalic as well) may be utilized by impulses from the cerebral cortex responsible for motor facilitation, while their possible role for cardio-vascular pressor and respiratory effects seems more equivocal. It is in agreement with the widespread origin of the cortico-reticular fibres that the facilitatory effects supposed to be mediated via the reticular centres may be obtained under experimental conditions from various parts of the cortex (see Kaada, 1951).

As mentioned above, reticular cells sending their axons in a rostral direction and passing beyond the mesencephalon are present within the medullary terminal area of cortico-reticular fibres. Cortical fibres to this area, therefore, may be capable of influencing the activity in the 'reticular activating system' as suggested by Kaada (1951, p. 240). Jasper, Ajmone-Marsan & Stoll (1952), Bremer & Terzuolo (1954), and French *et al.* (1955) have brought forward electro-physiological evidence for cortico-fugal projections from different parts of the cerebral cortex to the mesencephalic reticular formation which contains a fair number of rostrally projecting neurons (Brodal & Rossi, 1955). Bremer & Terzuolo, who have shown that stimulation of the cerebral cortex alters the activity in the ascending activating system, discuss the role which such cortico-reticular connexions may play in the mechanism of sleep and awakening, and French *et al.* point to their importance for the maintenance of attention and introspection and their possible capacity of modulating sensory inputs to the brain. Similar considerations might presumably also be applied to the medullary area which in part projects rostrally and receives cortico-fugal fibres.

SUMMARY

Lesions have been made in different parts of the cerebral cortex of adult cats, and the reticular formation of the pons and medulla have been searched in horizontal silver-impregnated sections (Glees's method) for the occurrence of signs of terminal degeneration.

Since terminal boutons in normal animals may show variations which resemble degenerating terminal boutons, only characteristic degenerating terminal fibres have been taken into account as evidence of terminal degeneration.

Fibres to the pontine and medullary reticular formation appear to take origin from all parts of the cerebral cortex. The 'motor area' is the most important source, but substantial contributions come also from the basal and medial surfaces. Only few fibres come from the temporal and occipital lobes. The fibres probably descend among those of the pyramidal tract.

Regardless of their source within the cortex the fibres are distributed to identical parts of the reticular formation. Scattered fibres may terminate all over the reticular formation, but the majority of them end in two fairly well-circumscribed areas, a pontine region corresponding to Meessen & Olszewski's (1949) nucleus pontis oralis, and a medullary area, corresponding to their nucleus reticularis gigantocellularis. The cortico-reticular fibres appear to be distributed in approximately equal numbers to both halves of the brain stem, but since quantitative estimates are difficult in silver-impregnated sections this statement may require qualifications.

Functional implications of the findings are briefly discussed. It is concluded that the organization of the cortico-reticular fibres demonstrated is compatible with the assumption that this fibre system is engaged in the transmission to the brain stem reticular formation of impulses mediating cortical effects on somato-motor activity, respiration and cardio-vascular functions. The fibres may also influence activity in the ascending activating system.

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EXPLANATION OF PLATE

Photomicrographs from the brain stem reticular formation. Glees method. × 850.

Figs. 1–3. From the normal cat, showing terminal boutons of different sizes and types on the same cell (fig. 1), boutons *en passage* (fig. 2) and solid irregular boutons (fig. 3).

Figs. 4–8. From cat B.St.L. 73, having a large fronto-parietal lesion (see Text-fig. 2). Terminal and preterminal degenerating fibres (arrows) are seen, figs. 4–7 from the medullary reticular formation, fig. 8 from the raphe of the medulla.

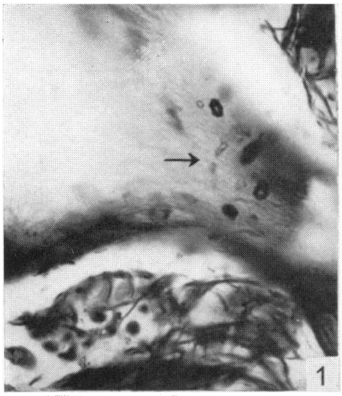
Fig. 9. From cat B.St.L. 6, showing preterminal and terminal degenerating fibres in the pontine reticular formation following a large fronto-parietal lesion.

Fig. 10. From the medial bulbar reticular formation in cat B.St.L. 12, having a lesion of the motor area (see Text-fig. 3).

Figs. 11–12. From the bulbar (fig. 11) and pontine (fig. 12) reticular formation in cat B.St.L. 29, having a lesion of the temporal lobe (see Text-fig. 5).

Fig. 13. Fragments of a fine terminal degenerating fibre in the medullary reticular formation of cat B.St.L. 8, having a temporal lesion (see Text-fig. 4).

Fig. 14. From the pontine reticular formation in cat B.St.L. 79, having a lesion of the basal surface (see Text-fig. 6).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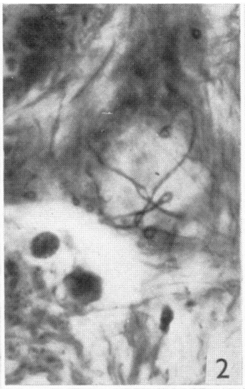
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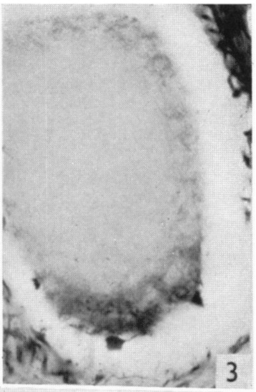
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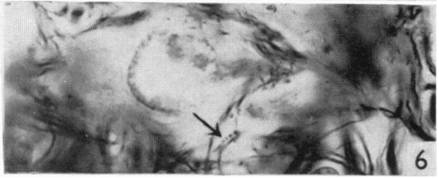
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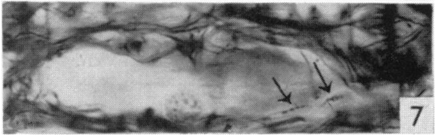
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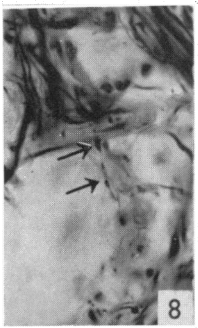
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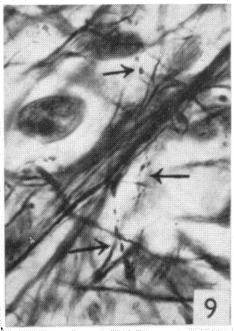
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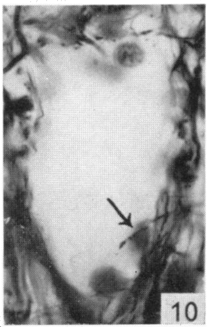
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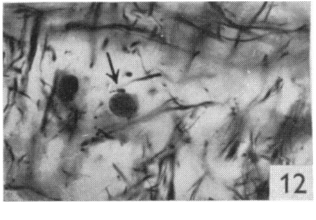
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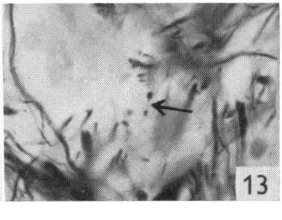
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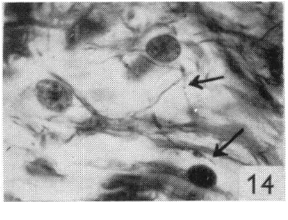
14

ROSSI AND BRODAL—CORTICO-RETICULAR FIBRES