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THE EFFECTS OF LESIONS IN THE CINGULAR GYRUS AND ADJACENT AREAS IN MONKEYS

BY

P. GLEES, J. COLE, C. W. M. WHITTY, and H. CAIRNS

From the University Laboratory of Physiology and the Departments of Neurosurgery and Neurology, Oxford

The attention of physiologists was directed anew to the anterior part of the cingular gyrus by the reports of Smith (1944, 1945) that this area was concerned in autonomic responses, and the findings of McCulloch (1944), using local strychninization, that the area had a widespread cortical suppressor effect. Clinical interest was also aroused by the marked behaviour changes noted by Smith (1944) and Ward (1948a) in monkeys following ablation of this region. The animals became unusually tame and appeared to lose their pre-operative fear of man. Their behaviour towards their cage-mates was also changed, so that Ward spoke of their treating them as inanimate objects. In man localized ablation of the area has been reported in a few cases only (Ward, 1948b; Mettler, 1949). Since July, 1948, we have removed the anterior part of the cingular gyri from a number of patients; our results will be reported later, since they can only be assessed by long-term observation. Meanwhile all we can say is that in advanced psychotics little temporary or permanent behaviour change has been noted, while in some obsessional psychoneurotics considerable improvement has occurred. There is no dramatic change such as is at times observed after standard leucotomy, and the results to date have not confirmed Fulton's suggestion (1949), based on the animal work, that in many successful cases of frontal leucotomy in man the common factor might be a lesion of the cingular area. Nevertheless, the clinical implications of the altered behaviour in animals following so limited a cortical lesion remain important, for the question arises whether the therapeutic response to operation in man is correlated simply with quantity of frontal tissue damaged or with loss of function of some specific part of the lobe. As the fibre connexions of the anterior cingular area are still by no means fully defined in primates, and the literature includes only one case in which the behaviour changes in a monkey have been correlated with a full neuro-histological study of the brain, it seemed desirable to attempt such a correlation in a series of animals. We report here the behaviour and histological changes in seven monkeys following an attempt at strictly localized surgical lesions of area 24, the anterior part of the cingular gyrus. As will subsequently be seen, such restricted lesions were not achieved, though all lesions included a large part of area 24, and additional damage was in the main limited to adjacent areas on the medial aspect of the frontal lobe.

The description of frontal lobe areas used in this paper follows Walker's (1940) map of the macaque brain, as they provide a convenient if approximate means of identifying cortical areas.

Material and Methods

Bilateral cingular gyrus lesions were made in one cebus and five rhesus monkeys and a unilateral cingular lesion was made in one cebus monkey. The animals were then observed for two to 14 weeks.

Operation.—In each case a bifrontal exposure was carried out under nembutal anæsthesia. The dura was opened on one side only, and in order to gain access to the medial surface of the hemisphere it was usually necessary to divide one or more of the cerebral veins passing from the dorsal surface of the frontal lobe into the sagittal sinus. The medial surface of the hemisphere was retracted to expose the cingular gyri, and in two cases it was necessary to incise the falx to expose the contra-lateral gyrus. The cingular lesions were made by extirpation with spatula, or by destruction with diathermy and suction, and were 1 to 3 cm. long, up to 1·0 cm. in depth, and usually occupied the whole width of the gyrus. In cebus monkeys additional injury resulted from sub-arachnoid and subdural bleeding, to which these animals showed a marked tendency.

Observation and Training.—The behaviour of the animals was noted at various times of the day and night, and by several observers. The animals were kept in a room along with other caged inmates and no special situations were created, apart from the presence or

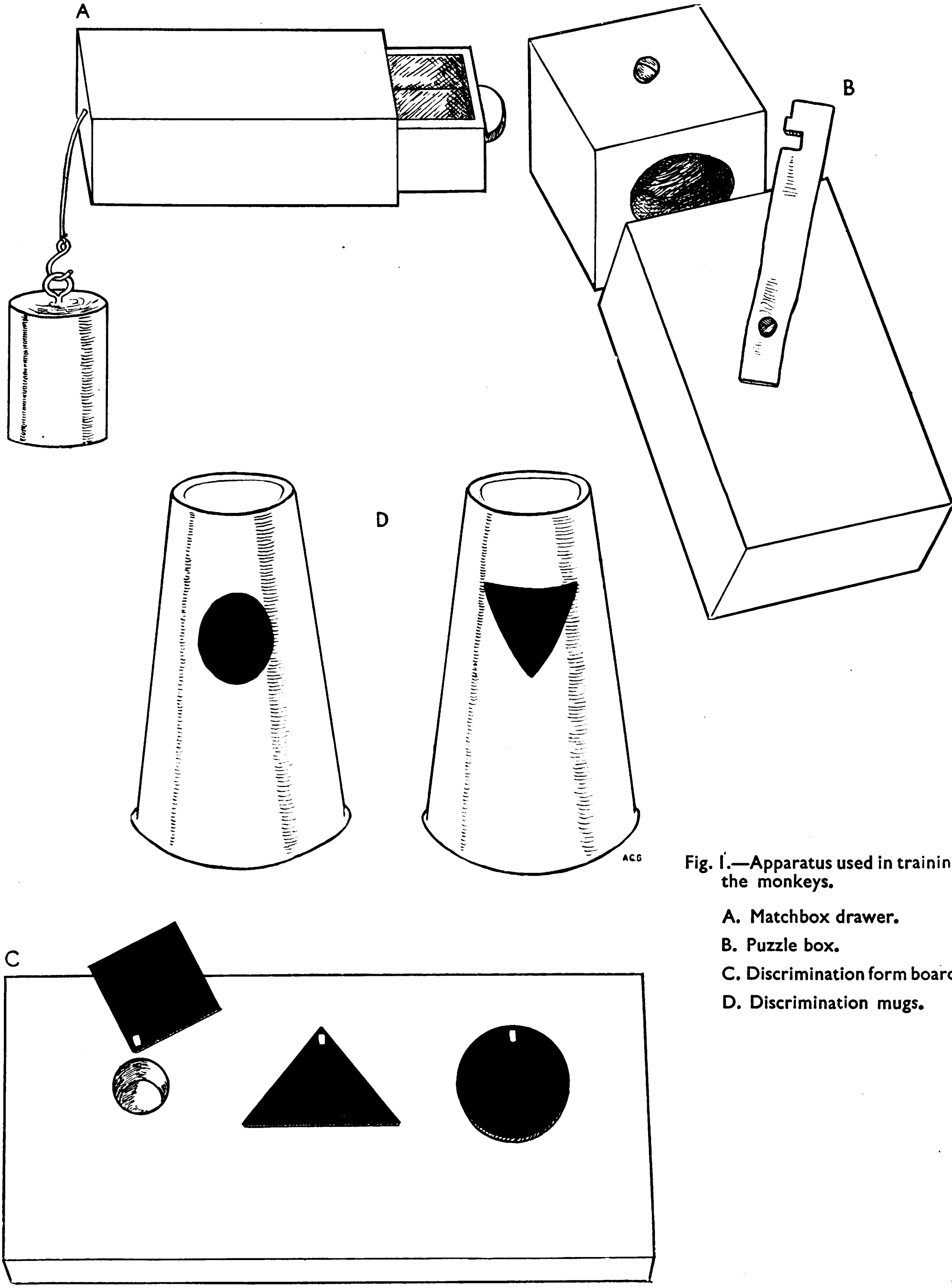


Fig. 1.—Apparatus used in training the monkeys.

A. Matchbox drawer.

B. Puzzle box.

C. Discrimination form board.

D. Discrimination mugs.

absence of a cage-mate and the special conditions of training. Individual variations of behaviour are of course marked in primates, even in the same species, so that our sometimes brief behaviour studies, where response to training is concerned, must be interpreted with caution. Two monkeys (M.C.G. 1 and 6) were trained before operation, and one (M.C.G. 9) was trained after operation to obtain food concealed in a box with a clasp, or to discriminate patterns or colours by choosing one of several shapes on a wooden block, or one of a series of inverted mugs with food under it (Fig. 1).

Histological Technique.—The Swank-Davenport modification of the Marchi technique was used for the histological studies of the brains.

The Lesions

Though the main destruction was in the anterior part of the cingular gyri, post-mortem examinations showed that the lesions were in fact more extensive, sometimes involving nearby parts of areas 6, 8, 9, 10, and 25, and the corpus callosum. This damage was the result of (1) division of cortical cerebral veins, which in all but one case was necessary to obtain exposure of the cingular gyrus ; (2) gentle retraction of the medial surface of the frontal lobes (areas 6, 8, 9, 10) ; (3) spread of diathermy effect from the cingular gyrus to adjacent parts ; (4) secondary necrosis which follows excision of any part of the brain, presumably from interference with blood supply ; (5) shearing stresses, the result of post-operative herniation of the brain through the dural opening (Holbourn, 1944 ; Falconer and Russell, 1944). Thus, with the greatest care and gentleness, we have found it impossible to avoid additional unintended damage, which the literature on local cortical extirpations of the medial surface of the cerebral hemisphere would not lead one to expect.

CASE REPORTS

A. Bilateral Lesions

M.C.G. 1.—Male *Macaca mulatta* (weight 3·5 kg.). An active, nervous, intelligent animal, trained to open a match box drawer using his thumb and index finger, not dominant over his cage-mate, an *Erythrocebus patas* (weight 2·5 kg.).

Operation.—December 1, 1948. About 1·6 cm. was extirpated by spatula and suction from both cingular gyri above the genu of the corpus callosum (Fig. 2).

Post-operative Behaviour.—On December 2 the animal paced continually around his cage, showing pilo-erection which had never been observed before. This behaviour continued unabated for a week or ten days. Then it very gradually decreased until the animal was sacrificed on January 15, 1949.

During the first seven post-operative days it was difficult to get the animal to take food from a hand held inside the cage, and he would only do so after walking past it several times. Although there was no disability of his limbs, when food was taken there was a most unusual tendency to use the mouth to pick it directly from the experimenter's hand. The animal continued to pace the cage while eating, whereas before operation he retired to sit and eat in a distant part of the cage. Not until December 8 would he take any notice of the match box drawer. He then opened it with his teeth, but did not take the bait from inside. However, before he was killed he readily used his hand to take food from the box.

In the early post-operative period if an observer's hand was placed in the animal's way as he paced round, he would jump over it, and continue pacing without backing-away as he would have done before operation. If, as he jumped, he was flicked by the hand, he would jump to the top of the cage as if startled, but immediately resumed his circumambulations and came back to the hand. This abnormal conduct appeared to decrease *pari passu* with the restlessness until both had almost disappeared.

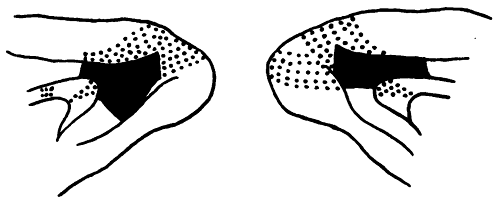
Post-operative Behaviour with Cage-mate.—During his continuous cage-pacing M.C.G. 1 walked into or over his cage-mate, the cebus, whenever the latter got in his way. When the cebus resented this M.C.G. 1 retreated momentarily, as if frightened, but immediately walked into the cebus again. Eight days after the operation M.C.G. 1 was frequently seen deliberately taking food from the cebus, which he had never done before operation ; and he was beginning to compete with the cebus in the normal way for a piece of food held or thrown inside the cage. This assertiveness continued and increased, so that by December 17 he was defending himself when the cebus attacked him for snatching food.

During the whole of the observed period before and after operation no grooming took place.

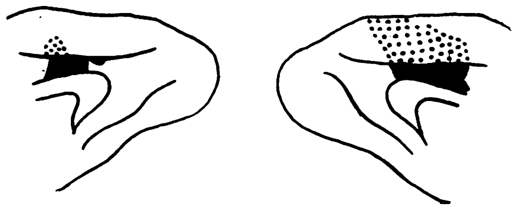
Neuro-histological Findings : Right Hemisphere.—The lesion on this side involved areas 24, 25, 9, and a portion of 10, as seen from the medial surface (Fig. 2). The lesions of areas 9 and 10 do not extend far on the dorsal surface of the hemisphere and involve mainly the medial part of the superior frontal convolution of these areas, and a small part of the middle convolution of area 9.

The right hemisphere was sliced in an oblique coronal plane through the genu of the corpus callosum and the anterior commissure. In the white matter underlying the injured part of the cingular gyrus a very finely myelinated fibre tract can be followed to terminate in the medial aspect of area 9.

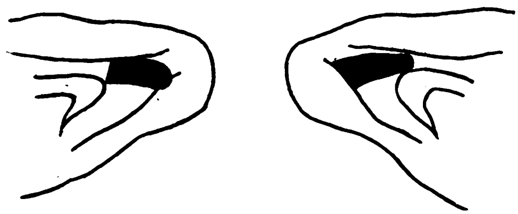
Horizontal sections also show numerous degenerating fibres from the injured part of areas 9 and 10 streaming into the anterior limb of the internal capsule. Some of these fibres are of a very coarse and some of a very fine calibre. Most of the coarser fibres can be seen descending into the medial portion of the cerebral peduncle, but some leave the internal capsule (posterior limb) by passing through the thalamus to enter the mid-brain. The finer fibres enter the thalamus at the level of the genu of the internal capsule. They then stream around the medial side of the anterior nucleus, thus forming its capsule, and some enter the anterior nucleus, while others



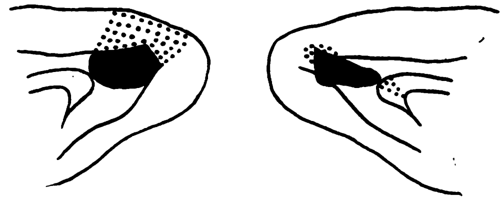
L. Fig. 2 (M.C.G.1) R.



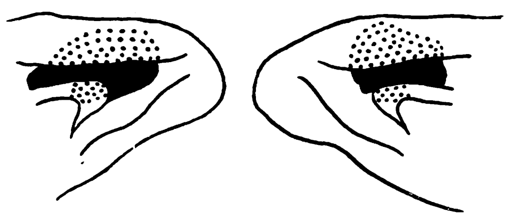
L. Fig. 3 (M.C.G 5) R.



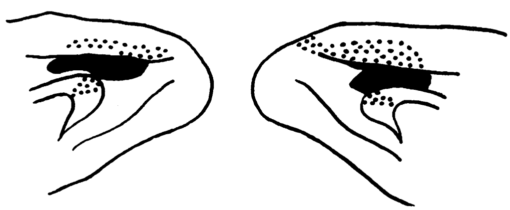
L. Fig. 4 (M.C.G.6) R.



L. Fig. 5 (M.C.G.7) R.



L. Fig. 6 (M.C G.8) R.



L. Fig. 7 (M.C.G.9) R

Figs. 2–7.—Areas in black indicate intentional damage of the cingular gyrus, while the additional unintentional damage to neighbouring regions, due to retraction of the hemisphere or to interference of blood supply, or to other causes, is indicated with dots. (L=left hemisphere. R=right hemisphere.)

terminate mainly in the rostral and lateral two-thirds of the dorso-medial nucleus.

Numerous cells of the head of the caudate nucleus have undergone degeneration, and large cells of the rostral and external segment of the globus pallidus are passing through a similar process.

Left Hemisphere.—The injury involved areas 24, 25, and 9 as seen from the medial surface, and has also cut most of the fibres of the cingulum. The hemisphere has been sliced in a sagittal plane, which reveals the histological changes detailed below.

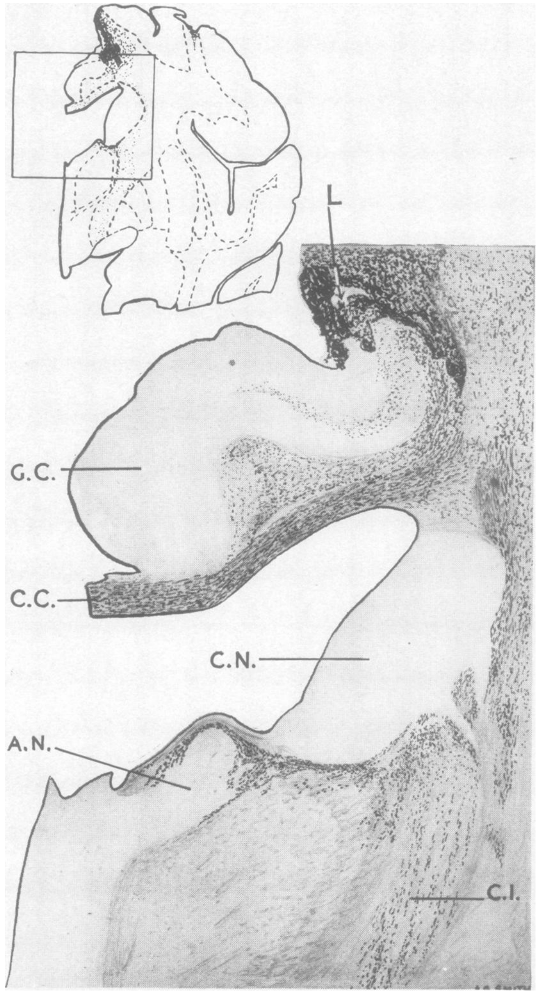


Fig. 8.—Enlarged drawing of a transverse section through the right hemisphere of M.C.G.5. Coarse fronto-pontine fibres descend in the internal capsule (c.i.) and fine fibres enter the stratum subcaudatum to terminate in the anterior nucleus (a.n.), or pass further posteriorly to terminate in the dorso-medial nucleus. (L=the lesion ; g.c.=remaining part of cingular gyrus ; c.c.=corpus callosum ; c.n.=caudate nucleus.)

Fibres from the cingular cortex can be traced into the posterior portion of the orbital cortex (area 14 of Walker) and into area 8. Fibres in the damaged cingulum can be traced anteriorly into the region of the lamina terminalis and posteriorly to the level of the splenium. The number of degenerated fibres in the retro-splenic portion of the cingulum is still very conspicuous. There is degeneration in the head of the caudate nucleus and in the globus pallidus similar to that on the right side.

In transverse sections of the brain stem, fibres already traced from area 9 can be seen in a medial position in the cerebral peduncle and terminate in the pontine nuclei. No evidence for a pathway to the reticular substance from the cortical areas injured could be found at pontine or medullary level.

M.C.G. 5.—Female *Erythrocebus patas* (weight 4·4 kg.). A very docile animal who submitted to stroking, salivating freely when petted. Untrained.

Operation.—February 23, 1949. Severe bleeding complicated the exposure of the cingular region. Two small lesions (total length 1·2 cm.) were made in the right cingular gyrus by suction. A smaller lesion (1 cm. long) was made in the left cingular gyrus approached through the falx (Fig. 3). There was considerable sub-arachnoid hæmorrhage on the right side.

Post-operative Behaviour.—Late in the first post-operative day a left-sided hemiplegia developed and severe fits occurred. By March 23, the paralysis had improved sufficiently for the animal to be able to walk, and the fits had ceased. At this stage the animal was slightly more restless than before operation, but she remained docile. She was killed on May 27.

Neuro-histological Findings : Right Hemisphere.—The ablation does not involve the whole width of the cingular gyrus, but sections show that the residual part has been undercut. An adjacent part of the corpus callosum is also involved. In addition damage has been caused to areas 6 and 8 on the medial surface and, from post-operative swelling against the edge of the bone flap, to area 4 on the dorsal surface.

The hemisphere was sectioned transversely. Degeneration of intra-cortical fibres can be traced from areas 6, 8, and 4 (anterior part), into the uninjured portions of the cingular gyrus. Fibres from the cingular gyrus can be traced to the septal and sub-septal cortex.

Sections through the thalamus show degenerating fibres coming from the white matter beneath the injured parts of areas 6, 8, and 24. They pass through the anterior limb of the internal capsule (on its medial border), enter the stratum subcaudatum of Sachs, and stream into the capsule of the anterior nucleus, where they are dorsal, lateral, and partially medial to the anterior nucleus (Fig. 8). Many fibres enter the anterior nucleus (Fig. 8a), but a considerable number also run posterior to it to terminate in the dorso-medial nucleus.

Left Hemisphere.—The lesion involves mainly a portion of the cingular gyrus and encroaches only slightly on to an adjacent part of area 6 on the medial surface of the hemisphere. On the dorsal surface of the brain some damage was seen in the motor cortex. In transverse sections degenerated fibres from the cingular lesion can be traced in the white matter adjacent to the gyrus cinguli as far back as the level of the splenium. Fibres also enter the septal cortex, the sub-callosal gyrus, and the gyrus rectus. Furthermore, small-sized fibre bundles can be traced from the lesion of the cingular cortex into the medial surface of areas 6a and 8.

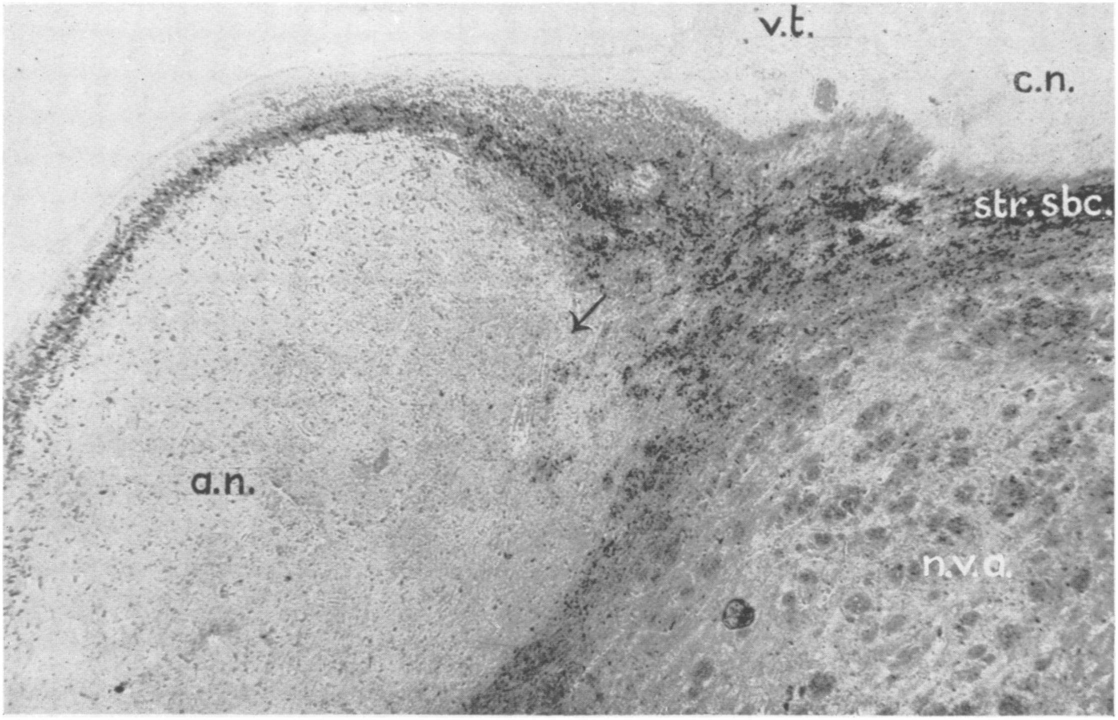
The caudate nucleus and globus pallidus were uninjured on both sides.

M.C.G. 6.—Female *Macaca mulatta* (weight 4·1 kg.), at the beginning of the menstrual cycle. A very aggressive animal which would attack a finger poked through the bars of its cage and would snatch food from the hand roughly. Dominant over her cage-mate, a female macaca of the same size. Trained to open a puzzle box, and to distinguish a triangle from a square and a circle (Fig. 1).

Operation.—June 1, 1949. Lesions just over 1 cm. long were made in the anterior portions of both cingular gyri by diathermy (Fig. 4).

Post-operative Behaviour.—The animal did both the puzzle box and triangle tests about eight hours after operation. She still showed aggressive behaviour, but this was less marked, her attacks being half-hearted. No increase in restlessness nor cage pacing was observed. She approached humans more readily than before when offered food by hand, and took it more gently. She remained dominant over her cage-mate, and could always get food first, but was less aggressive than before operation. No grooming by this animal was observed either before or after operation, but pilo-erection, not seen before operation, was observed while the monkey was sitting quiet in a corner from the first post-operative day onwards.

No further behaviour changes were observed before the animal was killed on June 22. In the three weeks after operation she never became as aggressive as she had been before.



a.n.=anterior nucleus ; n.v.a.=nucleus ventralis ant.; c.n.=caudate nucleus ; str. sbc.=stratum subcaudatum ; v.t.=vena terminalis.

Fig. 8a.—Photomicrograph of the anterior nucleus of M.C.G.5, right hemisphere. The nucleus anterior is surrounded by degenerated thinly myelinated fibres which reach the anterior nucleus via the stratum subcaudatum. The main point of inflow of afferent fibres to the anterior nucleus is marked by an arrow, but additional entering fibres come from other parts of the degenerated capsule of the anterior nucleus and appear as fine black dots within the substance of the nucleus. x 80.

Neuro-histological Findings : Right Hemisphere.—The lesion involves the cingular cortex in its most anterior portion ; there is also a slight involvement of Walker's area 25. Transverse sections show degenerated fibres streaming ventrally from the site of lesion towards the orbital cortex. They terminate in the gyrus rectus.

Left Hemisphere.—The lesion involves the pre-callosal part of the left cingular gyrus ; there is also a slight injury to area 10. Saggital sections show fibres from the injured zone passing to the sub-callosal gyrus and into the posterior portion of the orbito-frontal lobe. Furthermore, degenerated fibres pierce the corpus callosum and enter the septal cortex, while others terminate in the medial aspect of the superior frontal convolution (6A).

The caudate nucleus and globus pallidus are intact on both sides.

M.C.G. 7.—Female *Macaca mulatta* (weight 3·9 kg.), about to begin menstruation. Very wild, nervous and totally uncooperative but not aggressive. Untrained.

Operation.—June 15, 1949. Small lesions were made by diathermy (right 1 cm., left 1·2 cm. long) (Fig. 5).

Post-operative Behaviour.—On the evening after the operation the animal was so tame that she took food from a hand inside the cage and came readily to the front of the cage when offered food through the bars. This had not occurred before. When frightened she vociferated loudly and shrilly, which she had not done before ; there was also marked pilo-erection and the animal grimaced more frequently ; but this reaction did not prevent her returning to the hand for more food. All these behaviour changes persisted until the animal was killed on July 2. There was no obvious motor disability and no hyperactivity.

On the day after operation a small blister was noticed surrounding the right nipple. On the following day it had broken. No ulcer developed.

Neuro-histological Findings : Right Hemisphere.—The anterior portion of area 24 and a small portion of areas 25 and 9 were injured ; there was also an injury to the arm area of the motor cortex, probably due to pressure against the edge of the bone. The lesion of the cingular gyrus extends posteriorly to the level of the genu which is also slightly damaged. In transverse sections fibres can be traced from the damaged areas into the gyrus rectus and into area 9 dorsally. There is a little degeneration in the cingulum of very fine calibre fibres. The cortico-spinal system of this side shows a conspicuous number of degenerated fibres. The caudate nucleus and globus pallidus on this side were uninjured.

Left Hemisphere.—The lesion involves the anterior portion of areas 24, 25, and 9, with some encroachment on to area 10. In horizontal sections fibres can be traced from the cingular gyrus into the septal cortex. Only very few degenerated fibres are present in the cingulum. Numerous fibres from the injured zones of areas 9 and 10 run in the medial aspect of the anterior limb of the internal capsule, leave the internal capsule at its genu, and terminate mainly in the medial nucleus of the thalamus.

Some cortico-fugal fibres of coarse calibre from the injured portions of areas 9 and 10 terminate at pontine level. Fibres from the injured motor cortex can be traced down to the lumbar level of the cord.

There was some cell degeneration in the head of the caudate nucleus. The globus pallidus was intact.

M.C.G. 8.—Elderly male *Macaca mulatta*, 10-12 years old and weighing 11·7 kg.; rather gentle and lethargic. He took food readily from the hand and retreated grimacing when a bar was poked into his cage, showing no evidence of aggression. When a half-grown female macaca was placed in the cage he completely ignored her and made no attempt at sexual behaviour, and allowed her to take food. He could only be induced to attack if his face was blown into. Untrained.

Operation.—July 13, 1949. A lesion was made in the left cingular gyrus extending forward from the motor cortex area for about 3 cm. by diathermy. A similar lesion was made on the right side (Fig. 6).

Post-operative Behaviour.—Very little change took place in this old animal's behaviour, in spite of the large size of the lesions. For two days after operation he appeared unresponsive and unwell, but by the third day he had recovered. He remained mainly lethargic, but was slightly more active than he had been before operation. There was no cage-pacing. He took food gently from the hand as before, but no longer attacked when his face was blown into. Considerable pilo-erection, not seen before, was observed from the first post-operative day onwards.

A half-grown operated female *Macaca mulatta* animal (M.C.G. 9) was put in the cage on July 16. He took no notice of her, until she paced over his food dish when he was eating, then he gripped her in his hands and attempted to bite. He did her no harm and quickly let her go, but repeated this behaviour when she again paced over his food.

No further behaviour changes were observed up to the time the animal was killed on July 27, 1949.

In the second post-operative week two large ulcers (each 5 by 2·5 cm.) were observed on the chest and right thigh.

Neuro-histological Findings : Right Hemisphere.—The lesion on the right side involves areas 24, 6a, and 8 on the medial surface. The lesion of area 24 has penetrated the total depth of the gyrus and also the adjacent white matter. The forceps minor of the corpus callosum is damaged as well.

Left Hemisphere.—The lesion on this side is slightly more extensive than on the right, but covers essentially similar cortical areas, and a portion of the corpus callosum. No cortical injury could be observed on the dorsal surface of the cortex of either hemisphere.

Most of the Marchi sections of both hemispheres proved to be a failure, due to insufficient penetration.

M.C.G. 9.—Female *Macaca mulatta* (weight 3·1 kg.), sexually rather immature, very timid, retreating to the corner of the cage when offered food. Habitually sucked her middle finger. Dominated by larger female cage-mate. No training attempted before operation.

Operation.—July 6, 1949. Three separate lesions made by diathermy in the left cingular gyrus, in all about 2½ cm. in length. A large lesion was also made in the right cingular gyrus, but in this case only 1·7 to 2 cm. in length (Fig. 7).

Post-operative Behaviour.—Immediately after operation the monkey was markedly restless and was also clumsy in her movements. As she circumambulated she walked head-on into the " perspex " sides of her cage. When offered carrot she took it from the hand and even came across the cage to do so. Almost invariably she took the bait with her mouth, lurching forward and often missing the hand in an ataxic manner. This ataxia was probably unconnected with the specific lesion, as it is often noted during the first few post-operative days of any extensive intracranial procedure in monkeys. It was possible to stroke her as she paced the cage. Pilo-erection, not seen before operation, was observed from the first post-operative day.

A week later she was more hesitant about taking food and could not be stroked. Her movements were now less ataxic. Marked pilo-erection persisted.

During the whole of the first fortnight after the operation the animal was not observed sucking her finger, and she almost always took food from our hands with her teeth. With time her timidity appeared to return, but the tendency to the oral approach persisted for at least six weeks, especially after she had been frightened. At the end of three weeks finger-sucking had re-appeared, the oral approach to proffered food had almost been abandoned, and timidity had increased ; but a fortnight later it was more easily overcome by routine training than would have been expected from her pre-operative behaviour. No increase in vocalization was noticed.

Post-operative Behaviour with Cage-mate.—As soon as her general condition permitted, on July 16, this monkey was put in with M.C.G. 8. Although no longer ataxic she would knock into him, and pace right over his food. When this led to an attack she backed away and grimaced, but immediately repeated the offending act. On August 11, when placed with her pre-operative cage-mate, she was submissive and was bullied in the food situation, but she no longer walked into her cage-mate. No grooming was observed between these two animals, either before or after operation.

Twelve weeks after operation she was put into a cage with a small, timid male *Macaca mulatta* of her own size. On the following day she was observed both grooming and being groomed, also taking an active part in sexual behaviour. In the feeding situation neither monkey was dominant.

Post-operative Learning.—During ten days on which training was given, beginning five weeks after operation, the monkey learnt four discrimination tests* with an average of 125 trials for each test. This did not differ much from the results in four intact animals of approximately the same age (two macacas, two erythrocebus), who learned in an average of 23, 85, 104, and 153 trials. However, in learning a tendency to perseverate to a greater degree than had been noticed in the intact animals was observed. The animal was killed on October 18, 1949.

Neuro-histological Findings : Right Hemisphere.—The lesion of the cingular area is somewhat smaller than on the left side, but it extends into areas 6 and 8, with an infringement of the dorsal part of area 9.

Left Hemisphere.—The lesion involves the greater part of area 24 in the cingular region, and encroaches upon areas 6 and 8 with infringement of area 9 (medial surface).

On the dorsal surface of each hemisphere the medial portion of the motor area has been slightly damaged.

For histological purposes the right hemisphere was cut horizontally and the left sagittally. The histological examination of both hemispheres confirmed the findings in M.C.G. 1, where the lesions were similar ; as in that case, this one also showed a bilateral involvement of the tip of the caudate nucleus.

Degenerating fibres from the small area of damage in the motor cortex on each side could be followed down to spinal cord level. No fibre degeneration from the cingular gyrus ending in the reticular substances could be found.

B. UNILATERAL LESION

M.C.G. 4.—Male *Erythrocebus patas* (weight 1·8 kg.). An untrained animal, but sufficiently tame to take food from the hand through the cage bars. Not dominant over his cage-mate, a similar male cebus (2·5 kg.) with very similar reactions. M.C.G. 4 had previously been used for a motor cortex undercutting experiment.

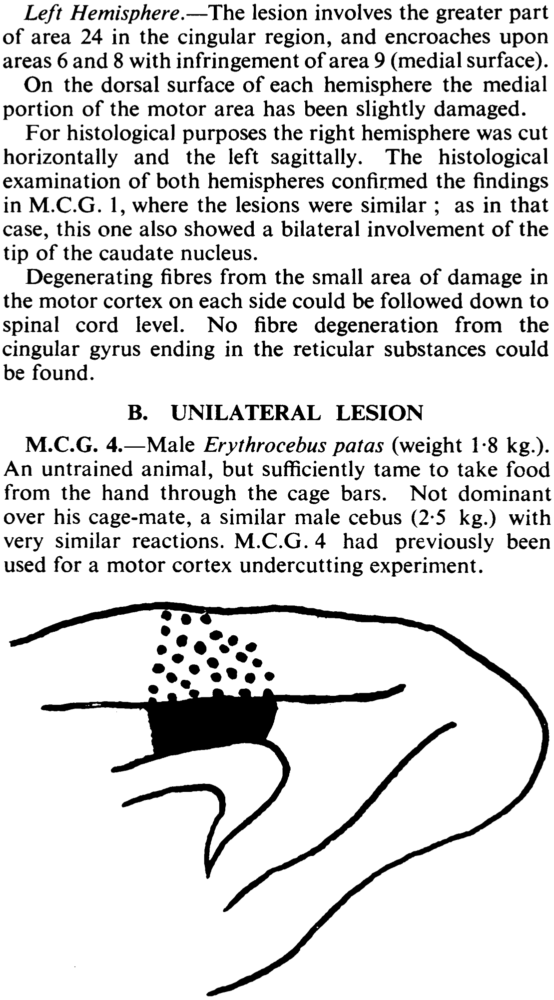


Fig. 9.—Extent of lesion in M.C.G.4. (L.)

* M.C.G. 9 was trained to four discrimination tests : (1) To discriminate position by always selecting the centre of three mugs of the same colour presented in a row ; (2) to discriminate between a red and a green mug by always selecting the green ; (3) to discriminate between a circle and a triangle painted on mugs, selecting the mug on which was the triangle ; (4) to discriminate between one 1 in. spot and two 1 in. spots painted on mugs by selecting the mug on which were the two spots. The mugs were inverted and screened from the animal's view by a shutter. The bait was placed under the mug which the monkey was trained to select, and the shutter was then lifted. Except in test 1, the position of the mug of the colour or design to which the monkey was trained was changed with that of the other mug in an irregular sequence. The monkey was considered to have learnt to discriminate when it had made ten consecutive correct choices.

Operation.—March 16, 1949. A lesion was made by diathermy in the anterior portion of the left cingular gyrus just over 1 cm. in length (Fig. 9).

Post-operative Behaviour.—His reaction was quite different from that after his previous operation. Some restlessness with a tendency to circumambulation, which increased if the animal was stimulated, was most noticeable ; but he never walked into and over his cage-mate as M.C.G. 1 had done. He continued to take food from the hand. He seemed rather more aggressive than before operation, and became dominant over his cage-mate.

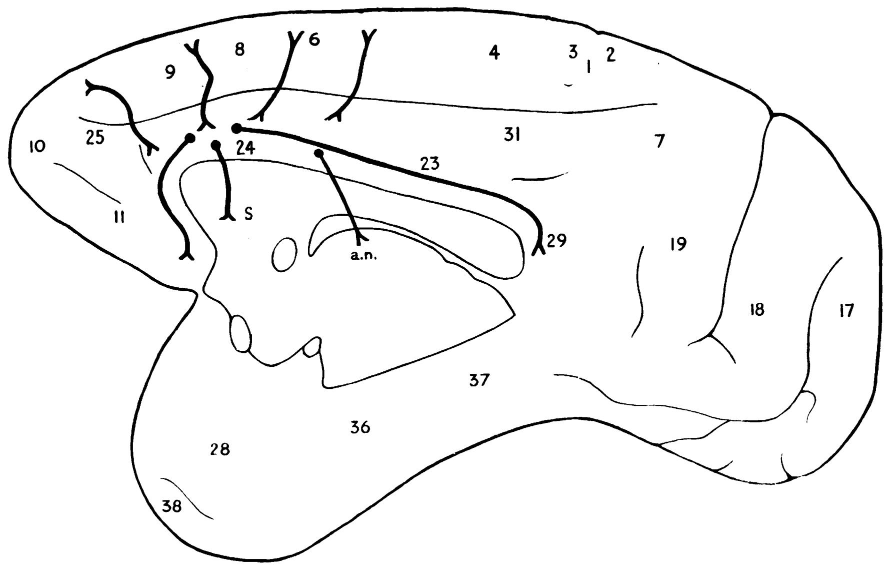
He tended to revert gradually to his pre-operative state, and when he was sacrificed on April 29, his restlessness was barely noticeable, and his behaviour less aggressive.

Thirteen days before this operation, a motor cortex lesion had been made on the left side to study the combined effect of lesions to 4 and 24 : the results of the motor cortex lesion (paralysis of the hand) had subsided before the second operation, and only the absent placing reaction on the right showed that cortical damage had been done.

Neuro-histological Findings.—The lesion of area 24 in this case involved the left hemisphere only, and in addition slight damage was caused to the medial surface to the anterior part of 6. Transverse sections show that the cingular cortex injury caused degeneration of fine fibres, some of which turn into the cingulum, but cannot be traced very far in a posterior direction. The damaged area sends small, but very well-defined bundles of fibres to the anterior part of area 6 and the posterior portion of area 8 : and from the injured portions of area 6 and possibly area 4 fibres terminate within the cingular cortex.

The injury to the cortico-spinal system is clearly outlined and degenerating fibres can be traced from area 4 down as far as the lumbar cord.

There is degeneration in the globus pallidus, cellular in nature, which is clearly marked in the anterior part of the external segment. More posteriorly, at the level of the motor cortex, numerous cells of the internal division are Marchi positive ; but the caudate nucleus is intact.



The symbol >—< indicates a two-way connexion.

A.N. = Anterior nucleus.

S. = Septal cortex.

Fig. 10.—Diagram showing medial aspect of a right hemisphere illustrating the connexions of the cingular cortex found in our experiments.

Discussion

Histology.—Although no pure area 24 lesion was achieved in these animals, the Marchi preparations clearly reveal the efferent pathways from this area.

Numerous intracortical connexions are seen (Fig. 10). From the supracallosal part of area 24 they stream into the septal cortex, and partially through the septal cortex into the subcallosal gyrus and posterior portion of the gyrus rectus, or area 14 of Walker. This is of particular interest as it may give anatomical support to earlier physiological work suggesting such pathways. Thus Smith (1945), Livingston, Fulton, Delgado, Sachs, Brendler, and Davis (1948a), Kaada, Pribram, and Epstein (1949) and others have shown in the monkey that vascular and respiratory responses were obtainable from a continuous stretch of cortex including the cingular cortex and the posterior orbital surface of the frontal lobe. Similar observations in man have been made on the orbital surface of the frontal lobe by Livingston, Chapman, Livingston, and Kraintz (1948b), Chapman, Livingston, and Livingston (1949), and on area 24 by Pool and Ransohoff (1949). Furthermore, in our animals well-defined small fibre bundles could be traced from the cingular lesion into the lower lip of the superior frontal convolution, a region which may be identical with the "cingular belt" demonstrated by Bailey, von Bonin, Davis, Garol, McCulloch, Roseman, and Silveira (1944) by physiological neuronography.

Fibres from the anterior portion of area 24 can also be followed for a considerable distance posteriorly, above the splenium, into area 29, and two-way connexions are seen to other adjacent areas (Fig. 10).

Fibres from the posterior part of the area terminate in the anterior nuclei of the thalamus in three of our animals (M.C.G.1, 9, and 5). There has been considerable difference of opinion about these connexions. Grünthal (1939) assumes that in primates the anterior nuclear mass of the thalamus projects mainly to the frontal granular cortex, and not to the cingular region. On the other hand, Le Gros Clark and Boggon (1932-33), showed that in the cat and rat the whole length of the cingular gyrus receives fibres from the anterior nucleus. Later, in only one monkey, the same authors (1934-35) found connexions between the cingular gyrus and the anterior thalamic group. Their work was confirmed by Walker (1938), again on a single animal, and later for man by the post-leucotomy studies of Meyer, Beck, and McLardy (1947). However, as Meyer and his colleagues have pointed out, there is a discrepancy between the anatomical investigations and the physiological studies of Bailey and others (1944), who found only the posterior and the inferior part of the gyri cinguli projecting to the anterior thalamic nuclei.

Our findings in three monkeys support the claims of Le Gros Clark and others that there is a connexion from the cingular area to the anterior nucleus. Our main lesions were in the cingular gyrus, and, furthermore, cortical injury which did not infringe the gyrus cinguli shows no Marchi granules in fibres from the injured cortical areas to the anterior nucleus. It is therefore probable that these cortical thalamic fibres come from the cingular gyrus, and not from the additional cortical injury.

Of further interest is the question whether in monkeys the whole cingular gyrus sends fibres to or receives fibres from the anterior nuclei. In the three monkeys which show the connexion most clearly the lesions reach comparatively far back, and extend into area 23. Our material does not show connexions between the anterior portion of the gyrus around and below the genu, and the anterior nuclei of the thalamus.

In view of the demonstration of a suppressor function in area 24 (Bailey and others, 1944; McCulloch, 1944; Smith, 1945; Kremer, 1947), we have searched for myelinated pathways from area 24 to subcortical centres. Neurophysiological observations have suggested a pathway from area 24 to the reticular substance (Smith, 1945; Magoun and Rhines, 1947), and in one of his monkeys with a lesion of area 24, Ward (1948a) found Marchi degeneration reaching the reticular formation of the pons. We are unable to confirm this finding. As has already been pointed out, it is difficult to make a pure lesion of area 24. The Marchi material of Ward's case is not free from additional cortical damage, and in none of our cases was the lesion strictly confined to that area. However, in one of our animals (M.C.G.6) there was an almost pure lesion of area 24, and in this case no fibres could be traced down into the reticular substance of the pons and medulla. The involvement of fronto-pontine fibres from areas adjacent to the cingular gyrus makes it very difficult to define whether frontal fibres end among pontine nuclei or in the reticular substance, and only a method for staining degenerating aborizations can decide this. A continuous cortical downstream of fibres is usually myelinated, and the failure to demonstrate a cortico-reticular pathway with a Marchi method may indicate that the route has relays in between. Ward also described Marchi degeneration as occurring in the medial longitudinal bundle, but this bundle even in the normal state contains Marchi positive granules. Similar granules can often be seen in the reticular substance for no apparent reason, and should not be mistaken for the anatomical substratum of a pathway so far only demonstrated by neurophysiological methods.

None of our lesions caused degeneration in the fasciculus subcallosus. The point is mentioned as degeneration in this tract has been noted in certain frontal leucotomy cases in man (McLardy, personal communication).

The foregoing findings give information about the efferent connexions of the area. We have also gained some evidence of the afferent pathways derived from the study of fibres running from the zones of unintentional damage in other cortical areas. We found fibres from lesions in areas 4, 6, 8, 9, 10 of the superior frontal convolution descending into the anterior cingular region. Some of these may represent the pathway from the frontal suppressor areas, such as 4s and 8s, found by strychninization experiments in the monkey (Bailey and others, 1944).

The cingulum itself seems to be a fibre tract which is not so intimately related to the gyrus cinguli as some have thought, an observation already made by Beevor (1891). When the cingulum was injured we could trace fibres into the retrosplenic area, but not into the occipital part of the fasciculus longitudinalis inferior. Rostrally, the fibres of the cingulum turned round the genu of the corpus callosum and could be traced into the region of the anterior perforated space.

In general our material suggests that the anterior part of the cingular gyrus, which includes most of area 24, has chiefly intracortical connexions. The more posterior part of area 24 and adjacent region of area 23 have thalamic connexions. This finding deserves consideration, as it throws doubt on the current conception that the anterior cingular cortex has thalamic connexions. If confirmed it would associate the anterior cingular region with the orbital frontal cortex of the frontal lobe, rather than with the thalamo-cortical projection areas.

Behaviour.—Two marked behaviour changes were noted in these animals : first, increased restlessness and hyperactivity, and secondly, something which can best be described as loss of their previous apprehension to certain aspects of their environment —what Smith (1944) has termed " tameness " and Ward (1948a) " loss of shyness of man ". The two changes did not both occur in all animals, though the latter was almost constantly present for a time.

The restlessness will be discussed first, as it is more objective and clearly defined. It was most striking in two monkeys (M.C.G. 1 and M.C.G. 9) and showed itself as a continual, restless pacing of the cage. The restlessness appeared to be independent of outside stimuli and would persist during feeding. It came on immediately after operation, unlike the delayed hyperactivity noted by Freudenberg, Glees, Obrador, Foss, and Williams (1950), and others in leucotomized animals, and was most marked during the first two post-operative weeks. Thereafter it gradually subsided.

Fulton, Jacobsen, and Kennard (1932) noted such a hyperactivity following frontal lobe lesions. Richter and Hines (1938) studied it in more detail, and concluded that an immediate post-operative restlessness occurred when damage to the tip of the caudate nucleus was associated with a lesion of the frontal cortex. However, Kennard, Spencer, and Fountain (1941), studying both caudate nuclear and large bifrontal cortical lesions, did not agree with Richter and Hines' suggestion. The well-marked cellular degeneration in the caudate nuclei in M.C.G. 1 and 9 lends support to the view of Richter and Hines that bilateral injury to the caudate nuclei, in addition to that of the frontal cortex, is necessary to produce this pattern of behaviour, while a unilateral involvement of the caudate nucleus, as in M.C.G. 7, has no such effect. In view of the physiological evidence that this nucleus may be an important part of the cerebral suppressor circuits, this point clearly requires further investigation.

The second and more constant change needs more detailed description. The animal appears fully aware of its environment, but its previous emotional reactions to its surroundings are changed. It will approach the human hand more readily to take food. If the hand is held in the cage the animal will continue its previous activity, even if this involves jumping over the hand. Moreover, if while doing this the hand flicks it smartly in the belly, it will retire for a moment to the back or roof of the cage, but almost immediately resumes its jumping over the hand. If some object, such as an iron bar, is poked into the cage it will retire momentarily to the back, but at once resumes its previous activity and ignores the bar as if it were a part of the cage. Even more striking, it will treat its cage-mate also as it does an inanimate part of the cage, leaping over it, knocking into it, sitting on it, and taking food from its hands. When the cage-mate shows signs of resentment, the other animal will retire momentarily, only to return again at once, and maybe repeat the offending act. All this makes a striking contrast to its own pre-operative behaviour, or to that of a normal animal.

It is difficult to find a single phrase to cover this behaviour : there seems to be, for the time being in the first weeks after operation, a loss of sense of danger, either from animate or inanimate objects. Sensibility and motor power seem unimpaired, and the appropriate stimulus—a flick of the observer's hand or an attack from its cage-mate—induces the appropriate withdrawal promptly. What seems lacking is the normality—particularly in its persistence—of emotional response to animate objects, with the awareness of potential dangers inherent in such objects. Apparent loss of fear, increased tameness, reduction of aggression, repetition of acts likely to provoke unpleasant reactions from cage-mates, would all tend to follow from this. In the jungle such a deficiency would not be consistent with survival of the animal : a fundamental function has for the time being been lost. The change is reminiscent of that noted by Bucy (1941) in animals following bitemporal lobe lesions. Such monkeys would pick up and carry to the mouth such an object as a living snake which would previously have caused a reaction of extreme terror. In discussing this, Bucy quotes Papez' (1937) conception of the " emotional mechanism " consisting of the hypothalamus, the anterior thalamic nuclei, the hippocampus, and the gyrus cinguli. There is also some resemblance to the human lobotomized patient who is still aware of his obsessions or his pains, but is without persistent affective response to them, and the apprehension this would cause.

Few other convincing behaviour changes were noted, for individual differences between one animal and another of the same type, and even between the same animal's performance under slightly changed external conditions, make anything short of a full study of perceptual or learning ability unreliable. With this proviso, in one animal learning ability appeared to be maintained at its expected level post-operatively, and in two others no loss of previous learning was noted. This contrasts with the results of Harlow and Settlage (1948) in monkeys with extensive bilateral removals of areas 8, 9, 10, 11 and 46.

The significance of the observation that two of our animals for a time post-operatively took food directly by the mouth rather than by the hand is obscure. It did not appear to depend on any neurological lesion of hand movement. This " oral approach " was also noted by Bucy (1941) in animals with temporal lobe lesions.

In the very old monkey an extensive bilateral removal of the anterior cingular area produced very little change in behaviour, a result which may be linked with the fact that the animal was at least 10 and possibly 12 years old.

In the single case of unilateral removal, there was some restlessness noted, but in other respects the behaviour differed from that in the bilateral lesions ; the animal remaining aggressive and apprehensive.

Autonomic Changes.—Of autonomic changes, pilo-erection was found in all our monkeys, as previously reported by Smith (1944 ; 1945), Kremer (1947), and Ward (1948a) ; it may be further noted that conspicuous salivation consequent upon emotional stimuli to M.C.G. 5 pre-operatively, ceased post-operatively only to reappear six weeks later.

Conclusions.—Although the lesions involved more than area 24, they all occupied only a relatively small portion of the medial surface of the frontal lobe. A tentative correlation of these limited lesions with the striking behaviour changes noted seems justified by the histological findings ; but, as has already been pointed out in the case histories, all behaviour changes, even such marked features as restlessness and tameness, slowly subsided, and disappeared completely in the longest survivor (M.C.G. 9) after three months. It seems that the cortical lesions have only a temporary effect on the animals, and some compensatory mechanism restores their pre-operative behaviour pattern.

Such marked behaviour changes, especially in emotional reaction to external environment, following so relatively limited a lesion of the cortex, have implications for the therapeutic operations on the frontal lobe at present used in psychiatry. The brevity of the changes noted in our animals may also be relevant, for the results of operation in man may be similarly short-lived, but still allow other psychiatric treatment to be effectively applied during the early post-operative period.

Summary

Lesions of the anterior cingular gyrus (area 24), with varying involvement of neighbouring areas, but still comprising a limited lesion of the medial frontal surface of the hemisphere, were made in five rhesus and two cebus monkeys : one was unilateral, the remainder bilateral.

The animals were subsequently observed for two to 14 weeks. Behaviour changes noted by other workers were confirmed. In all but two, a very old monkey with bilateral lesions, and the monkey with a unilateral lesion, there was an increased tameness and reduction of aggressiveness, with apparent loss of the sense of danger. These changes tended to disappear after a few weeks. Continual restless pacing occurred in three animals and also gradually subsided after two weeks.

Fibre connexions of the anterior part of area 24 could be demonstrated by the Marchi method into areas 6, 8, 9, 10, and 29, and into the anterior border of area 4. Most of these areas also send fibres back into the cingular cortex. From the posterior part fibres pass into the anterior nucleus of the thalamus.

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