THE SIGNIFICANCE OF HYPERKINESIS IN LESIONS OF THE ANTERIOR STRIATUM IN RHESUS MACACUS

BY

ERIC TURNER

From Queen Elizabeth Hospital, Birmingham

In the course of an investigation into respiratory control by cerebral structures (Turner, 1954), a comparison was made between the levels of kinesis shown by four animals with lesions in the anterior striatum and other animals with lesions elsewhere or with no lesions. It was found that the animals which had lesions in the anterior striatum were significantly hyperkinetic after operation (Figs. 1 and 2).

Further study of these four animals was directed towards elucidation of the neurophysiological mechanisms involved in the hyperkinesis they showed. Augmented forward progression in the monkey has been described by Ruch and Shenkin (1943), by Mettler and Mettler (1942), and by Mettler (1945). In the monkeys described here it took the form of long-continued, methodical pacing of the floor of the cage. The stereotyped pattern of the path covered depended on the shape of the cage, but since this was usually a long, narrow rectangle, the path was usually from end to end, the turns at the end being made in either direction indiscriminately. In addition, especially in the immediate post-operative period, the animals climbed up the walls of the cage, and bored their heads on the roof. One animal burst open its wound by doing this, and died of meningitis. Thereafter, the roof of the cage was made plain, not meshed, and no further injury occurred.

Hyperkinesis has been described from injury to various cortical areas in the frontal lobe, but Richter and Hines (1938) showed that the factor which consistently produced a gross increase in kinesis was damage to the anterior end of the caudate nucleus and putamen. Davis (1951) pointed out that such damage might be the result of impairment of the vascular supply, especially in relation to the orbital gyri. He also emphasized that special methods of recording the increased number of movements should be employed, and the reason for this necessity will emerge from the present study. Davis's recording apparatus has been previously described (Davis, 1951; Turner, 1954).

In an attempt to find out what factors might increase or decrease the hyperkinesis in these animals, they were studied under various conditions. The movements made in each hour of the 24 were separately recorded; the effects of light and of darkness, of time, of stimuli releasing previously taught conditioned reactions, of specific visual and auditory stimuli, and of anoxia were recorded. On the postulate that the kinesis was reflex in nature certain sensory modalities were selectively cut off—somaesthetic impulses in one animal, vision in another. The anatomical structures damaged were tabulated from serial sections, and the physiological results compared with the tables. All the animals were observed and examined for neurological abnormality before and after operation.

Experimental

Caudate 1.—A healthy, normal animal of 3 kg. was operated upon under "nembutal" anaesthesia in the stereotaxic apparatus. Lesions were made on each side within the estimated shape of the head of the caudate inside the dimensions: A 20, L 9 → 2, H + 4 → + 14, and A 18, L 9 → 2, H + 5 → + 15.

At the end of the application of these massive lesions the brain swelled considerably, and gas escaped from the puncture holes. While the destructive current was being passed, the animal breathed rapidly and audibly and movements of the legs were noted.

Four hours after the operation the animal was seen to be climbing up the walls of the cage, repeatedly being jolted to a halt by his head encountering the roof. This movement was performed over and over again. He was ataxic in his movements.

Next day it was noted that he was drowsy, and that he frequently showed periods resembling states of catalepsy from which he would start into sudden activity, during which he screamed and evinced myoclonic jerks, particularly of the shoulder girdles. Anything put near him he would grasp and hang on to for a prolonged period of time.

During the next four days he hung for long periods on to the bars of the cage, so much so that he did not feed himself though he bit voraciously at food advanced towards his mouth. This food he might hold in the mouth for some minutes before chewing and swallowing

FIG. 1.—Records of pre- and post-operative measurements in three animals with lesions in the heads of the caudate nuclei. "Kinesis" is in numbers of movements per hour, weight in kg., "ceiling" the simulated height (in thousands of feet) at which the animal failed to perform a conditioned reaction.

FIG. 2.—Similar records in two animals in which other lesions were performed.

it. He failed to turn his eyes to the left side, though he occasionally lunged towards food held in his left visual field. Frequently he would go into a state of immobility, all four extremities grasping the bars on the floor of his cage, his head lowered in a brooding fashion. At these times the eyes were kept open, but the pupils were contracted, and the eyes rolled upwards and laterally. The attacks lasted about 30 seconds. Between the attacks, which resembled catalepsy, there was slight increase in tone in all limbs, while extensors of the wrist and fingers showed slight cog-wheel rigidity. Tendon jerks were equal, and righting and placing reactions were present, though slow. Anti-gravity responses were present, but when the animal was raised again the digits did not flex. There was a vigorous grasp reflex to cutaneous and stretch stimuli.

Six days after the operation he began to pace about the floor of the cage, but still did not take both hands

off the floor to eat. He had difficulty in backing away either from food when he had bitten it, or in order to get at food that was below him or behind him. This he would vainly try to reach by craning his neck.

Three months later he had lost the myoclonic jerks, and was thought to be normally aggressive. With constant exercise he had become very muscular. Grasp was still easily elicited in the upper limbs, and he still bit repeatedly on any object put near his mouth however unenticing this was. He readily distinguished between food and ironmongery presented in a tray.

Caudate 2.—This normal animal of 2.2 kg. was operated upon in the stereotaxic apparatus. A lesion was placed by electrolysis in the head of the left caudate nucleus in the estimated outline of the nucleus between the co-ordinates A 19, L 9 → 2, H + 4.5 → + 14.5. The animal was not disturbed by the operation, and apart

from a habit of climbing to the top of the cage, showed no gross abnormality. Neurological examination showed it to be a normally aggressive animal without abnormality of tone, sensation, reflexes, or response to presentation of mixed objects. It was killed six weeks after the operation.

Caudate 3.—A normal animal of 2.3 kg. had lesions directed bilaterally at the heads of the caudate nuclei between the same co-ordinates as Caudate 2. During the post-operative period, he climbed consistently to the top of the cage, showed a moderately vigorous grasp reflex, and a more marked tendency to bite any object, including inanimate ones. These tendencies remained to some degree until the animal was killed two months later. Myoclonic jerks occurred only rarely in the neck muscles. When presented with a collection of peanuts and ironmongery he grabbed the nearest object irrespective of its nature. The nuts he peeled and ate, the other objects he rejected—but would pick up again and again and bite. There was no other neurological abnormality.

Caudate 4.—One further bilateral caudate animal was operated upon. It bored its head so persistently on the cage that it burst open the wound, contracted meningitis, and died 19 days after operation. During the post-operative period he showed myoclonic jerks of the shoulders and neck, and also periods resembling catalepsy. The sensory systems appeared to be normal.

Tests for Kinesis

These animals were examined in certain special ways. The number of bodily movements per hour was measured in the fashion described in a previous article (Turner, 1954). Comparison of the records before and after operation showed that they had become hyperkinetic. Tests of their resistance to anoxia in a low-pressure chamber showed that as a group they did not have any gross change in resistance (see Fig. 1). The animal with the unilateral lesion was considerably less hyperkinetic than those with bilateral lesions.

Several special investigations were performed in order to try to determine if any factors would increase or decrease kinesis. Observations over 24 hours showed that Caudate 1 had diminished numbers of movements from 6 p.m. when lights were turned out until 1 a.m. when it apparently slept until 9 a.m. For two hours it performed a few movements. Lights were turned on at 11 a.m. and it then showed a greatly increased number of movements during the rest of the day.

The numbers of movements per hour from 6 p.m. until 5 p.m. next day were: 23, 47, 33, 8, 7, 17, 14, 6, 0, 0, 0, 0, 2, 0, 5, 28, 804, 1031, 919, 992, 1036, 1024, 1036.

The unilateral caudate (Caudate 2) showed the following numbers of movements from 5 p.m.: 230, 540, 292 (lights out), 0, 0, 0, 0, 0, 2, 2, 1, 6, 0, 11, 17, 38 (lights on), 127, 175, 168, 154, 69, 187, 0, 211, 241, 226.

Caudate 3 had the following movements from 10 a.m.: 945, 1217, 1053, 1112, 1063, 976, 978, 1019 (fed), 672, 639, (lights out), 168, 14, 1, 2, 4, 5, 3, 19, 30, 0, 11, 1, 293, 581, (lights on), 565, 293, 360, 137, 169.

It would appear that the animals kept still during normal hours of sleep, and that the presence or absence of light was not the decisive factor in determining the kinesis of the animal. This corresponds with the findings in other animals used as controls.

Caudate 1 was tested in a cage in the flying chamber. This allowed the animal to be watched while the observer could be unseen or seen as he chose. Various stimuli were applied and the effect on the pacing was observed. The animal had been trained to move and stay away from a bell at one end of the cage, and from a buzzer at the other. Now these sounds cut down the number of excursions from one end of the cage to the other from 371 per hour to 207. When the bell was supplemented by a mild electric shock at the same end of the cage the number of journeys fell to 27 per hour. These stimuli were not applied, but the observer was made visible through a window at one end of the flying chamber. The numbers of peregrinations during two hours were 0 and 4 respectively.

Next day the number of movements per hour was 659, and three days later, the number of journeys, in the absence of any extraneous stimuli, was 1,453 per hour. The effect of stimuli diminished in time, but always the most potent was the sight of the observer, while the effect of the other stimuli quickly became negligible. Clearly a visual stimulus was the most potent of those tried.

The presence or absence of bars on the floor of the cage had no profound effect on the kinesis, though bars seemed to diminish the numbers of movements to some extent. Though this animal had an easily elicited "grasp reflex" it did not, therefore, prevent the animal from pacing.

Caudate 2 was tested in complete darkness, and the average number of movements fell from 218 per hour to 67, 63, and 62 on three separate days.

Caudate 1 had the spinal dorsal columns cut at cervical 3-4 level. The numbers of movements per hour fell temporarily to 424, but by the twelfth post-operative day had risen again to 1,060. It seemed that crude proprioceptive sensation together with vision was sufficient to maintain pacing.

During tests of resistance to anoxia it was noticed that the animals performed the conditioned reaction more consistently when they were slowed down by anoxia. At normal levels of oxygenation, their pacing activity interfered seriously with their performance.

Stimulation by Indwelling Electrodes

One animal had an indwelling electrode placed in the head of the caudate (Fig. 3) by the method of Delgado (1952). Stimulation of the unanaesthetized animal (1 m.sec., 65/sec., 4 V) resulted in a constant pattern of movement. The animal held its body erect, its head thrown back. The upper limbs were still, each arm held flexed at the elbow, the hand upwards towards the head, in the position of benediction. The legs performed an alternating movement like the stamping dances of African negroes. One leg was lifted up, bent at the knee, the other was stamped downwards. These movements of the legs were alternated on the two sides in

FIG. 3.—Track of indwelling electrode in head of caudate nucleus. Bipolar stimulation was used between the tip and a point 2 mm. above the tip. The internal capsule is not encroached upon by the track.

FIG. 4.—The greatest dimensions of the lesions in "Caudate 1". For full description see text.

FIG. 5.—A single lesion is present on the left side in "Caudate 2".

rhythmic fashion. In contrast to the progression seen in lesions of the head of the caudate, these movements seen on stimulation of the same region bore the appearance of recoil or retrogression. The movements were so unusual that they were spoken of in the protocols as the "caudate dance", and could be readily recognized. The animal did not stop breathing.

Anatomy

Dr. Turner McLardy has kindly furnished anatomical details of the lesions as shown in serial sections of the brains cut transversely in the plane perpendicular to Reid's base line and stained for nerve cells and fibres.

Caudate 1 (Fig. 4).—"The electrode entry tracks have become confluent in each hemisphere in an inverted cone of sterile cystic necrosis, replacing the medial half of the cortex and white matter of the dorsal frontal gyrus (which is mainly agranular and dysgranular in cytoarchitecture around the margins of the lesion, Betz cells occurring only at the caudal extremity), and the whole

of the cortex and white matter of the cingulate gyrus, from the level of the rostral tip of the corpus callosum to the level of the rostral tip of the anterior commissure. The corpus callosum on each side is penetrated over a slightly less extensive area. The cingulum and the subcallosal fasciculus are completely transected bilaterally. The electrode tip lesions are likewise almost symmetrical. On each side destruction of caudate nucleus amounts to roughly the middle antero-posterior third of its head (if the body of the caudate be defined as beginning at the level of the rostral tip of the anterior commissure in the midline), practically all fibres within the adjacent anterior limb of the internal capsule are cut and the dorsal septal nucleus is gone, whilst in the region of the ventral angle of the anterior horn of the lateral ventricle the dorsal half of the fundus striati is destroyed, together with an adjacent mesial segment of the putamen and lateral portion of the nucleus accumbens and of the lateral septal nucleus. In the left hemisphere the lesion continues ventro-posteriorly through the rostral-most tip of the globus pallidus, the antero-ventral margin of the

FIG. 6.—Bilateral lesions in the heads of the caudate nucleus in “Caudate 3”. The section on the left is stained by Nissl's method, that on the right for myelin. This figure is reproduced from *Brain* (77), by courtesy of the Editor.

anterior commissure, and the subcommissural fibres of the internal capsule, to terminate in the lateral pre-optic area. In the right hemisphere the lesion continues slightly more medially and ventrally, destroying the whole of the nucleus accumbens and the whole of the fundus striati dorsal to the olfactory trigone.

Caudate 2 (Fig. 5).—“The right hemisphere displays no pathological or experimental primary lesion. In the left hemisphere the electrode tracks cause only minimal transit damage to cortex and white matter of the dorsal frontal gyrus but cut the cingulum partially and the subcallosal fasciculus completely. The electrolytic lesion destroys the lateral third of the substance of the caudate nucleus at the level where the cross-sectional area of the head is greatest and cuts all fibres in the anterior limb of the internal capsule. Keeping just lateral to the ventral angle of the anterior horn it then destroys the whole of the fundus striati and an adjacent mesial segment of the putamen to reach the pia mater of the orbital prepyriform cortex just posterior to the lateral olfactory stria and just medial to the main antero-lateral ganglionic vessels. A ventral portion of the lateral medullary lamina of the lentiform nucleus is damaged, most of the fibres of the diagonal band are cut and a small focus of softening is apparent in adjacent temporal prepyriform cortex. The caudal extremity of the lesion terminates in the substance of the anterior commissure under the putamen and in the underlying lateral pre-optic area. Softening spreads laterally along the anterior commissure for a short distance into temporal white matter.”

Caudate 3 (Fig. 6).—“Throughout the levels of the

entry tracks in each hemisphere about half of the total digital white matter of the dorsal frontal white matter is destroyed. On the left side there is in addition destruction of the central one-third of the summit (cytoarchitecturally premotor) cortex of this region of the gyrus. The cingulum is cut bilaterally. On each side the electrolytic lesion is centred just below the dorsolateral wing of the anterior horn of the lateral ventricle, destroying, from the level of the rostral tip of the corpus callosum to mid-septal levels, the ventral half of the corpus callosum, the subcallosal fasciculus, and the dorsal two-thirds of the head of the caudate nucleus. On the right side about three-quarters of the fibres in the anterior limb of the internal capsule are cut, whilst on the left side almost the whole of these fibres are cut and a dorso-medial segment of the putamen is destroyed. On both sides the lesion terminates in the centre of the posterior end of the head of the caudate at the level of the rostral tip of the anterior commissure of the midline.”

Caudate 4.—“This brain (Fig. 7) displays evidence of acute meningitis and precise definition of the original experimental lesions is further complicated by softenings due to damage to ganglionic vessels in each hemisphere. The right entry tracks are clean but cut the cingulum; the left ones are broadened by necrosis, spare the cingulum, but open dorsally into a necrosed cone of premotor cortex. The corpus callosum is not heavily damaged. Structures which appear to have been bilaterally severely damaged by the electrolysis itself are the subcallosal fasciculus, the posterior half of the head of the caudate nucleus, all fibres of the anterior limb of the internal

FIG. 7.—Lesions in "Caudate 4". This animal had died of meningitis: see text.

capsule, a medial segment of the putamen, the whole of the fundus striati, orbital prepyriform cortex, the lateral olfactory stria, elements of the anterolateral ganglionic blood vessels, the lateral half of the nucleus of the diagonal band and all fibres connected with it laterally, the rostral-most tip of the globus pallidus, the anterior commissure, and the lateral pre-optic area. Subsequent softening has occurred in both hemispheres up the lateral medullary lamina of the lentiform nucleus and within the amygdaloid nuclear complex, in the rostral tip of the left putamen, and in the dorsum of the genu of the right internal capsule."

Discussion

The anatomical damage common to the various animals in this study is destruction to the head of the caudate nucleus, with damage to the cortex in the parasagittal region that varies between a needle puncture and gross destruction. The functional change common to all of them is locomotor hyperactivity in the form of persistent forward progression. The results of investigations into factors that might diminish or increase the already augmented progression suggest that this is still influenced by

somaesthetic and particularly by visual stimuli. The sensory impulses necessary for the exhibition of the progression have not been elucidated, but probably also include proprioceptive and/or visual stimuli. Lesions in the posterior columns of the cervical cord did not significantly reduce it. The inhibition caused by the auditory stimuli associated with a conditioned reaction was not in the ordinary way sufficient to stop the augmented progression, but when the animal was rendered anoxic in a low-pressure chamber in the course of another test the conditioned stimulus was then obeyed.

When results of stimulation of the caudate head are compared with those of lesions in this region they suggest that retrogression is favoured and progression is inhibited by some cerebral system which included the anterior caudate and fundus striati. It would be interesting if the reverse were true and progression were favoured by other parts of the caudate nucleus, but there is so far no information on this point. (One animal with tiny lesions in the tail of the caudate was placid, but showed no tendency to retrogression.)

Certain other physiological changes were seen, and may have borne a significant relationship to anatomical findings, but the number of animals is small and the results are accordingly uncertain. It has been suggested (Mettler, Ades, Lipman, and Culler, 1939; Denny-Brown, 1950; and Denny-Brown and Botterell, 1948) that the head of the caudate nucleus is involved in inhibition of "cortical automatisms" of which grasp and biting reflexes are examples. In the animal (Caudate 3) with lesions most completely confined to the head of the caudate there were definite but mild increases in grasping and biting. The animal, however, which showed the greatest increase in grasp and biting reflexes also showed the greatest amount of damage to the cortex (in the superior frontal gyrus), as well as damage to the head of the caudate and the fundus striati.

States of catalepsy in the immediate post-operative stage seemed to be associated with a tendency towards the appearance of myoclonic jerks of the neck and shoulder girdles. The anatomical damage in the two animals showing these features was extensive in the superior frontal cortex, the head of the caudate, and the fundus striati bilaterally. One animal with unilateral damage to the fundus striati (Caudate 2) did not show either feature. It seems likely that the important lesion was bilateral damage to the fundus striati and anterior portion of the globus pallidus.

Summary

Investigation of four rhesus monkeys with lesions in the head of the caudate nucleus showed that this was a crucial factor in determining augmented progression. A fifth animal with an implanted electrode in the caudate head showed characteristic rhythmic movements of a retrogressive type when the part was stimulated in the unanaesthetized state. Comparison with animals with lesions in

other parts showed that augmented progression was not a general feature of brain damage.

There was also an augmentation of grasping and biting reflexes in certain animals in the series. There was no significant change in resistance to anoxia in the group. The significance of the findings has been discussed in relation to the details of the damage in the animals as shown in serial sections.

It is suggested that certain inhibitory effects on the various movements which are augmented had depended on the integrity of the heads of the caudate nuclei, and that these effects may be concerned with active contrary movements, *e.g.*, retrogression instead of progression. Other inhibitory influences are still present, notably visual ones. No effects on respiratory function have been noted.

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