Athetoid and Choreiform Hyperkinesias Produced by Caudate Lesions in the Cat

Abstract. *Small, unilateral lesions, which damage exclusively the anteroventral region of the caudate nucleus of the cat, produce a stable and permanent behavioral change resembling human athetoid and choreiform hyperkinesias. These symptoms are not seen after generalized destruction of the caudate nucleus.*

Clinicopathologic data have for many years pointed to the frequent association between athetoid and choreiform hyperkinesias and lesions in the striatum (caudate nucleus and putamen) (*1*). A major obstacle to understanding the nature of these complex disorders has been the inability to reproduce any but evanescent manifestations of these symptoms by striatal lesions in lower animals (*2*).

In acute stimulation experiments (*3*), we have demonstrated that the anteroventral area of the caudate nucleus can exert an inhibitory influence on motor cortex activity. The limits of this region are shown in Fig. 1A. Adjacent regions of the caudate are purely facilitatory to motor cortex function.

These results suggested the possibility that lesions restricted to one of these areas might produce changes in motor behavior by bringing about an imbalance between inhibitory and facilitatory influences. If true, this would reveal a situation in which damage to a specific portion of an neural structure would produce symptoms not seen with larger, indiscriminate lesions of the structure in which the imbalance of opposing influences would not occur.

As a test of this hypothesis, we attempted to place electrolytic lesions within the "inhibitory" area, using a stereotaxically directed electrode. This was done in 12 adult cats which had been observed preoperatively for a period of 7 to 14 days. At the time of operation we were certain that each animal was free of neurological defects and unusual patterns of motor behavior. Postoperative observations continued for 4 to 9 months (*4*).

Six of the animals (cats 2, 5, 8, 9, 10, and 12) did not develop athetoid or choreiform movements postoperatively. Most of these cats showed adversive turning or circling movements during the first postoperative week, symptoms attributed to unilateral caudate injury by previous workers. Other symptoms included permanent loss or depression of the nonvisual placing and hopping reactions and also a mild, transient hypertonia in the contralateral limbs.

Three animals in this series (cats 1, 4, and 7), however, developed abnormal movements of the forelimbs, representing a permanent change in their basic behavior. These cats also showed the mild, transient hypertonia, but none of the other symptoms of the previous group. The hyperkinesias, which were both athetoid and choreiform in character, first appeared on the second or third postoperative day and were fully developed after 1 week.

The movements which we have termed athetoid consisted of incessant, alternating flexion and extension movements of the toes and paws of each

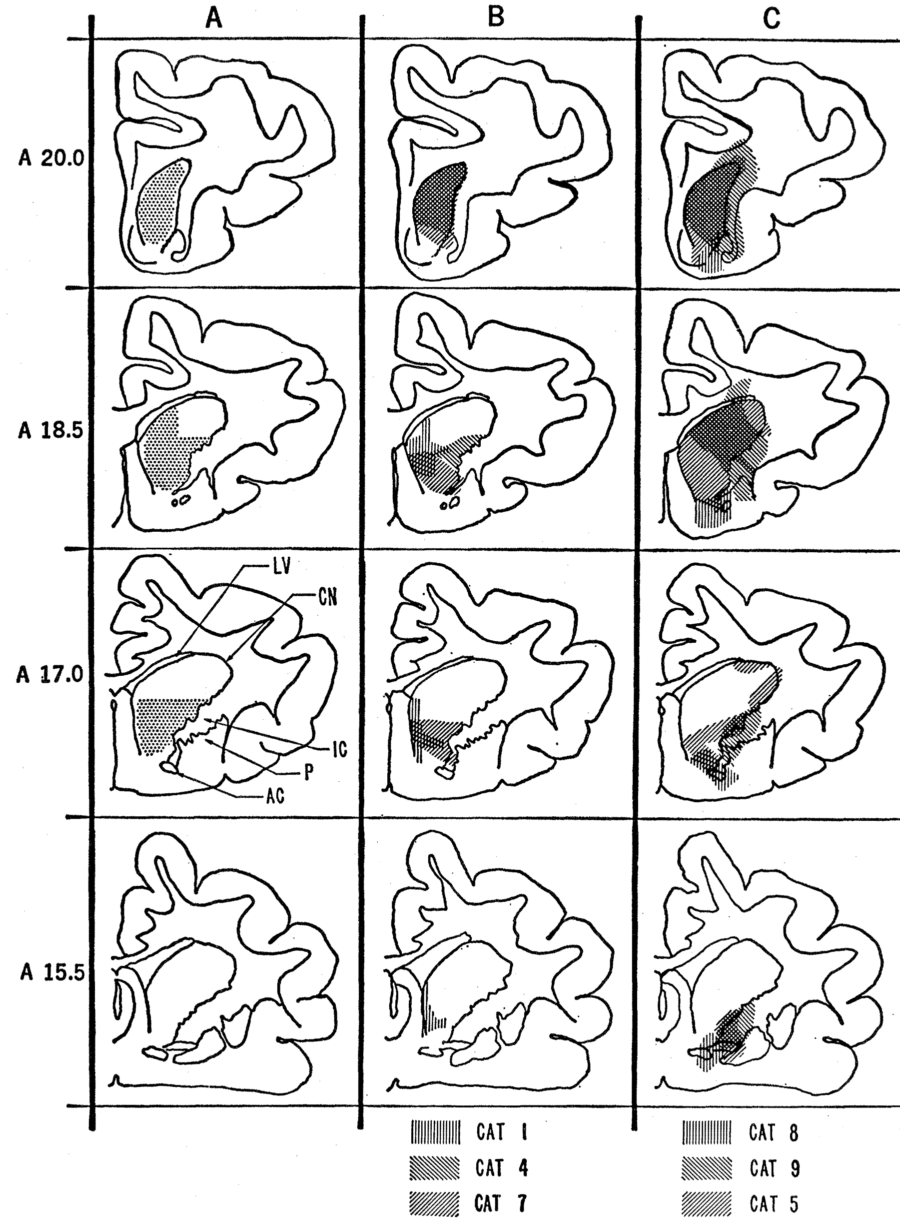

Fig. 1. Trace drawings of coronal sections at different levels of the cat brain. Numbers in left margin designate the level of section in Horsley-Clarke coordinates. (A) Extent of "inhibitory" region of caudate is indicated by dots. The "faciliatory" region occupied most of the unmarked regions of the caudate (*3*); *LV*, lateral ventricle; *CN*, caudate nucleus; *IC*, internal capsule; *P*, putamen; *AC*, anterior commissure. (B) Reconstruction of the lesions in the three cats that developed athetoid and choreiform movements. (C) Lesions in three of the animals that did not show athetoid or choreiform movements.

forelimb. Most of the time, the flexion-extension activity also alternated from one forelimb to the other, although occasionally the movements were repeated several times in one forelimb (usually that contralateral to the lesion). When the cats were in an upright position, each forefoot was lifted alternately from the floor and then replaced at a rate of 7 to 15 times per minute. The degree of flexion and hyperextension of the toes varied from time to time, usually inversely with the momentary frequency of the movements. Occasionally, a forepaw was held off the floor for several seconds, during which two or more cycles of flexion and extension movements occurred. When the animals lay on their sides, the intensity of the athetoid movements was greater, with hyperextension of the toes becoming particularly conspicuous. The movements also took on a writhing appearance in this posture. Figure 2A illustrates one cycle of the athetoid movements in cat 4. At the point in the film from which these frames were taken, the cat had been lying in this position for a couple of minutes with her eyelids shut. She appeared to be drifting into sleep, and the athetoid movements ceased shortly after this sequence. This was a characteristic occurrence in all three animals, and emphasizes the incessant and involuntary nature of these movements.

Cat fanciers have long been aware of the movement pattern which we have termed "athetoid," and refer to this behavior as "ecstatic kneading" (5). This name correctly indicates that such movements occur in a normal cat as an expression of actual or impending pleasure (for example, the presentation of food, or caressing). The three cats in this study showed these movements at all times, except during locomotion and when asleep. Preoperatively, these animals rarely displayed this behavior.

In cat 1, the frequency of the athetoid movements was high during the first postoperative month, but declined to about one-third the initial number per minute during the next 4 months. In cats 4 and 7, the movements were maintained at a constant rate throughout the postoperative observation period (8 and 7 months, respectively).

Cats 4 and 7 (but not cat 1) also exhibited movements which we feel are most appropriately called choreiform. These were a series of abrupt, gross, irregular movements involving the entire forelimb ipsilateral to the lesion. These movements appeared as episodes one to four times per minute and usually lasted from 2 to 4 seconds. At no time could we detect any type of eliciting stimulus for this activity. An example of a brief episode is shown in Fig. 2B. The frames are about 1/5 second apart. The cat is still watching the observer in frame 3, and "notices" the spontaneously raised paw only in frame 4. She then proceeds to lick it (frames 5 and 6). This reaction is strikingly similar to the behavior many neurologists have seen in chorea patients. Such an individual will frequently attempt to pretend that his motions are really voluntary. Thus, when his disease raises his hand involuntarily, he will, upon becoming aware that this has happened, use the hand voluntarily to scratch his head or rub his nose.

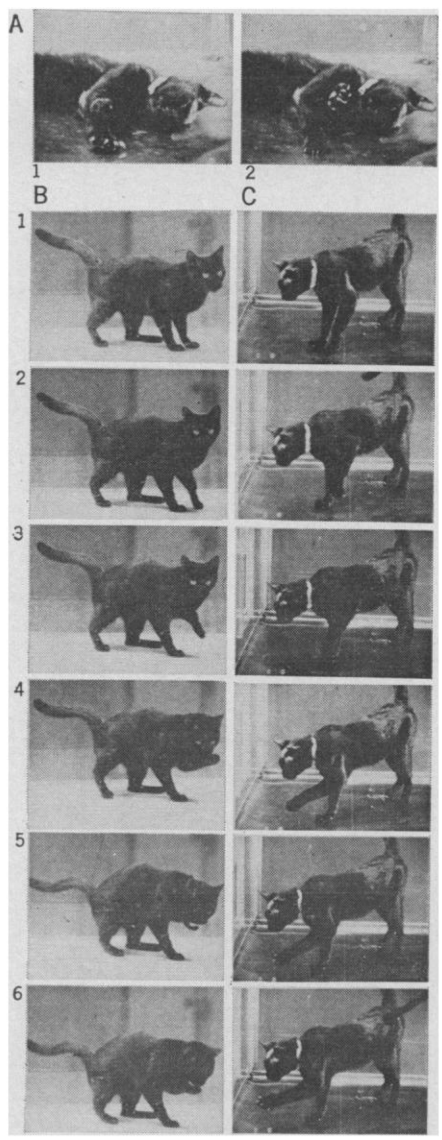

Fig. 2. Sequences from motion-picture records of cat 4. (A) Frames 2 seconds apart, taken 5 days postoperatively. (B) Three months postoperatively; frames are about 1/5 second apart. (C) Ten days postoperatively; frames are 1/4 second apart. This choreiform episode continued for 3 seconds after frame 6.

The beginning of a prolonged choreiform episode is shown in Fig. 2C. Note the unusual retraction of the shoulder in frame 1. These longer episodes typically involved spreading of the toes and extension of the claws, as seen in frames 5 and 6.

Autopsy included gross and microscopic examination of sections cut from the brains of each of the cats. Reconstructions of the lesions found in the three animals which developed athetoid and choreiform movements are shown in Fig. 1B. Note that damage is almost exclusively restricted to the "inhibitory" region of the caudate shown in Fig. 1A. The lesion in cat 1 damaged significantly less of the "inhibitory" region than the lesions in cats 4 and 7, and the former also extended slightly posteriorly into the "facilitatory" area of the caudate. We think this may explain both the diminution of the athetoid movements and the lack of choreiform activity in this animal.

The lesions of three of the group of six cats that did not show athetoid or choreiform movements are shown in Fig. 1C. In cats 5 and 9 the lesions significantly damaged the inhibitory region of the caudate, but equal or greater damage was incurred in the dorsoposterior "facilitatory" region of the caudate or the internal capsule. An exception to this pattern was cat 8, in which the lesion was small and centered mainly in the basal forebrain area, leaving the caudate virtually intact. This animal did not show adversive or circling movements, but placing reactions were depressed.

We therefore feel that these results strongly support our initial premise. There is a positive correlation between damage limited to the "inhibitory" area of the caudate and the appearance of unique motor symptoms. Future exploration of the "facilitatory" area of the caudate is needed to expand our knowledge of the nature of these interactions.

A second fundamental significance of this study is the introduction of an experimentally reproducible "animal model" showing permanent athetoid and choreiform hyperkinesias, produced by lesions of structures commonly damaged when these symptoms appear in man.

This may be of practical value in the study of specific drug and surgical treatments.

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References and Notes

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2. E. G. T. Liddell and C. G. Phillips, *Brain* **63**, 264 (1940); F. A. Mettler and C. C. Mettler, *ibid.* **65**, 242 (1942); G. D. Davis, *Neurology* **8**, 135 (1958); F. A. Mettler, *Trans. Amer. Neurol. Ass.* **91**, 304 (1966).
3. S. L. Liles and G. D. Davis, *Fed. Proc.* **27**, 387 (1968).
4. Three animals were discarded from this series. One developed pneumonia postoperatively, another had a totally misplaced lesion, and one cat's cerebral cortex was noted to be grossly malformed at autopsy.
5. H. A. Smith, *Rhubarb* (Doubleday, New York, 1946), pp. 149–151.
6. A more extensive account of this work will be published by the NIH in the proceedings of a workshop on Psychotropic Drugs and Dysfunctions of the Basal Ganglia, which was held 31 October to 2 November 1968 in Bethesda, Md
7. S.L.L. was an NIH predoctoral fellow (5-F1-GM-28, 258–04) during this work, which represents part of the research toward his Ph.D.

9 December 1968

The "Co-" in Coevolution

In a report describing the selective pressure of grazing by butterfly larvae on flowering time of *Lupinus amplus* through control of seed production, Breedlove and Ehrlich (*1*) introduced the quite correct but largely irrelevant information that "also discounted is the primary role of plant biochemicals as herbivore poisons." In this connection they quoted me, again quite correctly, as considering the toxic compounds of plants to be "primarily metabolic wastes." I appreciate their publicizing my viewpoint on this basic evolutionary question, but I feel that the isolation of this reference in a report on a subject so slightly related must necessarily have left most readers wondering why it was included at all.

Opposing viewpoints have developed largely as a consequence of the antecedent interests of the proponents of each. Students of plant-animal interactions have been greatly impressed by the impact of animals upon plant evolution. Students of plant evolution have been equally impressed by the influence of the total environment upon the diversification of plants. Many have failed to give full consideration to the inherent qualities of evolving plant systems as these determine the limits of potential plant evolution. Thus, Ehrlich (*2*) has expressed the view that selective pressure of animal depredation has determined the qualities of chemical production by plants, focusing his attention particularly upon those plant products which repel animals and relieve from animal depredation the plants that produce them. In expressing this view, furthermore, he has rejected my position that these, as well as the toxic products of plants that inhibit potential competing plants, are "primarily metabolic wastes." In this difference of opinion he expresses the common view of a large number of students of coevolution (of plant and animal species pairs) whereas my view is shared by many students of allelopathy (biochemical inhibition) among plants.

In allelopathic studies it is commonplace to encounter clear evidence of autointoxication traceable to the accumulation of toxic products released into the plants' own environment. The "fairy ring" effect of mushrooms is reflected in the behavior of *Helianthus rigidus, Hieracium pilosella, Salvia leucophylla, Artemisia californica*, and numerous other plants which inhibit chemically the growth of adjacent species but eventually suffer similar suppression when their chemical products become too concentrated in the environment (*3*). Were these toxic products to be retained in the protoplasm that produces them, the effects would be even more spectacular. It is therefore clear that excretion of these toxins by any means whatever is of immediate benefit to the plant that produces them. Such elimination may involve volatilization of terpenes in arid climates (*4*), leaching of phenols in humid climates (*5*), isolation in deciduous organs, or being rendered innocuous by chemical bonding as in the formation of glycosides. In any event, the primary result (in the sense of the first or most immediate) is relief from the deleterious consequence of autointoxication. There has been reported no respiring system, either plant or animal, that can long sustain its metabolic activity without production of some noxious products. Such metabolic inefficiency is esthetically difficult for most biologists to accept, but this fails to alter the facts.

The retention of some toxic plant products is made possible by their isolation within the plant body or by temporary blockage of their toxic potential through chemical bonding. Plant tissues laced with such materials are often rendered immune to attack by animals or infection by pathogens to which these compounds are toxic. Such protection constitutes a secondary benefit (in the dual sense of arising later in evolutionary time and of being less immediate a necessity to survival). However, the advantage thus attained may well be the basis of selective pressure resulting in the development of high concentrations of protective toxins, providing that these are so contained as to render them innocuous to the tissues that produce them. The secondary or protective role of these toxins may well be their principal role in the present ecology of a particular species. They remain, however, primarily metabolic wastes capable of destroying the system that produces them unless they are loosed into the environment or sequestered harmlessly within the plant.

It is clear that failure to make the distinction between *primary* and *principal* might easily cloud our understanding of the origin and functions of plant-produced toxins. To regard such plant products as primarily animal toxins renders impossible the explanation of how these products came to be. Associated animals are possessed of no mechanism by means of which they can call forth *de novo* the evolution of a specific metabolic mechanism in plants. To credit them with this role in the absence of such a mechanism constitutes a teleological (almost mystical) explanation which I am sure Breedlove and Ehrlich did not intend. If, however, a plant species has several alternative and simultaneous metabolic pathways already in operation, producing varying quantities of the numerous by-products characteristic of plants, selective pressure might well increase the proportion of one of these. Thus, the toxicity to animals of these metabolic wastes, no matter how important eventually, is subsequent and secondary to their elimination from protoplasm. No useful purpose is served by simplifying this explanation beyond the limits of reality.

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