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Delayed Alternation in Hemicerebrectomized Monkeys

Abstract. Monkeys subjected to extensive unilateral brain extirpation learned a delayed alternation task, although their rates of learning were significantly lower than those of a control group of normal animals. Visual field defects did not seem to account for the deficit.

It was recently reported that impairment on the delayed alternation task could be ". . . turned on and off . . ." by unilateral electrical stimulation to the sulcus principalis of the monkey brain (*1*). Earlier, deficit on this task had often been reported in monkeys as a result of bilateral damage to brain tissue, specifically the midlateral frontal cortex (*2*). Few studies, however, reported impairment after unilateral lesions (*3*). In each case of unilateral lesion the deficit was temporary, and in none did the animals undergo unilateral extirpations of the brain to the extent of those to be reported here.

Table 1. Number of days to criterion on delayed alternation. The data on delayed alternation performance has been supplemented by scores from another group of hemicerebrectomized monkeys with a similar background, which was not discussed in the text.

Subject No.	Days
Normal group	
126	10
127	17
129	13
130	13
135	20
Mean	14.6
Operated group	
106	31
116	24
121	31
123	42
124	37
Mean	33.0
Other operated animals	
109	54
112	27
113	18
120	27
122	46
Mean	34.4

The surgical procedure, hemicerebrectomy (*4*), involves the unilateral removal of all cerebral structures lateral to the hypothalamus and rostral to the midbrain (Fig. 1). Since a similar but less extensive operation has been applied to the treatment of certain neurological disorders in humans—for example, tumor, infantile hemiplegia, and epilepsy (*5*)—the resulting effects of hemicerebrectomy upon learning and retension abilities of primates are of considerable importance. Consequently, a series of experiments was designed to evaluate the behavior of hemicerebrectomized monkeys. The experiment discussed in this report utilized delayed alternation performance to measure one aspect of learning ability.

The subjects were immature rhesus monkeys, five normal and five hemicerebrectomized, that had received previous training on object-quality discrimination problems. Feeding was scheduled so that the subjects had been deprived of food for about 22 hours at the time of testing and, therefore, were well motivated for the raisin rewards.

An adaptation of the Wisconsin general test apparatus was located in a room in which normal laboratory noises were greatly muffled. The stimuli consisted of a single pair of identical objects (plain, black, wooden blocks, measuring 4¼ by 2¾ by ¾ in.), which covered two food wells that were located about 11½ in. apart in a light gray presentation tray. The wells were baited during a 10-second delay, while the opaque screen was interposed between the subject and objects. To serve as a starting point for the alternation sequence, displacement of either object was rewarded on the first trial, and subsequently 50 more trials were given each day.

The problem required the subject to alternate from a just previously rewarded choice to the object on the other side. By following a noncorrection procedure, a criterion of at least 86 percent correct responses over two consecutive days was used.

Normal animals required significantly fewer days to reach criterion than did the operated subjects (*6*). The latter, in fact, took over twice as long (Table 1). Figure 2 presents graphic data for the course of learning in each group. A pronounced overlap may be noted for the first 4 days, but after that time the curve of the normal group remains higher.

Although homonymous hemianopsia is an expected result of this surgery, the visual field defect did not seem to account for the delayed alternation deficit in these subjects. The animals demonstrated past high performance levels on visual discriminations between two dissimilar objects. Because the possibility existed that the field defect might be related to side preferences, the numbers of both total responses and errors made by each subject to each side were tabulated. In neither case did the operated subjects show a side preference significantly different from that of the normal subjects (*7*).

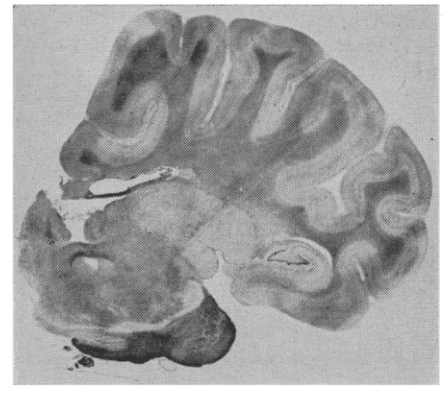

Fig. 1. This section of brain tissue, at about the level of the posterior commissure, is from a hemicerebrectomized monkey. The Kluver and Barrera double stain technique was used.

Even though the hemicerebrectomized group exhibited a level of performance lower than that of the normal group, it is believed more important to stress that the operated monkeys did meet the criterion of learning. This accomplishment emphasizes the observation that, several months after surgery, the hemicerebrectomized monkeys still retained structures necessary to the learning of this task.

The hemicerebrectomized monkey provides a useful preparation in which to study the function of remaining structures with an increased certainty, prior to histology, regarding the bilaterality

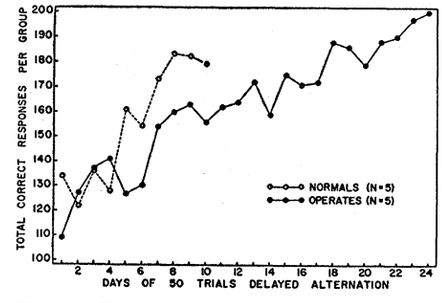

Fig. 2. Total correct responses, summed for each group daily, have been plotted. Totals for only the period during which each group remained intact are shown; that is, before any subject in each group met the criterion.

of subsequent surgical intervention. For example, previous work which has implicated the caudate nucleus with deficit on delayed alternation in the monkey (*8*) could be supplemented by this approach. Since the extensive extirpation permits relatively easy access to some remaining subcortical structures, which are generally difficult to reach, it is believed that this technique can provide a useful tool for further study of the role played by the subcortex in various tasks (*9*).

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7. With the Mann-Whitney U procedure, on left versus right responses a p of 0.075 for total responses and a p of 0.210 for errors were found.
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9. This research has been supported in part by grants from the U.S. Public Health Service and the United Cerebral Palsy Foundation.

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High Incidences of Transmissible Kidney Tumors in Uninoculated Frogs Maintained in a Laboratory

Abstract. Various workers have shown that the Lucké carcinoma, a transmissible kidney tumor of the leopard frog, occurs spontaneously at low incidence (6.7 percent maximum). However, we have consistently observed much higher incidences (50 percent maximum), a finding of probable significance in the epidemiology and natural transmission of the tumor. Age, metabolic level, and cross infection are being investigated as possible factors in determining the tumor incidence.

Kidney tumors of the type described by Lucké (*1*) are occasionally seen in leopard frogs (*Rana pipiens*) collected in the region surrounding Lake Champlain, Vermont. In the only extensive studies of spontaneous incidence, Lucké found tumors in 2.7 percent of newly caught frogs, and in 6.7 percent of uninoculated frogs kept in the laboratory for periods ranging from 6 months to 1 year or more (*2*). However, nine uninoculated groups maintained intermittently by us as controls in tumor transmission studies have in nearly every instance shown much higher incidences of tumors at the end of 6 months (*3*).

All groups are represented in Table 1, which shows that incidences ranging between 20 and 50 percent were observed between the 30th and 41st weeks. One particular group (group 5) was examined in greater detail. Of 87 frogs which survived for 30 weeks or died before that time with kidney tumor, 12 developed palpable tumors. The remaining 75, killed and autopsied at the end of 30 weeks, yielded two small tumors, as confirmed in histological sections, and four cases in which blanched, nodular areas were seen in the kidneys. On section, three were seen to be helminthic in origin, but the fourth was a small, although a typical, case of Lucké tumor.

Finally, normal-appearing kidneys from ten male and ten female frogs were fixed, and center segments representing one-fourth of each pair were sectioned serially. This method was adopted in order to survey the material without the laborious process of sectioning entire kidneys. The conservative assumption was adopted that histologically normal center sections represented normal kidneys. Among the 20 pairs of kidneys so sectioned, two were found which bore microscopic but typical and unmistakable tumor foci. Thus, 17 tumors (20 percent) were found among the original 87 frogs. However, it is estimated, on the basis of the two microscopic tumors found, that five microscopic tumors might have been expected in the remaining 52 pairs of kidneys which were grossly normal in appearance, but which were not sectioned. If so, the total number of tumors present in the group would be 22 or 25 percent.

Table 1 indicates that a considerable increase in the number of tumors is to be expected after 30 weeks. For that reason, the 18 remaining normal-appearing pairs of group 5 kidneys which were sectioned were also scored for the presence of the presumptive tumor transitional changes observed by Duryee (*4, 5*). Such changes were described by him on the basis of abnormal cells which occurred in tumor-bearing kidneys and in kidneys of frogs inoculated with Lucké tumor filtrates.

Of the 20 pairs of kidneys which we scored, four showed advanced tubule changes suggesting borderline neoplasia, while six others showed slight-to-moderate change of the same character. These ten cases consisted of occasional nephrons in which the proximal convoluted portions of the tubules showed nucleolar enlargement, pronounced basophilia, numerous cytoplasmic inclusions of various types, and mitotic figures (see *4*). Similar changes were not seen by us in the kidneys of several dozen frogs killed immediately upon arrival in the laboratory, but the changes were abundantly seen in a majority of cases in which frogs were inoculated with tumor-derived materials and examined histologically at a later date.

On the basis of an assumption, currently being tested, that kidneys bearing nephrons of transitional appearance are destined for neoplasia, it is estimated that of the total group of 87 frogs, 41 percent (36 individuals) either bore kidney tumors (25 percent) or were in preneoplastic condition (16 percent), if only the four advanced cases of transitional change are considered. As shown in Table 1, this figure agrees well with the incidence actually found in groups which were maintained a few weeks longer before their death, and suggests that such kidneys were destined to become grossly neoplastic within about 8 weeks.

When all ten cases with nephrons of the presumed transitional type are considered, it is estimated that 66 percent of the total group (25 percent bearing kidney tumors, plus an additional 41 percent in the transitional state) bore the tumor or were destined to develop tumors. This figure should be compared with Duryee's figure of 56 percent for combined transitions and kidney tumors in frogs inoculated with tumor filtrates and examined after 4 months or less (*4*).

The factors responsible for the observed high incidence of Lucké tumors are not yet known. However, environmental factors related to temperature and metabolic level, to age, and possibly to opportunities for laboratory cross-infection or contamination differed

Table 1. Occurrence of kidney tumors in uninoculated frogs maintained in the laboratory.

Group	Frogs (No.)	Time kept (wk)	Kidney tumors	
			(No.)	(%)
1	10	9	1	10
2	20	11	1	5
3	12	13	3	25
4	20	24	0	0
5	87	30	17	20
6	8	31	2	25
7	10	33	5	50
8	10	39	5	50
9	20	41	7	35
Total	197		41	
Mean		30		21