9. Dopamine β-hydroxylase activities for the lines used in these studies are (per milligram of protein): N1E-115, 88 pmole/min and N-18, 9 pmole/min [M. Goldstein, B. Anagnoste, L. S. Freedman, M. Roffman, K. P. Lele, in *Dynamics of Degeneration and Growth in Neurons*, K. Fuxe, L. Olson, Y. Zotterman, Eds. (Pergamon, Oxford, 1974), p. 99]; N-18, 30 pmole/min [B. Anagnoste, L. S. Freedman, M. Goldstein, J. Broome, K. Fuxe, *Proc. Natl. Acad. Sci. U.S.A.* **69**, 1883 (1972)]; and N18TG2, 140 pmole/min [B. Hamprecht, J. Traber, F. Lamprecht, *FEBS Lett.* **42**, 221 (1974).
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12. Hypoxanthine phosphoribosyltransferase activity was measured in cell extracts by conversion of [^{14}C]hypoxanthine to inosinic acid as identified chromatographically [J. D. Sharp, N. E. Capecchi, M. R. Capecchi, *Proc. Natl. Acad. Sci. U.S.A.* **70**, 3145 (1973)]. Hypoxanthine was used at concentrations below the Michaelis constant (K_m) for this enzyme, as determined by R. M. Wohlhueter [*Eur. J. Cancer* **11**, 463 (1975)] and J. A. McDonald and W. N. Kelley [*Science* **171**, 689 (1971)].
13. Homogenates for MAO and tyrosine hydroxylase assays were prepared from separate subcultures of stationary phase cells [S. H. Wilson, B. K. Schrier, J. L. Farber, E. J. Thompson, R. N. Rosenberg, A. J. Blume, M. W. Nirenberg, *J. Biol. Chem.* **247**, 3159 (1972)] in solutions of 0.1*M* KCl and 0.1*M* $KHPO_4$, *p*H 6.2, respectively. Samples were stored in plastic tubes (NUNC) and sonicated for 30 seconds at maximum setting with a microprobe (Biosonik IV). MAO activity was assayed by conversion of [^{14}C]tryptamine to toluene-soluble indoleacetaldehyde and indoleacetic acid [T. Nagatsu, *Biochemistry of Catecholamines* (University Park Press, Baltimore, 1973), pp. 203–205]. Harmaline (Sigma), a specific inhibitor of MAO [S. Udenfriend, B. Witkop, B. G. Redfield, H. Weissbach, *Biochem. Pharmacol.* **1**, 160 (1958)], completely blocked activity at 10^{-5}*M* in both neuroblastoma cells and fibroblasts. Tyrosine hydroxylase activity was assayed by release of tritiated water from L-[3,5-^{3}H]tyrosine as described [E. Richelson and M. Nirenberg, *Methods Enzymol.* **32B**, 785 (1974)], with the exception that pteridine reductase was omitted from the assays because activity was the same with or without it. Activities of tyrosine hydroxylase and MAO were measured within the range of linearity with respect to time and protein concentrations.
14. Tyrosine hydroxylase activities for N1E-115, NS-20, N-4, and N-18 have been reported as 980, 0, 4 and 2 pmole of product formed per minute per milligram of protein, respectively [T. Amano, E. Richelson, M. Nirenberg, *Proc. Natl. Acad. Sci. U.S.A.* **69**, 258 (1972)]. We have no explanation for the 16-fold lower activity seen here for N1E-115, but presume it results from a higher subculture number of 20 to 30.
15. The cellular metabolism of [^{3}H]dopamine was determined by exposing cultures to it for 30 minutes, extracting washed cells, and identifying labeled metabolites chromatographically by their comigration with authentic standards (*10*). In our study here, we used samples containing 100,000 count/min for the thin-layer chromatograms, which were run in solvent system A (*10*). The following compounds migrate together in system A and cannot be distinguished: 3,4-dihydroxyphenylacetic acid, 3-methoxy-4-hydroxyphenylglycol, and 3-methoxy-4-hydroxymandelic acid.
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Ultrastructure of the Auditory Regions in the Inner Ear of the Lake Whitefish

Abstract. *Hair cell polarization patterns were investigated on the sensory macule of the sacculus and lagena of the lake whitefish. The saccular hair cells are divided into four groups, with all of the cells within a group having the same orientation. Saccular orientations are anterior, posterior, dorsal, and ventral with respect to the axis of the animal. Two groups, one dorsal and one ventral, are found on the lagena. The saccular orientations are significantly different from those in tetrapods. Since this organ appears to have different functions in fish and tetrapods it is likely that the orientation patterns in fish are adapted to some aspect of audition—perhaps directional localization of sound.*

Sound detection in many species of teleost fish involves the sacculus and lagena, two otolithic regions of the inner ear (*1*, *2*). Stimulation of the sensory hair cells in these regions probably results from differential movement between the sensory macula (hair cell containing neuroepithelium) and a single overlying dense calcareous otolith (*2*, *3*). Physiological recordings along the length of the saccular macula show that different regions respond differently to the same signal, and that the level of microphonic response in any particular region may vary, depending on the direction of the sound field (and otolith movement) (*4*, *5*). These data suggest a complex interaction between the hair cells and the otolith, and may indicate mechanisms in the teleost ear for various types of signal analysis (for example, frequency) as well as directional localization of sound

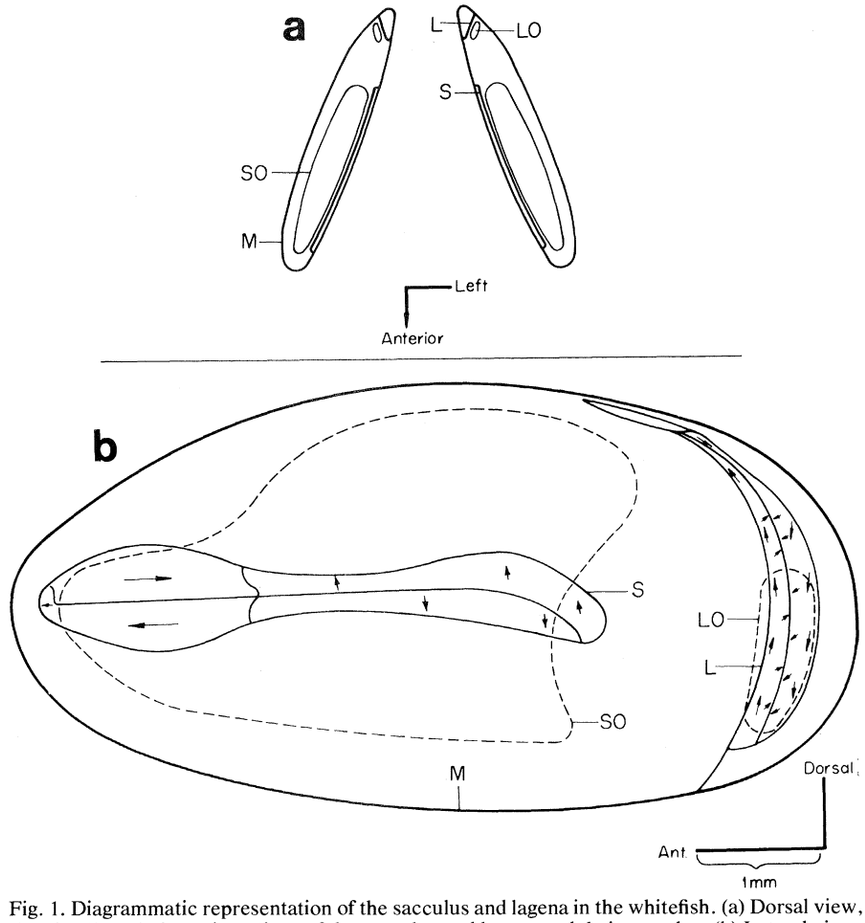

Fig. 1. Diagrammatic representation of the sacculus and lagena in the whitefish. (a) Dorsal view, showing the relative orientations of the sacculus and lagena and their maculae. (b) Lateral view, showing the sacculus and lagena with the orientation patterns of the hair cells on the different regions of macula. The arrows indicate the directions of orientation of the hair cells. The positions of the otoliths are indicated by dashed lines since they normally lie lateral to the maculae. It should be noted that the lower 95 percent of the lagena is at an angle of about 45° to the saccular macula, while the top of the sensory region is turned so that the sensory area faces ventrally. Abbreviations: *SO*, saccular otolith; *LO*, lagenar otolith; *S*, saccular macula; *L*, lagenar macula; and *M*, membranous chamber of the ear.

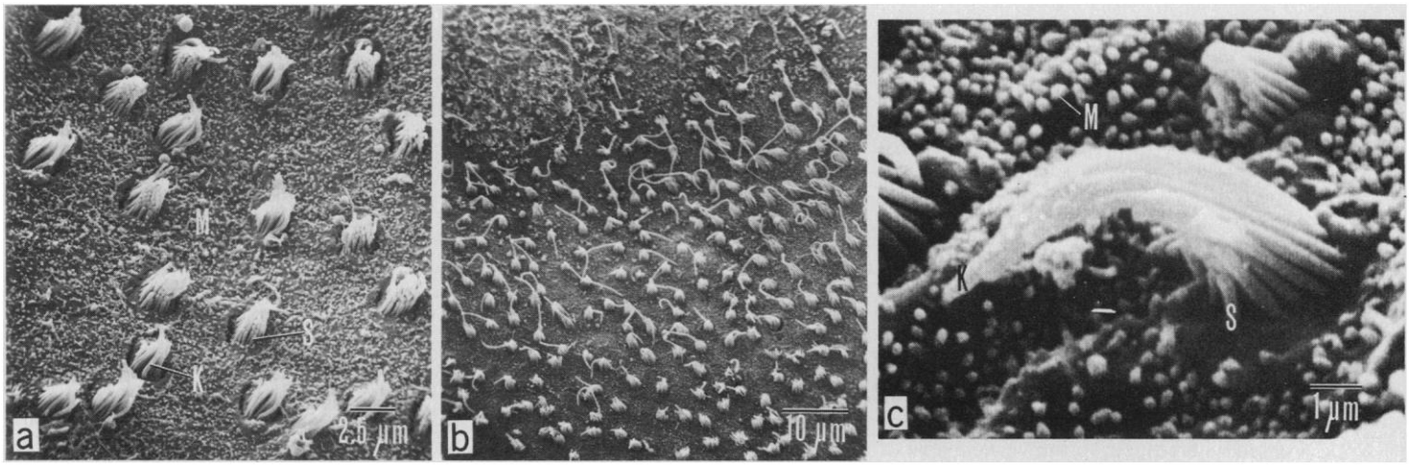

Fig. 2. Scanning electron micrographs. (a) Bidirectional pattern of the hair cells at the transition zone between dorsal and ventral groups in the posterior region of the saccular macula. These cells are typical of the most abundant cells in both the sacculus and the lagena. Abbreviations: *K*, kinocilium; *S*, stereocilia; and *M*, microvilli on support cells. (b) Border region of a dorsal hair cell group on the sacculus. The cells at the periphery have long kinocilia, and there is a graded transition to cells with short kinocilia. (c) Hair cell type found on the dorsal arm of the lagena and anterior tip of the sacculus not covered by the otolith. There is a long kinocilium, a bundle of stereocilia of almost equal length, and several shorter stereocilia.

sources (*5–7*). However, further analysis of inner ear functions requires a better understanding of inner ear morphology than is now available, especially at the ultrastructural level.

Perhaps the most significant functional anatomical aspect of the vertebrate inner ear is the presence of polarized sensory hair cells which respond to directional shearing stimulation (*8*) correlated with bending of the bundle of stereocilia toward or away from the eccentrically placed kinocilium (*8, 9*). The organization of the hair cells into groups with like polarization has been demonstrated in the inner ear regions in all vertebrate groups (*10–12*) and these data provide a morphological basis for the detection of direction (*5, 9*) or compression and rarefaction phases (*13*) of the stimulus. However, the data from tetrapods are not easily extrapolated to the function of the teleost ear since the roles of the sacculus and lagena in the two groups may be significantly different. Consequently, while some data on hair cell polarization are available for two teleosts (*12, 14, 15*), more extensive data are needed for a better functional understanding of the teleost ear. These data will also fill gaps in our knowledge of the evolution of the vertebrate ear.

As a step in the analysis of inner ear functional morphology, I present data on hair cell polarization patterns in the sacculus and lagena of the lake whitefish (*Coregonus clupeaformis*). The inner ears of whitefish (30 cm from snout to base of tail) were exposed and the sacculi opened dorsally. Fixation with 4 percent glutaraldehyde was started within 3 minutes after the death of the animal and continued for 2 days. The ears were then dissected from the head and washed with buffer, stained with 1 percent osmium tetroxide, and dehydrated in alcohol. The otoliths and otolithic membranes were dissected away and the tissues were dried at a temperature and pressure corresponding to the critical point of CO_2 with amyl acetate as the intermediary fluid. They were then mounted, coated with gold, and viewed with a JEOL JSM-U3 scanning electron microscope. In some cases the dissected sensory membranes were cleaned with an ultrasonic cleaner for 1 to 2 minutes after being transferred to alcohol. This process facilitated removal of excess otolithic membrane as well as the ciliary tufts from the hair cells, thereby permitting easier analysis of hair cell polarization than is possible with the cilia in place.

The whitefish sacculus and lagena are typical of those in many non-ostariophysans (species lacking the Weberian ossicles, bones that directly connect the swim bladder to the inner ear in the Ostariophysi) (*1, 2, 16*). The large sacculus is anterior to the smaller lagena, although in the whitefish the two regions are contained in a single chamber, which is oriented away from the midline of the animal at an angle of about 20° (Fig. 1a). Further, the hair cell surface of the lagena macula is turned 45° to the sacculus macula, which places it at an angle of 65° to the long axis of the fish.

The sacculus has a single large otolith (Fig. 1b) with a longitudinal groove on its medial side. This groove contacts most of the elongate sensory macula, although the most posterior portion of the macula is not covered by the otolith and the anterior portion of otolith curves away from the most anterior tip of the macula. The lagenar otolith is considerably smaller than that in the sacculus, and it covers only the broader lower half of the crescent-shaped macula.

Both maculae have a large sensory region, containing typical vertebrate sensory hair cells and microvilli-covered supporting cells, and a surrounding region containing only supporting cells (see Fig. 2a).

The sensory maculae and covering otoliths are separated by the otolithic membrane, which appears to hold the otoliths in place and limit their movement to some extent. The otolithic membrane is often lifted off the sensory maculae during dissections. In both the sacculus and lagena it extends beyond the bounds of the otolith and covers all of the sensory regions not covered by the otolith itself.

Hair cell polarization patterns are shown diagrammatically in Fig. 1b. The hair cells on the sacculus are divided into four groups, with all of the hair cells in each group oriented in the same direction. The anterior portion of the macula contains cells oriented anteriorly on the ventral half as well as on its anterior tip. The cells dorsal to this group are oriented posteriorly. The posterior half of the sacculus has hair cells oriented dorsally and ventrally, a pattern found in two other teleosts (*12, 14*) as well as a variety of terrestrial vertebrates (*10–12*). The transitions between dorsal and ventral groups and between anterior and posterior groups are simple and occur in two or three "rows" containing hair cells of both orientations (Fig. 2a). Transitions

from anterior to ventral and from posterior to dorsal groups are more complex. The cells between the groups are oriented approximately halfway between the orientations of the cells in the two groups, and there are generally several rows of these cells. Further, transition occurs more posteriorly on the macula for the more medial cells than for the cells closer to the margin of the macula.

The lagenar hair cells are oriented in a general dorsal or ventral direction, although the precise direction differs on different portions of the macula. In the lower half of the macula the cells are oriented with respect to the vertical axis of the fish, and this orientation is maintained when the macula curves. The anterior cells are oriented about 20° posterior of dorsal, while the posterior cells are oriented about 20° anterior of ventral. At the transition zone, cells may be oriented 45° to 90° from the vertical axis of the fish. The cells on the dorsal arm are parallel to the margins of the macula itself and transition between the two groups follows the simple pattern found on the sacculus.

Some variation was found in the ciliary patterns of various hair cells. Most of the cells on the sacculus and on the ventral half of the lagena have stereocilia which are graded in size, as well as a kinocilium which is 1.1 to 1.5 times longer than the longest stereocilia (Fig. 2a). The peripheries of the sensory regions on both maculae have cells with short stereocilia and long kinocilia. These cells "grade" into the more abundant cells with short kinocilia within 5 to 20 rows (Fig. 2b). A third type of cell is found on the dorsal arm of the lagena macula (other than at the very periphery of the macula) and at the anterior tip of the saccula (Fig. 2c). This cell has a long kinocilium, several equally long sterocilia, and several shorter stereocilia. These cells are found in several (but not all) areas not covered by the otolith. In no instance did I find any kinocilia with a bulbous swelling at the tip, as found in several other vertebrates (*10–12*).

While related experiments are necessary to elucidate the functional mechanisms of the teleost ear, my data suggest a number of points regarding the participation of the sacculus and lagena in sound detection. The variation in polarization patterns, combined with the shape and positions of the maculae, provides hair cells that are oriented in a variety of directions. This potentially would give the animal more information on stimulus direction than it could obtain if the cells were oriented only dorsally and ventrally, since the axes of stimulation of the various hair cells cover a wide range of directions. Further, since the two ears are oriented in opposite directions from the midline of the animal, more refined directional information would be available to the fish than if only a single ear were in use. However, the amount of this directional information available to the fish would be related to the independence of neuronal innervation to cell groups with different directional orientations.

While it is evident that the sacculus and lagena could play a role in sound localization (*2, 5, 6, 17*), the role of the hair cells in the orientation groups is not so clear. These cells number well over 4000 per group on the sacculus. One possibility is that individual neurons innervate large numbers of hair cells, providing enhanced sensitivity for stimulus detection (*15*). Another suggestion is that the large sensory maculae may be involved in some sort of signal analysis (*5, 7, 18*). Such an analysis would be based on variations in relative movements between macula and otolith for different signals. The movement pattern could be analogous to the vibration modes found on the tympanic membrane of the cat (*19*) and the tympanum of the locust (*20*), where different frequencies and intensities cause different regions to vibrate. If innervation of the sacculus and lagena were sufficient for discriminating responses to stimulation in different regions of the maculae (even if the regions were relatively large), then the teleost ear might be able to analyze signal frequency and intensity.

My data also provide a preliminary basis for discussion of the mechanisms of hair cell stimulation. While it is likely that the hair cells directly under the otoliths are stimulated through some sort of direct or indirect contact with the otoliths, cells covered only by otolithic membrane are likely to respond in different ways because of the different physical properties of the otolithic membrane without the overlying otolith. Even if the extensions of the otolithic membrane beyond the borders of the otolith couple the cells to the movements of the otolith, the nature of the thin membrane suggests a system that is lightly coupled and likely to affect underlying cells differently than the cells under the otolith.

As a final point, it is interesting to compare the structure of the sacculus and lagena of the whitefish with the structure of those organs in other vertebrates. The data are limited, but the presence of hair cells in four discrete directional groups appears to be limited to the whitefish and several other teleost species (*21*). This condition has never, to the best of my knowledge, been reported for the sacculus in any tetrapod, although in several species hair cell polarization follows the curvature of the saccular periphery, with the result that cells are oriented in more than two directions. However, the cells still belong to only two discrete groups (*10–12*). Further, data for two teleost species (*12, 14*) indicate that they have the more typical bidirectional vertebrate saccular pattern. What remains to be elucidated, then, is whether the pattern found in the whitefish is typical of species that use the sacculus in a particular fashion, such as in sound detection involving bone conduction (*17*), while other species of fish, as well as terrestrial vertebrates, use their sacculi in association with other organs, such as the swim bladder, or in ways not requiring a high level of directional analysis or auditory signal processing.

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18 February 1976

Cross-Modal Matching and the Primate Frontal Cortex

Abstract. *Rhesus monkeys with selective lesions of the prefrontal system were tested on a tactile-visual cross-modal matching task. Monkeys with lesions in the banks and depths of the arcuate sulcus were impaired, while normal controls and monkeys with lesions in the banks and depths of the sulcus principalis and in the anterodorsal part of the head of the caudate nucleus were not.*

In a recent review of transfer of information between sensory modalities Ettlinger concluded that there is no unequivocal evidence of cross-modal matching abilities in the monkey, although such abilities are demonstrated by the chimpanzee and man (*1*). However, if the stimuli used in the cross-modal experiment are edible and inedible shapes (thus more easily discriminable and relevant to the animal), the rhesus monkey is capable of cross-modal matching (*2*). As revealed by neuroanatomical studies, several cortical areas in the monkey brain are foci where information from various modalities converges (*3*). These are the vicinity of the arcuate sulcus, the inferior parietal lobule, and the depths of the superior temporal sulcus. Damage to such areas might be expected to impair performance on a cross-modal task. We now report the effects of discrete prefrontal lesions on tactile-visual cross-modal matching by the monkey.

The subjects were 14 rhesus monkeys (*Macaca mulata*). Four of these sustained ablations confined to the banks and depths of the arcuate sulcus, four had both the banks and the depths of the sulcus principalis ablated, four had electrolytic lesions aimed at the anterodorsal part of the head of the caudate nucleus [which receives projections from the sulcus principalis (*4*) and is functionally related to this area (*5*)], and two served as normal controls. All the lesions were bilateral and were made at least 16 months before the monkeys were tested. As the animals are being used in further experiments, we have not yet made histological examinations. Prior to this experiment, the ability of the animals on delayed response and delayed alternation tasks was measured; as expected (*6, 7*), the animals with lesions within the sulcus principalis and in the head of the caudate nucleus were impaired on both of these tasks, but those with arcuate lesions were not.

The monkeys were tested in a Wisconsin General Test Apparatus (WGTA). The discrimination stimuli were palatable or unpalatable "cookies" of 16 shapes made from Dixons powdered diet for monkeys (41-B) according to procedures described earlier (*8*). Before the actual testing was begun, the monkeys were trained to accept the cookies in the darkened WGTA.

For a particular day's testing cookies of two shapes, one palatable (positive) and one unpalatable (negative), were used. The pair was chosen so that the shapes were clearly discriminable. Examples are a star paired with a sphere or a disk with a cross. Each day, ten palatable and ten unpalatable cookies were mixed together on a tray (17 by 18 cm) and presented to the monkey. In the darkened WGTA, the monkey was allowed to feel and eat the selected shapes. After the animal had eaten at least eight palatable positive shapes, the experimenter lowered the opaque screen and covered the tray beneath the transport cage with a cardboard sheet to prevent the animal from subsequently noticing the discarded negative shapes (the floor of the transport cage was constructed in such a way that discarded shapes dropped out of reach of the animal). The light of the WGTA was then turned on, and one new pair of shapes, which the animal had investigated and tasted in the dark, were placed on the tray 8 cm apart. The animal was allowed to look at the shapes as the experimenter manipulated them and placed them on the tray. The tray was pushed forward after 20 seconds, and the animal was allowed to choose one of the shapes. This procedure was repeated daily for 20 days. Eight pairs of stimuli were used during the first 8 days and then the shapes were recombined in various ways to form the pairs for the following 12 days' testing.

Table 1. Performance of monkeys on cross-modal and visual discrimination tasks.

Subject	Cross-modal (percent correct)	Visual discrimination (percent correct)
Lesions within the arcuate sulcus		
1	50	85
2	50	100
3	60	100
4	60	70
Lesions within the principalis sulcus		
1	60*	75
2	65	85
3	75	95
4	80	80
Lesions in the caudate nucleus		
1	70	80
2	70	90
3	75	95
4	85	80
Normal controls		
1	70	75
2	75	75

*Because he demonstrated severe perseveratory deficits on previous tests, we suspect that this animal's lesion may have invaded the inferior convexity (*6*).

The normal monkeys were capable of cross-modal matching ($P = .01$, binomial two-tailed test) (Table 1) as were the monkeys with lesions of the sulcus principalis ($P < .01$) and the head of the caudate nucleus ($P < .01$). However, performance of the animals with arcuate lesions was no better than that predicted by chance ($P = .50$). The group of animals with arcuate lesions differed from the other groups [$2\hat{I} = 7.76$, d.f. = 1, $P < .01$, information statistic (*9*)], but the other groups did not differ significantly from each other ($2\hat{I} = 0.50$, d.f. = 2, $P < .80$).

The design of this transfer task cannot exclude the possibility that any observed impairment is due to loss of visual or tactile discrimination. Dorsolateral frontal lesions can, in some circumstances, produce impairment of visual, tactile, or auditory discrimination (*6*), characterized by difficulty in withholding responses to unrewarded stimuli in discrimination tasks. It is generally believed that this impairment is seen only when the dorsolateral lesion encroaches into response control areas on the inferior convexity of the frontal lobe (*6*); this area was not included in our lesions. As determined by earlier testing on an object discrimination reversal test, only one monkey had a perseveratory deficit.