(*3, 12, 13*). The solid circles measure the values of the current at the peak of the transient phase evoked by depolarization. The line through them intercepts the abscissa at 70 mv, a value similar to the height of the spike recorded in the absence of clamp (Fig. 1*C*). It can be argued that the slope of the line through the solid circles should give an approximate value of the conductance between cytoplasm and external fluids at the peak of activity. If this is correct, the results indicate that the resistance measured between inside and outside with the method described decreases by a factor of only 2 to 3 during activity. Two principal sources of error should be considered: On the one hand, capacity of the unclamped regions of the motoneuron tends to decrease the value of the resistance measured during activity, since this measurement is made a short time after application of the clamping pulse; on the other hand, any resistance (other than membrane resistance) common to both electrodes will not only decrease the effectiveness of the clamp on the membrane but will also decrease the percentage change in measured resistance between rest and activity by adding a constant quantity to each.

When the clamped region separates one part of the neuron from another, voltage changes in one part cannot affect the other. Thus, the clamped area cannot lie between A and B regions, since A activity elicits B firing even in the presence of the clamp. The foregoing results are consistent with the original hypothesis (*1–3*) that the A spike originates in the axon but suggest that the B spike does not involve more than a part of the soma-dendritic membrane.

K. Frank
M. G. F. Fuortes
P. G. Nelson

National Institute of Neurological Diseases and Blindness, Bethesda, Maryland

References and Notes

1. M. G. F. Fuortes, K. Frank, M. C. Becker, *J. Gen. Physiol.* 40, 735 (1957).
2. T. Araki and T. Otani, *J. Neurophysiol.* 18, 472 (1955); ——— and T. Furukawa, *Japan. J. Physiol.* 3, 254 (1953); L. G. Brock, J. S. Coombs, J. C. Eccles, *J. Physiol. (London)* 117, 431 (1952); ———, *ibid.* 122, 429 (1953).
3. J. C. Eccles, *The Physiology of Nerve Cells* (Johns Hopkins Press, Baltimore, 1957).
4. P. Fatt, *J. Neurophysiol.* 20, 27 (1957).
5. W. Freygang and K. Frank, *Federation Proc.* 17, 49 (1958); *J. Gen. Physiol.* 42, 749 (1959).
6. W. H. Freygang, Jr., *ibid.* 41, 543 (1958).
7. T. Tomita, *Japan. J. Physiol.* 6, 327 (1956).
8. A. Bak, *Electroencephalog. and Clin. Neurophysiol.* 10, 745 (1958).
9. I. Tasaki and C. S. Spyropoulos, *Am. J. Physiol.* 193, 309 (1958).
10. W. Rall, *J. Cellular Comp. Physiol.* 46, 373 (1955).
11. J. S. Coombs, D. R. Curtis, J. C. Eccles, *J. Physiol. (London)* 139, 198 (1957).
12. J. S. Coombs, J. C. Eccles, P. Fatt, *ibid.* 130, 291 (1955).
13. K. Frank and M. G. F. Fuortes, *ibid.* 134, 451 (1956).

18 February 1959

Cortical Correlates of Auditory Localization

Abstract. Responses were recorded simultaneously from a number of electrodes on the auditory cortex of one hemisphere of cats. Response amplitudes at different electrodes reached maxima and minima at different real or apparent locations of a click stimulus.

Although we have fairly extensive knowledge of the stimulus correlates of auditory localization, the physiological correlates still appear to be undetermined. The experimental evidence presently available indicates two major possibilities. One is that spatial location of the auditory stimulus is translated into locus of maximal activity within one side of the auditory system. This type of theory, generally referred to as a place theory, has been seen often, not only in audition (*1*) but in the "local sign" theories of other sensory modalities as well. The other possibility is that auditory localization is related to the ratio of the response magnitudes of the two sides of the auditory system (*2*). This may be referred to as a bilateral ratio theory. The research reported here was designed to test the validity of a place principle in auditory localization.

A six-channel electroencephalograph was used in conjunction with a bank of six oscilloscopes to photograph and measure simultaneous responses to click stimuli at six locations on the auditory cortex (AI and AII) of one hemisphere. Changes in the magnitudes of the responses recorded from each of the electrode locations were explored as a function of changes in the real and apparent location of the click stimuli (*3*). The subjects were 15 cats anesthetized with Nembutal.

Moving an actual (click) source in space gives the type of results illustrated in Fig. 1, which shows response amplitudes at different electrode locations reaching maxima or minima, or both, at different source locations. These data suggest (i) that there may be in the auditory cortex of one hemisphere elements that are differentially sensitive to the spatial location of a stimulus source (*4*) and (ii) that these elements are not distributed homogeneously through the auditory area.

When apparent location of the click stimuli is manipulated by changing the binaural time interval while holding the binaural intensity ratio constant, results of the type illustrated in Fig. 2*A* are obtained. These data were obtained with click stimuli of equal loudness in both ears. It can be seen that response amplitudes at different electrode locations reach peaks or troughs at different binaural time intervals (or apparent locations). When the loudness of the first click is made greater than the loudness of the second click, the relationship among average or general response magnitudes at the various electrodes changes, as is illustrated by comparing Figs. 2*A* and 2*B*. In Fig. 2*A* electrodes 2, 3, 4, and 5 show similar average response magnitudes, while in Fig. 2*B* the response magnitudes are clearly different, the average response magnitude at electrode 2 being enhanced, that at electrode 4 being relatively unaffected, and those at electrodes 3 and 5 being depressed. The curves in Fig. 2*B* also are more nearly parallel than those in Fig. 2*A*. The extent to which these changes take place as the result of manipulation of the binaural intensity ratio is related, as might be expected, to the amount by

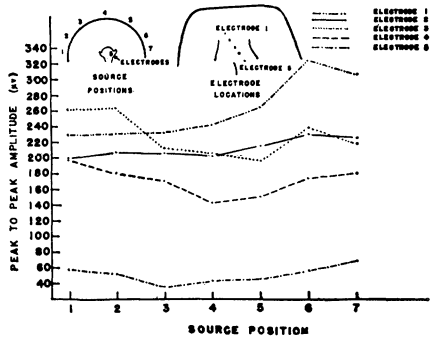

Fig. 1. Amplitude of cortical response to clicks (28 db SL at electrode 1) as a function of source position and electrode location.

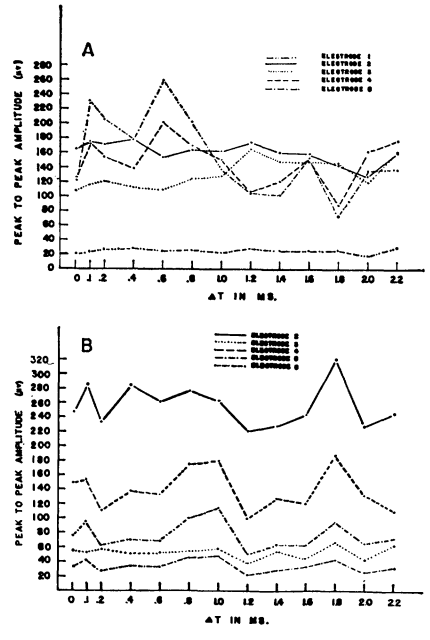

Fig. 2. Amplitude of cortical response to binaural click stimuli as a function of binaural time delay (Δt). First click, ipsilateral. *A*, First click, 20 db SL; second click, 20 db SL. *B*, First click, 30 db SL; second click, 10 db SL.

which the intensity ratio is changed. These graphs were obtained from the same animal and with the same electrode locations, except as noted in the legends. Similar results have been obtained with several orientations of the electrode array within auditory area AI, and with click No. 1 both ipsilateral and contralateral to the recording electrodes.

These data suggest that the angular location of auditory stimuli may be represented in the auditory cortex of one hemisphere by means of a place principle.

PAUL D. COLEMAN
Institute for Applied Experimental Psychology, Tufts University, Medford, Massachusetts

References and Notes

1. J. V. Bekesy, *Physik. Z.* 31, 824, 835 (1930); E. G. Boring, *Am. J. Psychol.* 37, 157 (1926); T. J. Bowlker, *Phil. Mag.* 15, 318 (19(L. A. Jeffress, *J. Comp. and Physiol. Psychol.* 41, 35 (1948); H. Pieron, *The Sensations* (Yale Univ. Press, New Haven, Conn., 1952).
2. M. R. Rosenzweig, *J. Comp. and Physiol. Psychol.* 47, 269 (1954).
3. The work reported here was supported by National Science Foundation grant No. G-3850.
4. Single elements sensitive to the apparent location of auditory stimuli have been seen in the olivary complex by Robert Galambos.

9 February 1959

Nature of Colchicine Resistance in Golden Hamster

Abstract. The unresponsiveness of the golden hamster to colchicine has been shown to be the result of a resistance of individual cells to the drug. This resistance makes it possible to use hamsters with heterotransplanted tumors for testing the in vivo effects of colchicine on the tumors, with no toxic host reactions.

Orsini and Pansky (*1*) have reported a resistance on the part of the golden hamster to the toxic and mitotic inhibitory effects of colchicine. In a study of lethal effects, Turbyfill and Soderwall (*2*) showed that this resistance was at least 100 times greater in the hamster than in other animals. Whether this unresponsiveness is the result of a systemic inactivation of the drug or the result of a resistance of the individual cells has not been determined. The experiments described in this report indicate that the golden hamster has a true cellular resistance to the action of colchicine.

The first experiment was undertaken to determine whether heterologous tissues grown in hamsters were sensitive to colchicine. Three transplanted human testicular tumors (*3*), a teratocarcinoma of the ovary of a mouse (*4*), and a spontaneous anaplastic hamster carcinoma (*5*) were maintained in the cheek pouches of cortisone-conditioned weanling golden hamsters, as described previously (*3, 6*). Experimental animals bearing tumors of approximately the same size received intraperitoneal colchicine (*6*) in dosages listed in Table 1, while tumor-bearing controls received no treatment. The tumors and a piece of duodenum were removed 18 hours later and examined microscopically. By means of an ocular reticule, the mitoses in 40 areas of constant size were counted in each tumor. Likewise, the mitoses were counted in 40 of the host's intestinal crypts, which were considered to be similar to each other in size and shape.

In a second experiment to determine the effect of colchicine upon isolated cells in vitro, we grew embryonic hamster tissue in plasma clot and human cells of the D-189 strain (Mavar) (*7*) on glass. The growth medium was made up of calf serum, chick embryo extract, and Hanks balanced salt solution (20:10:70), to which Eagle's basal medium concentrates, penicillin, and streptomycin were added. When suitable growth was obtained, 0.2 ml of serially diluted colchicine in balanced salt solution was added to the cultures (the final concentrations are listed in Table 2). Control cultures received only balanced salt solution. Six hours later they were fixed in Bouin's fluid and stained. At least 200 consecutive human and 400 hamster mitoses were differentially counted for each concentration of colchicine. The results were expressed as the percentage of mitoses which had ball-like configurations with no evident spindles typical of colchicine-induced metaphase arrests.

Table 2. Effects of colchicine upon human and hamster cells in vitro. Values represent the percentage of mitoses with the configuration of colchicine-induced "arrests" (see text).

Final concentration	Human strain D-189 (Mavar) cells	Hamster embryonic cells
(Control)	6	7
$10^{-9}M$ colchicine	16	
$10^{-8}M$ colchicine	36	
$10^{-7}M$ colchicine	99	5
$10^{-6}M$ colchicine	100	36
$10^{-5}M$ colchicine		85
$10^{-4}M$ colchicine		95
$10^{-3}M$ colchicine		96

The results of mitotic counts for the in vivo experiments listed in Table 1 indicate that colchicine had no effect on the mitotic index (the number of mitoses in a given area) of the hamster intestinal crypts or of the spontaneous hamster carcinoma within the dosage range used. There was a striking increase, however, in the mitotic index of heterotransplanted tissues of human and mouse origin, especially at the higher dosages employed. These effects generally began to appear at the 0.1 mg per 100 gram body-weight level but occasionally were noticed at the 0.05 mg per 100 gram level. Cells arrested in vivo displayed mitoses typical of colchicine treatment (*8*).

No abnormalities attributable to colchicine could be detected on gross examination in the 65 hamsters treated at 0.25- and 1.0-mg/100 g levels. This was in contrast to findings for a group of 21 C_3H mice treated with the same doses of colchicine on a weight-for-weight basis. After 18 hours four mice died and the remainder had humped backs, ruffled fur, and marked diarrhea.

The results of in vitro studies (Table 2) indicated that hamster cells had at least a 100-fold greater resistance to colchicine than human cells. A few normal metaphases viewed on end were indistinguishable from colchicine-induced metaphases, and this accounted for the "arrests" noted in the control group. Many normal anaphases and telophases could be found in the hamster tissues at concentrations of colchicine as great as $10^{-5}M$, indicating that in spite of the large percentage of arrests found, considerable resistance was maintained at this high level.

Table 1. Effects of colchicine on heterologous and homologous tissues grafted in the hamster. All values represent the average number of mitoses per unit area per animal studied (see text), plus or minus one standard deviation. Number of animals in parentheses.

Tissue	No. of mitoses				
	Control	Dosage*			
		0.05 mg	0.1 mg	0.25 mg	1.0 mg
Pitt 89 (human) choriocarcinoma)	46 ± 12 (11)	112 ± 97 (8)	569 ± 154 (7)	540 ± 79 (5)	540 (2)
Pitt 61 (human embryonal carcinoma)	45 ± 8 (6)		104 ± 16 (4)	493 ± 42 (4)	
Deac 3 (human embryonal carcinoma)	63 ± 29 (16)	64 ± 12 (5)	175 ± 81 (6)	574 ± 42 (7)	
Mouse ovarian teratoma	64 ± 12 (6)		262 ± 183 (5)	744 ± 89 (4)	
Hamster carcinoma	13 ± 4 (8)			14 ± 2 (10)	14 ± 7 (9)
Hamster intestinal crypts	62 ± 15 (16)	69 ± 14 (10)	63 ± 12 (19)	57 ± 12 (17)	64 ± 10 (7)

* Doses are of colchicine (1 mg/2 cm³) per 100 g of body weight.