Cell. Regul. **2**, 65 (1970); H. W. Chen and H. J. Heiniger, *Cancer Res.* **34**, 1304 (1974); H. F. Acevedo, E. Campbell, J. C. Frich, Jr., D. W. Hayeslip, J. Gilmore, *Cancer* **37**, 2847 (1976).

18. B. E. Cham and B. R. Knowles, *J. Lipid Res.* **17**, 176 (1976).
19. R. Keller, *Immunology* **27**, 285 (1974).
20. G. B. Warren, M. D. Houslay, J. C. Metcalfe, N. J. M. Birdsall, *Nature (London)* **255**, 684 (1975); S. Rottem, J. Yashov, Z. Neeman, S. Razin, *Biochim. Biophys. Acta* **323**, 495 (1973); K. R. Bruckdorfer, R. A. Demel, J. DeGier, L. L. M. Van Deenen, *ibid.* **183**, 334 (1969); D. Papahadjopoulos, G. Poste, B. E. Schaeffer, *ibid.* **323**, 23 (1973).
21. Supported by the Veterans Administration and by NIH grants CA 14045 and CA 15811. We thank R. Rodman, Jr., R. R. Taintor, C. C. Moore, J. E. Brisbay, R. Christensen, C. Hendersen, and M. S. Knowlton for assistance.

1 February 1977; revised 5 April 1977

Binocular Differences in Cortical Receptive Fields of Kittens After Rotationally Disparate Binocular Experience

Abstract. *Kittens were afforded visual experience only while wearing goggles fitted with prisms that rotated the inputs to the two eyes equally but in opposite directions about the visual axes (16° for experimental subjects, 0° for control subjects). Subsequently, receptive-field organization of the visual cortex was studied, special attention being given to the preferred orientations of binocular cells. For each group, the distribution of interocular differences in preferred orientation centered about the prism rotation experienced during early development. Thus, for moderate amounts of relative rotation, the development of interocular matching of orientation specificity in binocular cells of the visual cortex reflects the correspondence of early visual input between the two eyes.*

The two functional characteristics of visual cortical neurons that have received perhaps the most attention are binocularity (or ocular dominance) and orientation specificity. For most cells, a distinct, optimally oriented stimulus evokes a maximal response, and most cells are activated by stimuli to either eye. Each of these properties is susceptible to the effects of early experience: complete visual deprivation during early development substantially reduces the number of orientation-selective cells present in the adult, and monocular visual deprivation or profoundly anomalous early binocular experience (such as experimental strabismus) can severely disrupt the normal development of binocularity (*1*).

For binocular cells in the normally reared adult cat, the preferred stimuli for the two eyes are similar, particularly receptive-field location and orientation. Correspondence in receptive-field location is largely provided by the innate topographic mappings of the retina within the visual system, although visual experience has a crucial role in the final adjustment of this correspondence (*2*).

Although receptive-field orientations of binocular cells in the normally reared adult cat are well matched (*3*), kittens that are visually inexperienced (*4*) or binocularly deprived by reverse suturing (*5*) lack such matching. We have further examined the role of visual experience in the development of interocular matching of receptive-field orientations. We raised kittens whose only visual experience was with a visual field optically rotated 16° between the left and right eyes, and found that the subsequent distribution of interocular differences in the preferred orientations of cells was centered about the rotational disparity experienced during early development. To our knowledge, the results reported here are the first to show that the binocular matching of this fundamental aspect of the functioning of visual cortical cells develops so as to correspond to the visual environment.

Three litters of kittens and their mothers were placed in a darkroom at ages 7 to 10 days and kept there except for daily periods of 1 to 2 hours of visual experience between the ages of 4 and 12 weeks. During the daily exposure periods, the kittens wore goggles molded from silicone rubber sealer (Dow Corning) and held in place by Velcro straps behind the head and under the chin. Each eyepiece was fitted with a pair of small right-angle prisms cemented together. Such an arrangement optically rotates the visual field around its center without mirror reversals; the angle of rotation is exactly twice the angle by which the two prisms are misaligned. For three kittens, the visual fields were rotated 8° counterclockwise in the left eye and 8° clockwise in the right eye (the +16° condition). For one kitten, the rotations were 8° clockwise in the left eye and 8° counterclockwise in the right eye (the −16° condition). Three control kittens wore goggles fitted with prisms that did not rotate the visual fields (the 0° condition).

The kittens had visual experience while wearing the goggles in a well-illuminated room containing toys and obstacles suitable for climbing, in the presence of littermates and an experimenter. Frequent checks were made to ensure that the kittens' eyes were open and clearly visible to the experimenter. Occasionally the prisms became fogged; when this happened, the kitten was placed briefly in a lightproof box while the prisms were cleaned. For each kitten, the total of visual experience over the 8-week period was between 50 and 100 hours.

In general, all kittens showed good visual behavior while wearing their goggles. The kittens played with each other and with toys, climbed on and jumped off furniture, avoided obstacles, stalked moving targets, and followed the experimenter to explore other rooms. Visual orientation and depth discrimination were evident in these behaviors and confirmed in informal testing (for example, visual cliff and visual placing).

Subsequently, receptive-field organization of visual cortex was studied in all kittens using conventional techniques of extracellular unit recording (*6*). Each kitten was studied during from one to three recording sessions separated by at least 3 weeks, at ages ranging from 5 months to 1 year. Kittens remained in the darkroom between recording sessions. For recording, subjects were prepared under ketamine hydrochloride and ether anesthesia. Small craniotomies were made 4 mm posterior to instrument zero and 2 to 3 mm lateral to the midline. Subjects were then immobilized with gallamine triethiodide (Flaxedil) (20 mg/ml) administered at a rate of about 1 ml/hr and placed in an atraumatic head holder facing a translucent gray tangent screen at 46 cm. Pupils were dilated with ophthalmic atropine sulfate (1 percent), nictitating membranes were retracted with ophthalmic phenylephrine hydrochloride (2.5 percent), wound margins were infiltrated with a long-lasting local anesthetic [procaine in peanut oil, 15 mg/ml (Zyljectin)], and ophthalmic proparacaine hydrochloride (0.5 percent) was applied topically on the corneal surfaces. Each eye was focused on the tangent screen by corneal contact lenses, and the optic disk and area centralis were projected onto the screen and mapped separately for each eye. Artificial pupils (3-mm diameter) were used to improve depth of field. Glass or metal microelectrodes were aimed at the posterolateral gyrus, usually so as to traverse the medial bank. Moving visual stimuli consisting of slits, dark bars, and edges were back-projected on the tangent screen during record-

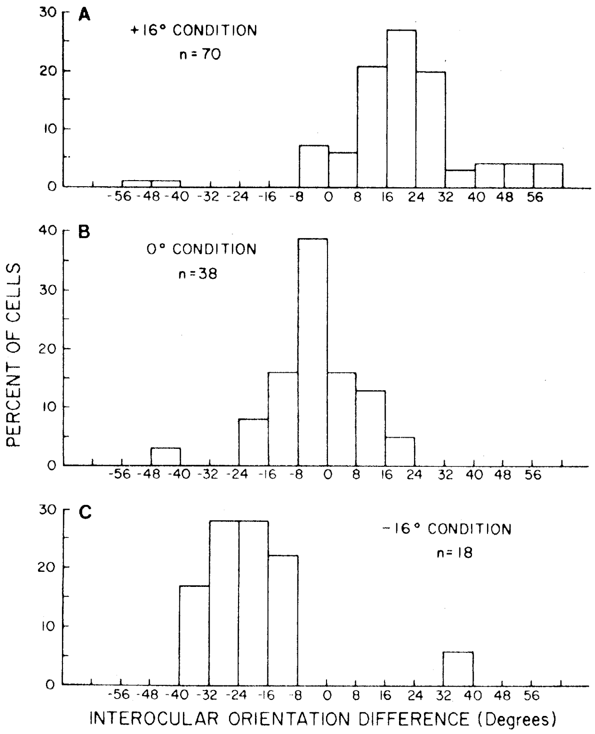

Fig. 1. Distributions of angular disparities between left- and right-eye preferred stimulus orientations of binocular visual cortical cells. (A) cells from kittens raised wearing goggles that introduced a relative rotation around the visual axes of +16° between the left and right eyes. (B) cells from kittens raised wearing goggles that produced no rotation of the visual fields (0°). (C) cells from a kitten raised wearing goggles that rotated the left and right visual fields by −16°.

ing from a cell, and the cell's receptive-field properties were studied separately for each eye with the other eye occluded. Using an audio monitor and sometimes peristimulus time histograms compiled on-line by a computer of average transients, we made careful and repeated determinations of the optimal values of several receptive-field parameters including size, location, orientation, preferred speed and direction of movement, and edge preference. Any cell that was not held long enough to permit repeated tests in both eyes and any parameter that did not yield the same value repeatedly were excluded from the data.

Most cells exhibited well-defined orientation preferences in both eyes; of 188 cells studied, 128 met this criterion. All possible stimulus orientations (vertical, diagonal, and so forth) were about equally represented in the sample, and there were no differences among conditions in this regard. Twenty-two cells were binocular but with poor or undefined orientation specificity in one or both eyes, 32 cells were strictly monocular, and 6 cells were unresponsive to visual stimuli in either eye. There were 81, 77, and 83 percent binocular cells in the +16°, 0°, and −16° conditions, respectively. Virtually all receptive fields were within 10° of the area centralis.

For each of the 128 strongly binocular cells, the angular difference was calculated between the preferred orientations in the two eyes. Since these measurements were made while the animals were immobilized by Flaxedil, it was necessary to correct for the slight intorsional eye rotations about the visual axes that sometimes accompany the mild visual axis divergence produced by this drug (*7*). Each kitten's pupils were photographed in strong light to obtain the natural angle of inclination between the two slitted pupils. The same angles were obtained from photographs of the immobilized subject with the pupils slitted by topically applied ophthalmic pilocarpine hydrochloride (6%), and a correction factor for each kitten was calculated as the difference between the two states. Each cell's interocular difference in preferred orientations was adjusted by using the subject's correction factor; the values reported are corrected values. The correction factors were small, usually between 0 to 3 degrees; statistical analysis of the uncorrected values yielded the same significance levels and led to the same conclusions as the analyses of the corrected values presented below.

The distributions of interocular differences in the preferred stimulus orientations of cells in the +16° condition, the 0° condition, and the −16° condition are shown in Fig. 1. For each of the three conditions, the distribution was centered about the prism rotation experienced during early development. The mean interocular orientation disparities were +19.5°, −2.7°, and −20.9° respectively (*8*). The difference between the +16° condition and the 0° condition is significant ($t = 6.50$, $P < .001$) as is the difference between the −16° condition and the 0° condition ($t = 4.84$, $P < .001$). The mean disparity for the 0° condition does not differ significantly from zero ($t = 1.40$, $P > .10$); nor do the mean disparities for the two experimental conditions differ significantly from the disparities imposed during early experience (for the +16° condition, $t = 1.53$, $P > .10$; for the −16° condition, $t = 1.36$, $P > .10$).

The breadth of tuning of individual cells was unrelated to the intergroup differences. The orientation selectivity of each receptive field was judged; when only cells with narrow tuning in both eyes were considered, the mean interocular disparity in the +16° condition was +16.9° and that of the −16° condition was −15.9°. Both means are significantly different from 0° disparity. Similarly, there was little variability among kittens within conditions; in particular, the mean disparities of each of the three +16° kittens differed significantly from 0°.

We considered the possible effects of compensatory eye movements. Had the kittens made such movements only while wearing goggles, the subsequent analysis of the receptive fields would have shown no differences among groups in interocular orientation disparity: the distribution of disparities would have been centered on 0° in all groups, as it is in normally reared cats. Another possibility is that such movements both occurred and persisted after removal of the goggles and during photographing of the pupil slits and were then abolished by Flaxedil paralysis of the eye muscles. In this case the application of the correction factor to each cell's measured interocular orientation disparity would have led to differences in mean disparity among conditions in the reported direction. This possibility was discarded because the correction factors were too small to produce the observed effects, so that the *uncorrected* disparities showed closely similar and statistically significant differences among groups. A final possibility, that compensatory adjustments of eye position occurred and persisted even under Flaxedil, was ruled out by comparing directly the angles between kittens' pupils, which did not differ appreciably among the three groups either before or after administration of Flaxedil. In short, it seems unlikely that the effects reported here were mediated by compensatory eye movements of any sort; rather, the differences among groups in interocular orientation disparity evidently reflect differences in the binocular organization of visual cortex.

We conclude that the development of interocular correspondence of receptive-field orientations reflects the correspondence of early visual inputs between the two eyes for moderate amounts of relative rotation. Preliminary results from additional kittens suggest that even greater rotation (24°) may be more disruptive of binocularity; other investigators have reported similar results using large, surgically induced eye rotations (*9*) during early development.

Controversy has arisen concerning whether the orientation preferences of visual cortical neurons are innately determined (*10*) or whether such preferences directly reflect the orientations experienced during the visual sensitive period (*11*). Our results imply the existence of at least some plasticity in the development of cells' orientation preferences. It is possible, however, that innate mechanisms favor the systematic representation of all orientations in the visual cortex, that is, orientation hypercolumns (*12*), but that visual experience is crucial to the alignment of the two monocular orientation representations. Under this interpretation, the goggle experiences served to align these patterns of orientation representation so that the two monocular orientations differed systematically across the cortex.

PAUL G. SHINKMAN
CHARLES J. BRUCE

Department of Psychology,
University of North Carolina,
Chapel Hill 27514

References and Notes

1. D. H. Hubel and T. N. Wiesel, *J. Neurophysiol.* **28**, 1041 (1965); T. N. Wiesel and D. H. Hubel, *ibid.*, p. 1029.
2. J. D. Pettigrew, *J. Physiol. (London)* **237**, 49 (1974); R. Shlaer, *Science* **173**, 638 (1971).
3. C. Blakemore, A. Fiorentini, L. Maffei, *J. Physiol. (London)* **226**, 725 (1972); D. H. Hubel and T. N. Wiesel, *ibid.* **160**, 106 (1962).
4. C. Blakemore and R. C. Van Sluyters, *ibid.* **248**, 663 (1975).
5. ———, *ibid.* **237**, 195 (1974).
6. B. E. Pfingst, C. J. Bruce, P. G. Shinkman, *Exp. Neurol.* **46**, 215 (1975); P. G. Shinkman, C. J. Bruce, B. E. Pfingst, *Science* **184**, 1194 (1974).
7. P. O. Bishop, W. Kozak, G. J. Vakkur, *J. Physiol. (London)* **163**, 466 (1962).
8. We represented each interocular difference as lying in the range +90° to −90°; this convention has the advantage that the expected mean of a random distribution is zero but the disadvantage of accentuating values near the extremes (±90°). For this reason, two cells with disparities larger than 80° (one in each 16° condition) were discarded. The statistical conclusions reported are unaffected by the exclusion of these cells.
9. C. Blakemore, R. C. Van Sluyters, C. K. Peck, A. Hein, *Nature (London)* **257**, 584 (1975); U. Yinon, *Exp. Brain Res.* **24**, 215 (1975).
10. M. P. Stryker and H. Sherk, *Science* **190**, 904 (1975).

→ C. Blakemore and G. F. Cooper, *Nature (London)* **228**, 477 (1970); H. V. B. Hirsch and D. N. Spinelli, *Science* **168**, 869 (1970); J. D. Pettigrew and L. J. Garey, *Brain Res.* **66**, 160 (1974).

12. D. H. Hubel and T. N. Wiesel, *J. Comp. Neurol.* **158**, 295 (1974).

13. Supported by PHS grants MH-17570 to P.G.S., MH-14269 to the Experimental Psychology Program, HD-03110 to the Biological Sciences Research Center, and MH-11107 to the Neurobiology Program, and by a grant from the Office of Research Administration to P.G.S.

6 October 1976; revised 13 January 1977

Oscillation and Chaos in Physiological Control Systems

Abstract. *First-order nonlinear differential-delay equations describing physiological control systems are studied. The equations display a broad diversity of dynamical behavior including limit cycle oscillations, with a variety of wave forms, and apparently aperiodic or "chaotic" solutions. These results are discussed in relation to dynamical respiratory and hematopoietic diseases.*

There are a number of chronic and acute diseases in which a primary symptom is the altered periodicity of some observable; for example, the irregular breathing patterns in adults with Cheyne-Stokes respiration (Fig. 1a) (*1*) and the fluctuations in peripheral white blood cell counts in chronic granulocytic leukemia (CGL) (Fig. 2a) (*2*). Previous theoretical studies of the control of respiration (*3*) and the control of hematopoiesis (*4*) have associated disease processes with oscillatory instabilities in mathematically complex models. Here we associate the onset of disease with bifurcations in the dynamics of first-order differential-delay equations which model physiological systems. We have two goals: (i) to bring to the attention of theoreticians two examples from medicine of complex and poorly understood dynamics; and (ii) to show that simple mathematical models of physiological systems predict the existence of regimes of periodic and aperiodic dynamics, similar to those encountered in human disease. This work is an extension of the work of Li and Yorke (*5*), May (*6*), May and Oster (*7*), and others on the periodic and aperiodic behavior encountered in discrete time population models (*8*).

Consider the ordinary differential equation

$$\frac{dx}{dt} = \lambda - \gamma x \qquad (1)$$

where x is a variable of interest, t is time, and λ and γ are positive constants giving the production and decay rates, respectively, of x. Then $x = \lambda/\gamma$ in the limit of $t \rightarrow \infty$. In many physiological systems, λ and γ are not constants but depend on the value of x at some earlier time (*3*, *4*). Thus, the instantaneous rate of change of x at time t will depend on x_τ, the value of x at time $(t - \tau)$. We consider two complementary examples to illustrate the effects of allowing either λ or γ (but not both) to be nonlinear functions of x_τ. One is for the control of CO_2 elimination while the second embodies control of cell production.

In respiratory studies it has been established that the ventilation (V) is a sigmoidal function of arterial CO_2 concentration (x) (*9*). We assume that the CO_2 response curve is $V = V_\mathrm{m}x^n/(\theta^n + x^n)$, where V_m is the maximum ventilation, and θ and n are parameters adjusted to fit experimental observations (*10*). We further assume that CO_2 is removed from the blood at a rate proportional to its concentration multiplied by the ventilation (*3*), and that the blood is a well-stirred fluid. Therefore we assume that the arterial CO_2 control system may be described by

$$\frac{dx}{dt} = \lambda - \frac{\alpha\, V_\mathrm{m} x {x_\tau}^n}{\theta^n + {x_\tau}^n} \qquad (2)$$

where λ is the CO_2 production rate, τ is the time between oxygenation of blood in the lungs and stimulation of chemoreceptors in the brainstem, and α is a constant. The justification for Eq. 2 is heuristic: the equation reproduces certain qualitative features of normal and abnormal respiration.

As either the steepness of the CO_2 response curve or the delay time increases, the steady state becomes unstable and low-amplitude oscillations (Fig. 1b) or high-amplitude oscillations, in which there is a distinct apnea (Fig. 1c), are observed. Similar breathing patterns are observed clinically (*1*, *3*, *11*). Cheyne-Stokes respiration is often found in patients who have increased delay times between oxygenation of the blood in the lungs and stimulation of chemoreceptors in the brainstem, and also increased sensitivity to CO_2 (*11*). A phenomenon analogous to Cheyne-Stokes respiration in humans has been induced in dogs by inserting a circulatory delay between the heart and the brain (*12*). There are other pathological conditions in which highly irregular breathing patterns are observed; for example, apneic breathing in premature infants (*13*). We have not found a parameter range for Eq. 2 in which such complex patterns exist.

It is possible to analyze the stability of Eq. 2 in the neighborhood of the steady state (where $dx/dt = 0$). If at steady state x_0 is the CO_2 concentration, V_0 is the ventilation, and S_0 is the slope of the CO_2 response curve, then assuming parameters in the normal range (*14*), the instability condition can be computed (*15*) and is

$$S_0 > \frac{\pi V_0}{2\lambda\tau} \qquad (3)$$

For the parameter values cited we find instability for $S_0 > 7.44$ liter/min mm-Hg. At the instability the period of the oscillation is 4τ (*15*). These ana-