event. One such genetic change in the pathogenesis of CML appears to be the acquisition of the Ph[1]. We have demonstrated the presence of a novel 8.2-kb *abl*–related transcript in four of four Ph[1]-positive CML cells and cell lines. Recently, a similar sized *abl*-related RNA transcript (8.0 kb) was found in the leukemic cells of five of six patients with Ph[1]-positive CML, but was absent in Ph[1]-negative CML (*14*). Together, these results suggest a close correlation between the presence of the Ph[1] and an abnormal c-*abl* transcript. Indeed, this novel transcript may serve as a leukemia-specific marker analogous to the Ph[1] marker in patients with CML. It is possible that the translocation of c-*abl* from chromosome 9 to the Ph[1] that occurs in CML results in altered transcription of the c-*abl* locus manifest by the appearance of the novel 8.2-kb message. Such an altered transcript might give rise to an abnormal c-*abl* product that could somehow be related to the pathogenesis of CML. Alternatively, the altered messenger RNA could lead to alterations in translational processing of the transcript resulting in changes in the rate of synthesis of the c-*abl* oncogene product.

Although the Ph[1] is probably critical to the pathogenesis of CML, the blast crisis stage of CML probably cannot be accounted for by the Ph[1] alone, since this marker may be present for years in the chronic phase of the disease before blast transformation occurs. If the acquisition of the Ph[1] leads to an abnormal c-*abl* product, it may be possible to explain the inevitable progression of CML from the chronic phase to blast crisis as a quantitative increase in this novel c-*abl* product. The high levels of c-*abl*–related 8.2-kb message in the cell lines derived from blast crisis CML cells compared to chronic phase cells is consistent with this hypothesis. However, there could be other explanations of the enhanced expression of c-*abl*–related RNA message in CML blast crisis cell lines. For example, the enhanced expression could be a reflection of selective pressure in vitro for cells expressing relatively high levels of c-*abl* RNA. This possibility could be addressed by comparing levels of c-*abl* RNA expression in fresh, uncultured blast crisis CML cells and chronic phase cells from the same patient. Alternatively, c-*abl*–related RNA expression may diminish as cells mature and differentiate. For example, expression of RNA related to the *myc* oncogene markedly diminishes in HL-60 promyelocytic leukemia cells as the cells are chemically induced to differentiate (*15, 16*), and a similar phenomenon may occur with respect to the *abl* oncogene during differentiation of CML cells. Since chronic phase CML cells consist predominantly of relatively mature granulocytes, they might be expected to show lower levels of c-*abl* expression than the immature and less differentiated blast phase cells.

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The Latency of Pathways Containing the Site of Motor Learning in the Monkey Vestibulo-Ocular Reflex

Abstract. *The vestibulo-ocular reflex helps to stabilize retinal images by generating smooth eye movements that are equal to and opposite each rotatory head movement. It is well known that the reflex undergoes adaptive plasticity or "motor learning" whenever there is persistent image motion during head turns: the resulting changes in the reflex occur gradually and help to restore image stability. A new approach makes it possible to identify the pathways containing the site of motor learning according to their total latency in response to natural vestibular stimuli. The fastest pathways required 14 milliseconds to initiate a vestibulo-ocular reflex, but the site of motor learning was in pathways having latencies of at least 19 milliseconds.*

The capacity for adaptive regulation or "motor learning" plays an important role in establishing and maintaining the excellent performance of the adult vestibulo-ocular reflex (VOR). In normal individuals, the VOR helps to minimize image motion during head turns; it does so by generating smooth eye movements that are equal to and opposite each rotatory head movement. If visual or vestibular inputs are altered so that the VOR is no longer appropriate to stabilize visual images, an adaptive mechanism modifies the VOR and corrects its performance. The adaptive changes occur over a gradual and repeatable time course and, once acquired, are retained if either visual or vestibular inputs are withheld (*1, 2*).

The site of motor learning has not yet been discovered, but existing knowledge of the neural mechanisms underlying the normal VOR suggests several parallel pathways in which learning could occur. These include (i) the classical disynaptic reflex arc (*3*), (ii) a less-direct brainstem pathway that is thought to perform a mathematical integration of vestibular inputs (*4*), and (iii) an inhibitory side loop through the flocculus of the cerebellum (*5*). Because these three classes of pathways contain different numbers of synapses, they might exert their first effects on eye movement at different latencies after a transient vestibular stimulus: recordings of the VOR at short latencies after a rapid and sudden head acceleration might reveal the latency of the pathways containing the site of motor learning.

Motor learning was induced in the VOR by fitting two rhesus monkeys with optical devices that altered the normal

relationship between head movement and image movement. "Times-two" (×2) telescopic spectacles doubled the apparent size of the stationary surroundings, providing images that could be stabilized by doubling the normal amplitude at the VOR. "Times-zero" (×0) goggles contained a well-focused visual scene that moved exactly with the head, providing images that could be stabilized by reducing the amplitude of the VOR to zero. While wearing the optical devices the monkeys sat in a specially designed primate chair. The vestibular stimuli for adaptation were provided by the monkeys' active head turns (*2*).

We defined the state of VOR adaptation in the usual way, with sinusoidal vestibular stimuli. During VOR tests, monkeys sat in a primate chair and active head movement was prevented by securing hardware implanted on the monkey's skull to the ceiling of the chair. The spectacles were removed, the room lights were extinguished, and the magnetic search coil technique was used to monitor eye movement while the chair and monkey were subjected to sinusoidal oscillation at ±25 deg/sec by a servocontrolled turntable (*6*). Sinusoidal imposed head velocity causes sinusoidal smooth eye velocity, and the "gain" of the VOR can be estimated as peak-to-peak smooth eye velocity divided by peak-to-peak head velocity. In normal monkeys, VOR gain was 0.95 to 1.0 for sinusoidal frequencies over the range 0.1 to 2.0 Hz, and was about 1.15 at 4.0 Hz (*7*). After wearing the ×2 spectacles for 4 to 5 days, the two monkeys had VOR gains of 1.5 and 1.7 over the frequency range 0.1 to 2.0 Hz. After wearing the ×0 goggles for 4 to 5 days, they had VOR gains of 0.5 and 0.3. The gain changes were independent of testing frequency; thus VOR gain was always slightly (0.15) higher at 4.0 Hz than over the range 0.1 to 2.0 Hz.

Our new observations have come from testing the performance of the VOR during sudden, rapid changes in head velocity. Figure 1 shows records from a typical experiment in a monkey with a VOR gain near 1.0. As before, experiments were conducted with the monkey in complete darkness. The vestibular stimulus was a triangle wave of head position that underwent a change in the direction of movement every 400 msec. The position records show most clearly the function of the VOR—smooth eye movement is equal and opposite to head movement. However, the velocity records provide the best monitor of the eye movements during the changes in head velocity; these were digitized during the experiment (*8*) and subjected to quantitative analysis. For each direction (left or right) and for two amplitudes (10 or 30 deg/sec) of stimulation, at least 20 records were aligned on the onset of the change in head velocity. Eye and head velocity were averaged for 100 msec before and 400 msec during and after the stimulus. Records containing saccadic eye movements were not used in making the averages. Figure 2A shows on an expanded time scale the averages that resulted from this procedure. The stimulus was a change in head velocity that had an amplitude of 30 deg/sec and required 40 to 50 msec to reach final velocity. The response was a change in eye velocity that had a clear onset (arrow) and a measurable latency (which averaged 14.2 msec) (*9*). The standard deviation of eye velocity was small.

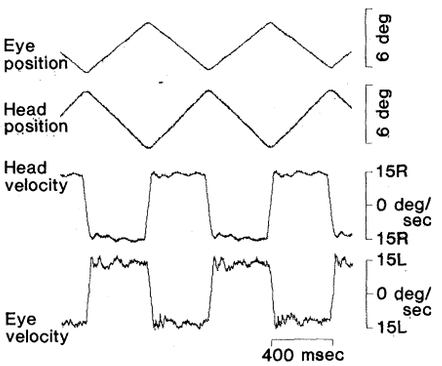

Fig. 1. The VOR during rapid changes in head velocity in a normal monkey. Changes in head velocity occurred every 400 msec, were 30 deg/sec in amplitude, and occurred in total darkness. The smooth eye movements of the VOR can be seen in greater detail in the eye velocity records. We have selected a segment of data in which the monkey made no saccadic eye movements to emphasize the smooth compensatory nature of the VOR. Upward deflections indicate rightward positions and velocities.

To determine the latency of the pathways that undergo adaptive modification, we compared responses like those in Fig. 2A after monkeys had been adapted to have different VOR gains. Figure 2B shows three eye velocity averages, all produced in one monkey by leftward steps of head velocity 30 deg/sec in amplitude, but on 3 days when VOR gain was 0.3 (low), 1.0 (normal), and 1.7 (high). Note the differences in the steady-state eye velocity before and af-

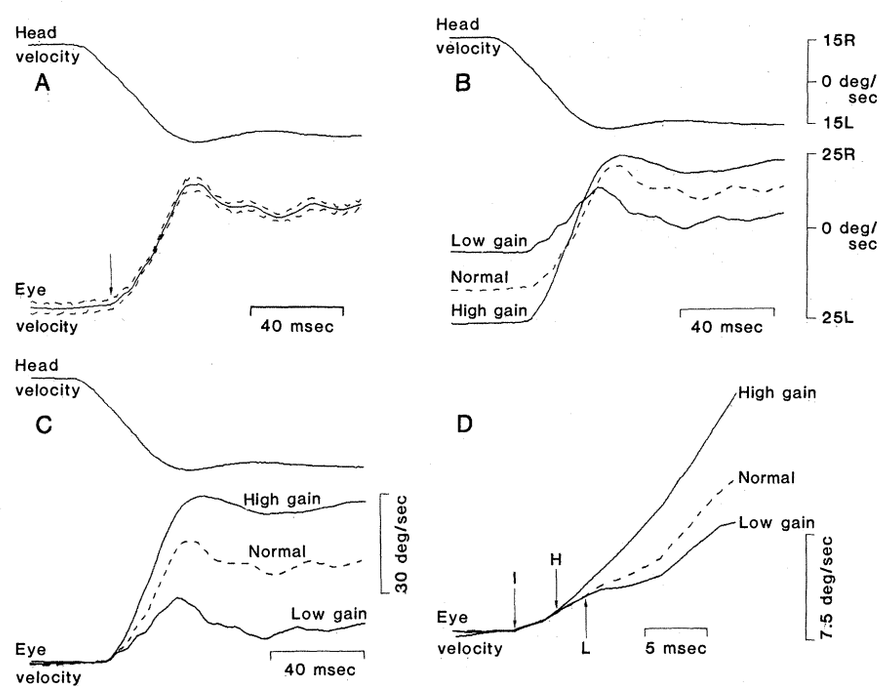

Fig. 2. Effect of adaptive changes in VOR gain on the eye velocity caused by rapid changes in head velocity. (A) Fast sweep-speed records showing average eye and head velocity for a rightward stimulus of 30 deg/sec. The dashed lines indicate 1 standard deviation of eye velocity. The vertical arrow shows the onset of the change in eye velocity caused by the head velocity stimulus. (B) Comparison of the eye velocity averages in one monkey when VOR gain was 1.7 (high), 1.0 (normal), or 0.3 (low). Note the gain-related changes in steady-state eye velocity before and after the stimulus. The change in head velocity was 30 deg/sec in amplitude. (C) Comparison of the same eye velocity averages as in (B), but with the low-gain and normal records shifted vertically to facilitate comparison of the eye movements at short latencies after the onset of the change in head velocity. (D) Magnification of the short-latency events in (C). The start of the record is 10 msec after the onset of the change in head velocity. The arrows indicate the onset of the eye velocity response (I) and the times at which the high- (H) and low-gain (L) responses deviated from the normal average.

ter the change in head velocity. Figure 2C shows the same three traces, but now with the normal and low-gain traces shifted vertically so that the three averages are superimposed just before the change in head velocity. The initial trajectory of the response is the same in all three gain states, whereas the adaptive changes are evident at later times. Figure 2D shows the early part of the eye velocity responses at high magnification. To estimate the time at which the high- and low-gain averages of eye velocity deviated from the normal eye velocity, we have measured magnified records like those in Fig. 2D. For increases in VOR gain, the averaged eye velocity records deviated from the normal averages at latencies averaging 18.6 msec after the onset of the head velocity stimulus (4.4 msec after the onset of the VOR); for decreases the eye velocity deviated from normal at latencies averaging 19.9 msec [5.7 msec after the onset of the VOR (*10*)]. Similar results were obtained when the VOR was tested with gentler changes in head velocity that had exponential trajectories and required 100 msec to reach a final value. The high- and low-gain responses did not deviate from the normal averages until 6.5 msec (4.25 and 8.75 msec in the two monkeys) after the onset of the VOR.

An intriguing feature of Fig. 2 is the sequence of inflections in the eye velocity records taken when VOR gain was low. Similar but smaller inflections occur at the same times in the normal and high-gain records, but none are apparent in the head velocity record. If the inflections were a response to some undetected component of the stimulus, we would have expected them to be larger when VOR gain was higher (*11*). Therefore, we believe that the inflections are a genuine part of the response and that they reflect the contributions of VOR pathways having different latencies.

Our data imply that the VOR is driven by several parallel pathways having different latencies and that the site of motor learning is in pathways having latencies of at least 19 msec, roughly 5 msec longer than the pathways with the shortest latency. Although it is not yet possible to be specific about the anatomical site of changes, our data may exclude the classical disynaptic reflex arc, which would be expected to drive the earliest part of the VOR (*12*). If we assume that synaptic delays are on the order of 0.5 msec, as is generally found with electrical stimuli, the 5-msec difference between the latency of the VOR and the latency of the modifiable pathways would allow for a rather large number of intervening synapses. However, it may take much longer for presynaptic activity resulting from natural stimuli to affect the firing of a postsynaptic cell. For example, Purkinje cells in the flocculus of the cerebellum receive di- or trisynaptic inputs from the vestibular nerve, but respond to sudden changes in head velocity with latencies 10 msec longer than was seen in vestibular primary afferents (*13*). Thus, the modifiable pathways may contain as few as one or two extra synapses (*14*). Definitive interpretation of our data, however, must await neurophysiological studies using the same rapid changes in head velocity used here.

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8. To obtain voltages proportional to eye velocity, the eye position signal was processed by an operational amplifier circuit that was an effective differentiator up to 50 Hz. A voltage proportional to head velocity was taken from the tachometer output of a turntable (Contraves Goertz). Both signals were digitized at sampling rates 500 or 1000 Hz; results did not depend on sampling rate.
9. This value agrees with the data of J. Lanman, E. Bizzi, and J. Allum [*Brain Res.* **153**, 39 (1978)].
10. The numbers given here represent average values for the two monkeys, for leftward and rightward head accelerations, and for changes in head velocity of 10 and 30 deg/sec. In one monkey, the values were smaller for decreases in VOR gain than for increases, while in the other monkey the opposite situation obtained. Across both monkeys and all stimuli, the delay between the onset of the VOR and the deviation of eye velocity records from normal ranged from 2 to 9 msec.
11. To obtain an independent monitor of the trajectory of the head velocity stimulus, we analyzed the eye velocity records obtained from a calibration search coil that was held stationary in the world while the chair and field coils underwent rapid changes in velocity. The resulting records mirrored the head velocity monitor from the tachometer on the shaft of the turntable, and showed no evidence of extra inflections during the rapid change in head velocity.
12. The conduction times in disynaptic VOR pathways are very short: the total delay from labyrinth to abducens motoneuron is 0.9 to 1.7 msec in rabbit [S. M. Highstein, *Exp. Brain Res.* **17**, 301 (1973)] and 1.2 to 2.0 msec in cat [R. G. Baker *et al.*, *Brain Res.* **15**, 577 (1969)]. Thus it would be difficult to argue that any other pathway was responsible for the earliest part of the response to rapid changes in head velocity.
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15. Supported by NIH grant EY03878, BRSG grant 05355, the McKnight Foundation, and the Alfred P. Sloan Foundation. I am grateful to L. E. Westbrook for her attention to the monkeys, to M. Stryker and A. Lander for their comments on an earlier version of the manuscript, and to F. Miles for lending me his set of magnifying spectacles.

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Phencyclidine-Induced Immunodepression

Abstract. *Phencyclidine ("PCP" or "angel dust") and some of its derivatives are psychotomimetic drugs that have been used in general anesthesia for some time. This drug blocks potassium ion channels in brain tissue, and there is a specific PCP binding to lymphocytes. In a study of the effects of this drug on immunocyte function, it was found that humoral and cellular immune responses in vitro were depressed when immunocytes were treated with PCP before biological assay. This finding has implications for PCP abuse and also for the use of its derivative in general anesthesia, where it may contribute to postoperative infection.*

Phencyclidine ("PCP" or "angel dust") is a psychotomimetic drug that is abused in epidemic proportions in many areas (*1, 2*). The schizophrenia-like syndrome that sometimes occurs with PCP abuse (*3*) or that is seen as a hallucinogenic reaction to general anesthesia (*4*) has stimulated a search for the mechanisms producing these adverse effects (*5–8*). Although the neuropharmacological effects of PCP have received attention, the effects of PCP on the immune system have not been studied. We have found that PCP acts as an immunodepressant, at least in the immunological parameters studied in vitro. This finding is important for restoring the mental health of the PCP abuser as well as in situations in which PCP derivatives like ketamine are used for general anesthesia during surgery (*9*).

Our investigation of the effects of PCP on the immune system was based on the hypothesis that some forms of schizophrenia could be considered an autoimmune disease of the central nervous sys-