receptive than ancestral females, it is doubtful that this increased receptivity is the cause of the isolation. The courtship latency and duration data indicate that geopositive and ancestral males have similar mating propensities, but in male choice experiments with ancestral males an almost equal number of matings occur with geopositive and ancestral females. The next significant index was found for ancestral males and geonegative females. Since geonegative females are no more receptive than ancestral females, the isolation observed cannot be attributed to differences in mating propensity between female types.

The absence of any correspondence between standard measures of mating propensity and the outcomes of the male and female choice experiments suggests the existence of courtship discrimination at some level in these populations. However, for the four derived strains I used, there is no apparent relation between this sexual discrimination and the direction of evolution. Furthermore, though an element of female preference is being measured by both female and male choice tests, the two types of tests give conflicting preference patterns in more than one instance. Inspection of the data shows that there is a closer correspondence between the results of multiple choice and female choice tests than between either of these and male choice tests. Caution should be exercised in interpreting results of male or female choice experiments for other reasons as well. What appear to be tendencies toward strong isolation, as in tests with the geotactic strains and the ancestral population, may in fact cancel each other out in multiple choice tests. No data exist to suggest which of the three experimental designs represents the closest approximation to breeding conditions of natural populations; but with the exception of those species in which males and females are distributed on different substrates, the multiple choice situation may be the most realistic.

While the strains in this study are not species, the pattern of the isolation described in this report has been found in these strains at two other time points during their history (*8*), and there is no reason to expect the trend to change. Mayr (*2*) proposed that selection may bring about behavioral changes before morphological changes during evolution, an idea that has been substantiated for the geotactic (*9*) and phototactic (*10*) strains used in this study. Multivariate analysis (*11*) of the mating behavior of these strains may provide insight into the question of gain or loss of courtship elements. Similar degrees of isolation have been found among other laboratory strains (*12*), suggesting that premating isolation may develop more rapidly than postmating isolation.

For the strains I have described, there appears to be no relation between mating preference and the direction of evolution. Thus the relationships proposed by Kaneshiro (*3*) and Watanabe and Kawanishi (*4*) are not general concomitants of the evolutionary process. However, a consistent relationship having predictive value might exist for certain species groups. Such relationships might depend on the ecological and evolutionary history of a particular group. Evolutionary events may occur differently for species that arise from a single female founder and that colonize an island, compared to species occupying mainland areas in large numbers (*13*). Sympatry and allopatry, which have been shown to impose asymmetrical character displacement for reproductive isolation, provide still another model for examining evolutionary directions (*14*).

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$$I = [(n_{11} + n_{22}) - (n_{12} + n_{21})]/n$$
where n_{11} is the observed number of matings between females of the first strain and males of the first strain, n_{12} is the number of matings between females of the first strain and males of the second strain, and n is the total number of observed matings [H. Stalker, *Genetics* **27**, 238 (1942)]. The standard error (S.E.) of I [C. Malogolowkin-Cohen, A. S. Simmons, H. Levene, *Evolution* **19**, 95 (1965)] is given by S.E. = $\sqrt{[(1 - I^2)/n]}$. Similarly, the female (I_1) and male (I_2) isolation indexes are given by
$$I_1 = (n_{11} - n_{12})/n$$
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Spatial Localization After Strabismus Surgery: Evidence for Inflow

Abstract. *Strabismics pointed to targets (without sight of the hand) before and again after surgery that altered the position of the deviating eye in its orbit. Patients having this surgery for the first time were able to use proprioceptively derived information about the surgically altered eye position. In contrast, patients who had similar operations, but on muscles that had been operated on one or more times in the past, were apparently deprived of this information. The important afference may be supplied by the tendon organs.*

How do we know which way our eyes are pointing? Since the time of Helmholtz, the prevailing opinion has been that signals sent to the eye muscles from the brain (efferent, or outflow, signals) provide this information, whereas inflowing (proprioceptive, or afferent) signals are not used (*1*). Although it has been anatomically established that eye muscles contain spindle organs and tendon receptors, and although there is also physiological evidence demonstrating the properties of these receptors, their function remains unclear (*2*).

We have been testing eye-hand coordination in patients undergoing extraocular muscle surgery for strabismus. The results from those patients undergoing surgery for the first time are not consistent with the outflow model and suggest that these patients are using inflow information that apprises them of the changed position of the eye in its orbit. The results from a second group of patients who had repeated surgery on the same eye muscles suggest that the tendons are important structures in supplying this afference.

We required patients to point with an unseen hand to a small light in totally dark surroundings (created by a light-proof box that fit over the head and neck of the supine patient). It contained three light-emitting diodes (LED's) at arm's length, one placed in the median plane, one 10° to the left, and one 10° to the

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Table 1. Type and amount of strabismus, type of surgery, and mean shifts in pointing responses after surgery. Abbreviations: RXT or LXT, right or left exotropia; LX(T), intermittent left exotropia; RET, right esotropia; AXT, alternating exotropia; RLR or LLR, right or left lateral rectus; RMR or LMR, right or left medial rectus.

Patient	Strabismus (prism diopters)	Amount of surgery (mm)		Mean shifts in pointing responses (degrees)	
		Recess	Resect	Rotated eye	Intact eye
			First surgery		
M.W.	25 RXT	RLR 7.5	RMR 5	4.5	0.8
C.T.	25 RXT	RLR 7.5	RMR 5	1.6	−4.2
A.M.	25 LX(T)	LLR 7.5	LMR 5	1.3	−8.3
J.F.	25 LXT	LLR 7.5	LMR 5	6.1	0.7
L.B.	20 RXT	RLR 8	—	4.8	−1.0
I.L.	20 RET	RMR 5	—	2.3	3.1
K.O.	20 LXT	LLR 7	—	2.1	−4.6
J.P.	20 AXT	LLR 7	—	1.6	−3.7
G.F.	25 LX(T)	LLR 7.5	—	4.6	−4.7
Mean ± standard deviation				3.2 ± 1.8	−2.4 ± 3.6
			*Repeated surgery**		
L.B.	12 RXT		RMR 6	13.1	3.9
M.B.	20 RXT	RLR 6	RMR advanced to original insertion	17.7	−1.5
A.S.	25 RET	RMR 3	RLR 7.5	21.6	0.4
L.K.	35 RET	RMR 4.5	RLR 7	12.0	2.3
T.W.	40 RXT	RLR 7	RMR 7	12.2	3.6
Mean ± standard deviation				15.3 ± 4.2	1.7 ± 2.3

*Previous surgery: L.B., recessed RLR; M.B., recessed RMR, resected RLR; A.S., two prior marginal myotomies of the RMR; L.K., four prior surgeries with the RMR myotomized once and recessed three times, and the RLR resected once; T.W., three prior surgeries with at least one resection of the RLR.

right of the midline. On the outside of the box, a centimeter scale extended across the positions of the LED's. The patient touched the scale when asked to point to the apparent position of a target (only one of which was on at a time), and the experimenter recorded the position of the fingertip to within 0.5 cm. The patient was always tested monocularly. A random sequence of six to ten pointing responses for each target was taken 24 hours before and again after surgery (*3*). After surgery, the altered eye was occluded by a bandage until the time of testing, some 7 to 48 hours later. The surgically altered eye was always tested as soon as the bandage was removed and before the patient had any visual experience with that eye.

The first patients tested had had no previous surgery, were old enough to understand the instructions, were going to have only one eye operated on, and had a nonparalytic form of horizontal strabismus (*4*). The expectation, based on outflow theory, was that the brain would be uninformed about the surgical rotation of the eye in the orbit and therefore there should be a large pointing error when the rotated eye was used in the eye-hand open-loop pointing task and no error when the intact eye was used. Table 1 shows the average shifts (the mean postoperative pointing response minus the mean preoperative response) for the nine patients in this group. The average amount of shift with the altered eye was only about 25 percent of the amount the eye was turned by the surgery (true for eight of the nine patients) (*5*). For four of the patients only a small shift was recorded with the altered eye, whereas a large shift, in the opposite direction, was measured with the intact eye (*6*). These results indicate that the oculomotor system had access to information about the position of the rotated eye in its orbit before there had been any visual experience. Information about eye position must have been obtained from nonvisual, proprioceptive sources (*7*).

One patient (L.B.) had a cosmetically unacceptable result from surgery and so underwent surgery again. When the pointing tasks were repeated, the altered eye gave rise to a large shift in pointing responses (13°). We then tested four additional patients who were having repeated surgery on the same eye muscles. The testing procedures were as they had been with the first patients. Large shifts in pointing responses were obtained with the treated eye, and relatively small ones with the intact eye (Table 1). This group of patients followed the outflow model's prediction: the oculomotor system seemed unaware that the eye had been turned, an effect largely confined to the treated eye.

Our admittedly speculative hypothesis is that in some not yet understood way the tendon end organs are important elements in a scheme for eye position proprioception. If the effects of the recession surgery include a formation of scar tissue that takes some time (at least days or weeks) to develop, perhaps this scar tissue destroys or distorts tendon afference that could have been present immediately after surgery. We suggest that patient L.B., when operated on the second time, lost by the resection procedure the tendon organs on her right medial rectus, having already lost by scarring the tendon afference from her right lateral rectus. She was then left with no afference about horizontal eye position and produced the very large pointing error. All other patients with repeated surgery would be presumed to have, either by scarring or resection, no tendon receptors left.

This is a difficult hypothesis because all established facts about tendon organ function indicate a role in phasic responses to stretch and never any suggestion of a role in supplying positional information (*8*). Perhaps they play a role in gating proprioceptive input from other sources. It may be that the proprioceptive information about eye position—from whatever source—takes some time to be used. The shortest interval between time of testing and time of surgery was 7 hours, and 24 to 48 hours was more common. Perhaps outflow is used as the short-term indicator of eye position, whereas inflow allows for modification and recalibration of this fast system over longer periods of time, a concept proposed by Ludvigh (*9*).

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3. For some of our patients, eyes were monocularly tested with a patch over the untested eye. Later modifications to the testing apparatus made use of a light-polarizing material to dissociate the targets to the two eyes and allowed randomization of the sequence in which the two eyes were assessed. There was no apparent effect of this modification on the pointing responses. Patients always saw only one small light in an otherwise totally dark room. Although some of our patients were amblyopic, their visual acuity in all cases was adequate for performing the task. Variability, as measured by the standard deviation of the pointing responses to each target, was around 2° in most cases. Absolute accuracy in localizing was not determined because the analysis was concerned with the shift in pointing responses after surgery. This was assessed by subtracting the mean response to each target before surgery from that after surgery. A positive shift is one in the direction predicted by the outflow theory.

4. The surgery always involved the recession of one of the horizontal rectus muscles; the muscle (at the tendon) was moved backward on the globe and reattached. In about half of the cases, a resection of the other horizontal muscle was also performed. Resection involves the removal of most or all of the tendon and the reattachment of the muscle to its point of original insertion [H. M. Burian and G. K. Von Noorden, *Binocular Vision and Ocular Motility* (Mosby, St. Louis, 1974), pp. 434–450].
5. A conservative estimate of the amount of rotation of the eye produced by the surgery was assessed by alternate cover tests after 1 week. At the time of the pointing test, the amount of eye turn from surgery was usually more than that found 1 week later, as the eye "settles in" to its resting position.
6. A model predicting these opposite effects requires the concept of a cyclopean projection center for the origin of egocentric localization. The position of the covered eye will influence localization responses made with the uncovered eye (H. Ono and E. Weber, *J. Exp. Psychol. Hum. Percept. Perform.*, in press). If we assume that our strabismic patients also have some binocular interaction when pointing monocularly, we can account for the directions of the shifts. Assume that the covered or nonseeing eye, irrespective of whether it has been operated on or not, is registered as being too far nasal, that is, not converged to the same point in space as the seeing eye, but overconverged. The direction of the target would then appear to be shifted toward the uncovered eye.
7. The surgery can be considered anatomically symmetrical in the recess-resect procedure. It is as if the muscles are detached from the globe, the globe turned, and the muscles then reattached. In a mechanical sense the length-tension characteristics, and possibly any spindle afference, could also be unaffected by this form of surgery. But, much, if not all, of the tendon is removed in the resected muscle, so any potential afference from the tendon organs would be lost. These tendon receptors are found in human extraocular muscle [(*1*), p. 154]. In the recession-only procedure, there is mechanical, and presumably proprioceptive, asymmetry. No consistent pattern emerges between the recess-resect or recess-only procedures (Table 1).
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Long-Term Stress-Induced Analgesia and Activation of the Opiate System

Abstract. *Exposure of rats to a series of inescapable shocks produced in sequence both an early naltrexone-insensitive and a late naltrexone-reversible analgesic reaction. Activation of the opiate system was necessary and sufficient to produce an analgesic reaction 24 hours later on exposure to a small amount of shock. The amount of inescapable shock which induced naltrexone-reversible analgesia also produced hyperreactivity to morphine 24 hours later.*

Exposure to a variety of painful or stressful events produces an analgesic reaction (*1, 2*). This phenomenon, called stress-induced analgesia (SIA), has received considerable attention because it has been thought to provide insight into the psychological and physiological factors that activate endogenous pain control and opiate systems. Both electrical stimulation and opiate peptide microinjection into portions of the medial brainstem elicit analgesia (*3*). It has been speculated (*4*) that endogenous opiates are released in response to stress and inhibit pain by activating this midbrain system. However, the results of manipulations designed to assess the involvement of opiate systems in SIA, such as reversal by opiate antagonists, establishment of cross-tolerance to morphine, and pituitary and adrenal manipulations to prevent the release of β-endorphin, have been inconsistent (*2, 3*). Consequently a number of investigators have proposed that both opiate and nonopiate forms of SIA exist (*2, 3, 5*).

If there are opiate and nonopiate forms of SIA, it is important to learn what determines which form occurs. Recently, Lewis *et al.* (*5, 6*) suggested that the temporal characteristics of the aversive stimulation may be critical in determining which type of analgesia is elicited. They found that naloxone, dexamethasone, and long-term treatment with morphine blocked the analgesia elicited by 20 minutes of intermittent foot shock. However, 3 minutes of continuous foot shock resulted in an analgesia that was unaffected by these manipulations. Thus either the pattern, amount, or duration of shock is critical.

Maier and his colleagues have shown that the inescapable shock used to induce learned helplessness (80 5-second shocks at 1-minute intervals) (*7*) produces both the usual short-term SIA measured within 30 minutes of the end of the session and a long-term form that can be reinstated 24 hours later by a brief exposure to shock (*8*). Both of these analgesic reactions were blocked by naltrexone (*9*) and were completely cross-tolerant with morphine (*10*). Moreover, this opiate-mediated SIA is only activated if the subject was previously exposed to inescapable shock (*8*). Rats that were allowed to escape shock did not experience analgesia, whereas subjects administered an equivalent amount of uncontrollable shock did. This was true for both short-term and long-term SIA. The organism's learning that there is no escape from an aversive stimulus may, therefore, be another variable determining whether opiate systems are activated.

It should be noted that the stressor in studies of SIA has typically been inescapable. Further, if learned helplessness is important in triggering opiate-mediated SIA, then the shock parameters should be critical. Many shocks over an extended period may be required for such learning to occur. A brief exposure—whether intermittent or continuous—should be insufficient for such learning and should lead only to nonopiate-mediated changes in pain reactivity. It follows that both nonopiate and opiate forms of SIA should occur sequentially during a long series of inescapable shocks.

To test this idea, we injected 20 rats with naltrexone (14 mg/kg) and 20 rats with saline. This dose was used because it blocks both short- and long-term analgesia (*9*). Twenty minutes later the rats were placed in restraining tubes and tested for baseline pain sensitivity by measuring the latency period before they flicked their tails at least 0.5 cm laterally away from radiant heat. Half of the rats in each group were given 80 5-second, 1-mA inescapable shocks through tail elec-

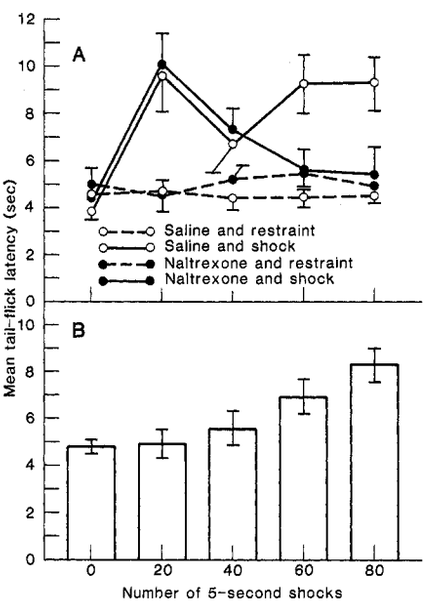

Fig. 1. (A) Mean tail-flick latencies during inescapable shock or restraint following administration of naltrexone or saline. (B) Mean tail-flick latencies for subjects given 0, 20, 40, 60, or 80 inescapable shocks and then, 24 hours later, exposed to a few additional shocks.

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