PRCs is very good (Fig. 4, A and B), but simulation with as few as 20 elements yields credible results (Fig. 4C). The model predicts the shape and slope of the PRC, the effect of stimulus intensity, the overlap of branches at the discontinuity, and the stochastic noise in free run but does not predict the long-term drift and adaptation phenomena. Simulation runs based on the use of this oscillator model instead of the analytical representation of the PRC yield the expected synchronous and alternating 1:1 modes as well as the usual $n:(n + 1)$ and $m:n$ phase locks. I make no claim for the "truth" of the model, which is introduced only to show that a simple mechanistic explanation with a minimum of ad hoc assumptions can account for the versatile synchronization behavior of *Mecopoda*.


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8. In southeast Asia there are several sibling species of *Mecopoda*, loosely referred to *M. elongata* (L.): morphologically they are very similar, but their songs and geographic distribution are diagnostic. I am provisionally using code letters to identify them: species S is found in the lowlands of peninsular Malaysia and is the common species in Singapore; at 25°C it chirps every 2.1 s, and each chirp consists of 8 to 13 pulses (wing strokes). Species N is from Bali, Indonesia: it sings at a rate of 4.5 chirps per second at 25°C, and each chirp consists of 4 to 5 pulses. Voucher specimens and tape recordings of these two and two additional species have been deposited in the British Museum (Natural History).
9. The Poincaré map is defined by

$$\phi(i + 1) = 1 - f[\phi(i)] + \phi(i) + T_s/T_0 \pmod 1$$

where $T_s$ is the stimulus period and $f[\phi(i)]$ is the perturbed cycle length $T$ given by the PRC (*14, 16*). The branches of the PRC were fitted with simple polynomial functions and, at each stage in the iteration of the Poincaré map, superimposed with random noise of magnitude appropriate to the particular insect; the intrinsic period $T_0$ at each iteration was corrected by the empirical adaptation function discussed above.
10. Technically these are "echemes" in the terminology of W. B. Broughton [*Physiol. Entomol.* 1, 103 (1976)]; "chirp" is easier to use, and in this case, closely onomatopoeic.
11. Extrapolation of the linear least-squares fit to the data from three individuals yields a temperature of 9.2°C at zero CR. This is near the mean of the range reported by T. J. Walker, *J. Comp. Physiol.* **101**, 57 (1975).
12. If I use precisely timed, computer-generated chirps previously recorded on tape, the overall system error in detecting chirp onsets is about 2 ms; with natural song the first pulse of some chirps may be missed, which introduces an error of about 25 ms equivalent to 1 to 2% of the chirp period.
13. *Mecopoda* males were kept in screen cages on food plants and misted with water daily. Captive adults lived as long as 4 months: the characteristics of stridulation became established about 10 days after molting and remained unaltered thereafter. Temperature ranged from 24° to 30°C and was recorded with each run. Runs were taped on a Sony TC-D5M with two Audio Technica AT-811 microphones. Stimulus generation, data acquisition, and analysis were carried out on an XT-compatible computer fitted with a 12-bit analog-to-digital and digital-to-analog interface. Stimulus signals were amplified and played back through a piezoelectric tweeter. Oscillographic and fast Fourier transform spectral analysis of the artificial chirp showed it to be virtually indistinguishable from the original. A signal volume equal to that of the natural chirp was taken as the 0-dB [sound pressure level (SPL)] reference; SPL levels for signals at other volumes were calculated from relative oscillographic amplitude.
14. For general discussion of phase response (or resetting) curves, see L. Glass and M. C. Mackey, *From Clocks to Chaos* (Princeton Univ. Press, Princeton, NJ, 1988). See also T. Pavlidis, *Biological Oscillators: Their Mathematical Analysis* (Academic Press, New York, 1973). For a classical example, see D. S. Saunders, *J. Comp. Physiol.* **124**, 75 (1978).
15. Hysteresis of this type is also present in purely physical systems: see J. P. Gollub, T. O. Brunner, B. G. Danly, *Science* **200**, 48 (1978).
16. If the maps are iterated without superimposed simulated noise, some of them yield classical period-doubling cascades and chaotic regions. The presence of noise obliterates most of these phenomena, but bifurcations are sometimes discernible. See L. P. Kadanoff, in *Regular and Chaotic Motions in Dynamic Systems*, G. Velo and A. S. Wightman, Eds. (North Atlantic Treaty Organization Advanced Science Institutes, Series B, Plenum, New York, 1985), p. 118; R. M. May, *Science* **186**, 645 (1974); M. R. Guevara, L. Glass, A. Shrier, *ibid.* **214**, 1350 (1981).


17. I thank D. R. Ragge of the British Museum (Natural History) for helpful suggestions and advice on the taxonomy of *Mecopoda*.

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# The Role of Ocular Muscle Proprioception in Visual Localization of Targets


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**The role of ocular muscle proprioception in the localization of visual targets has been investigated in normal humans by deviating one eye to create an experimental strabismus. The passively deviated eye was covered and the other eye viewed the target. With a hand-pointing task, targets were systematically mislocalized in the direction of the deviated nonviewing eye. A 4- to 6-degree error resulted when the nonviewing eye was offset 30 degrees from straight ahead. When the eye was deviated, the perceived "straight-ahead" was also displaced, by a similar amount, in the same direction. Since the efferent motor commands to the displaced and to the nondisplaced eyes are presumably identical by the law of equal innervation, the mislocalization of visual objects must be attributed to the change in proprioceptive information issued from the nonviewing, deviated eye. Thus proprioception contributes to the localization of objects in space.**


IN ORDER TO LOCALIZE AN OBJECT IN space, when the head is fixed, the central nervous system (CNS) must use a combination of visual (retinal) information and a knowledge of the position of the eye in orbit. Two major hypotheses have been put forward to explain how eye position is sensed: the outflow or efference copy hypothesis, first suggested by Von Helmholtz in 1867 (*1*), which is based on sensing the motor commands to the ocular muscles, and the inflow or afferent hypothesis, first suggested by Sherrington in 1918 (*2*), which is based on sensing proprioceptive inputs from the ocular muscles themselves.

Until recently, the efferent copy hypothesis has been accepted as the correct mechanism for visual target localization. No certain function was attributed to ocular muscle proprioception. But recent anatomical studies confirm widespread projections of orbital muscular afferents to a variety of CNS structures concerned with the control of movements of the eyes and of the head (*2*). Physiological studies, too, suggest a role for proprioception in various visual functions, such as development of the orientation of receptive fields (*3*). Finally, studies in humans with naturally occurring strabismus give hints of a functional role for proprioception in the localization of visual targets. We have found that some strabismics (*4*), either eso- or exo-deviated, when tested in a hand-pointing task, make errors as large as 10° to 20° in the direction of the nonfixing eye.

From these observations, we hypothesized that the visual localization mechanism relies on both afferent and efferent information derived from both eyes, whether or not both eyes are used to fixate the target. To test this hypothesis we deviated the non-


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viewing eye in normal subjects (Ss) by means of a suction scleral lens and found that such an artificial strabismus resulted in mislocalization of targets by the unperturbed, viewing eye.

In a first experiment, we tested the effect of a sustained passive deviation of one eye, covered, on the localization, as indicated by the hand, of visual targets viewed by the other eye. The ability of the Ss to indicate the perceived position of a punctate target was quantified by means of a technique commonly used in prism adaptation studies in which the S indicates the position of a visual target with the index finger (*5*). Our experiment took place in total darkness so that the S was unable to use vision to correct for any errors in localization. Three target positions were chosen to appear 38 cm from the S's eyes. One target was in the midsaggital plane of the S and the other two at 9 cm from the center (12° as seen by the S's eyes), one on each side of the center one. The experimental conditions were varied after each set of 15 pointings (5 pointings to each of the three targets). A typical series of three sets of pointings usually started with a set in normal monocular viewing (no mechanical deviation of the covered eye), followed by a set with the lens-fitted eye (Fig. 1) deviated in one direction, and finally with another set in normal monocular viewing.

Each of the five Ss showed large errors in localization induced by deviation of the covered eye. Nevertheless, none of the Ss noticed any apparent change in the position of the target as viewed by the undeviated eye, either while the covered eye was brought to its deviated position or during sustained deviation (*6*).

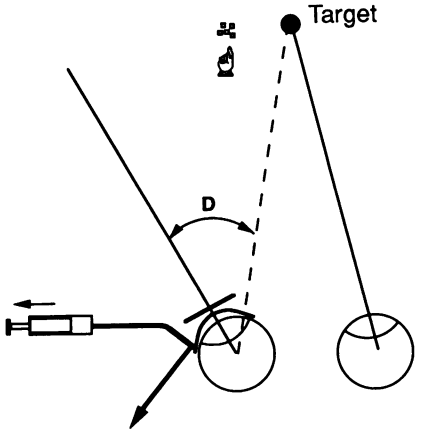
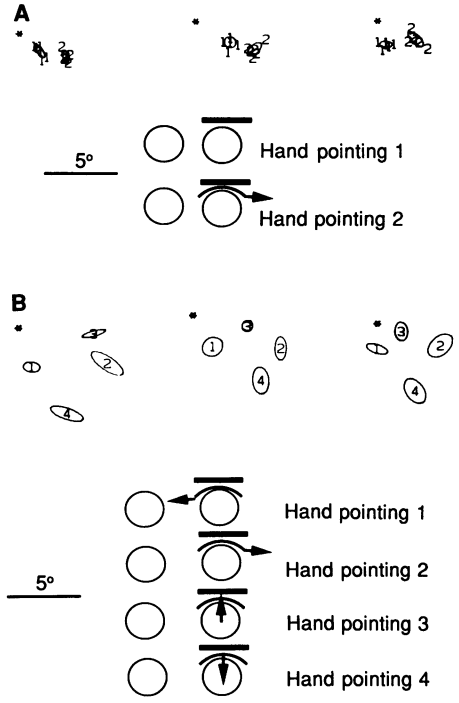



**Fig. 1.** Experimental arrangement. A suction lens was used to induce a sustained deviation of one eye. The lens was secured to the cornea through a light air vacuum produced by a syringe. A vacuum of about 0.8 atmospheres yielded perfect adherence of the lens. The deviated eye was covered, and the S viewed the target with the normal eye. Adherence of the lens to the sclera was ascertained at regular intervals throughout the experiments by requesting the S to fixate a target 30° in the direction of the deviated eye and report about the visual perception of the target. Absence of diplopia in this fixation condition and creation of a diplopia on adding extra tension on the deviated eye was a cue for perfect lens adherence to the cornea.

**Fig. 2.** Typical pointings to three target positions (*) (**A**) The pointing map compares the performance of a S in normal monocular viewing (1) and with the right eye deviated to the right (2). The drawings depict the visual conditions. Individual marks (five trials directed toward each target) and confidence ellipses (centered on the mean pointing positions) are represented for each condition. (**B**) Comparison on a single map of the means of the pointing trials directed to the three targets when the left eye was successively deviated to the left (1), to the right (2), up (3), and down (4).




We obtained two data sets, one under normal viewing condition, and one when one eye, covered, was offset 30° from the viewing eye (*7*). Since the 30° eye deviation was referred to the head, which was fixed in space, the angular misalignment of eyes varied for each target. For example, with the right eye deviated 30° to the right, the eye misalignment was 18° while fixating the right target, 30° for fixation of the central target, and 42° for the left target (Fig. 2A). This allowed us, in a single experiment, to derive a curve describing target localization error as a function of eye misalignment. In normal viewing, the Ss slightly mislocalized the targets; the systematic error was about 2° for all three targets. With the right eye passively deviated, the location of the target presented straight ahead was judged, on average, to be 4.08° ± 0.81° to the right of its actual position. A similar localization error was found for the left target, whereas the position of the right target was judged to be only slightly to the right of its perceived position in normal viewing. All Ss also showed more variability of response when the eye was deviated than in the normal viewing condition. We have no explanation for this observation. In subsequent experiments we determined the average errors in localization resulting during deviation of the covered right eye to the left, to the right, up, and down, again with fixation of the left eye (Fig. 2B).

In order to draw plots of the error of localization, averaged over the five Ss, all values were adjusted by subtracting any average systematic error measured in pretest runs. Thus, the effect of the sustained deviation was corrected for the offset found in normal viewing. The average data from five Ss for nasal and temporal deviations of the right eye (Fig. 3, top) and left eye (Fig. 3, bottom) are shown. An average linear relation relating pointing error to eye deviation was calculated for a symbolic eye by combining, through summation, the linear regression lines fit to the data for nasal (Eq. 1) and temporal (Eq. 2) deviation of right and left eye.

$$E_n = 0.13D_n - 0.7 \quad (1)$$

$$E_t = 0.16D_t - 1.6 \quad (2)$$

$E_n$ and $E_t$ are the error in degrees resulting in the nasal and temporal directions, respectively, as a result of nasal ($D_n$) and temporal ($D_t$) deviation of the symbolic eye.

The equations suggest that in the angular range studied, the pointing error is about 13 to 16% of the angular deviation of the nonviewing eye. Extrapolation of the curves also suggests that a deviation of less than 10° would produce no effect or an effect too small to be reliably measured.

In a second experiment, we attempted to eliminate the possibility that our results were due to an effect of ocular muscle stretching on the hand motor control system (*8*). Therefore, we evaluated the effect of the mechanical deviation of the covered eye on the perceived position of a target without using a pointing task. In this experiment, the S was requested to say when the position of a target, moving slowly in a horizontal plane, appeared straight ahead. The experimenter recorded the corresponding target position. The effect of the mechanical deviation was established by comparison with the perceived straight ahead direction in the monocular, otherwise normal, viewing condition.

For this experiment, a target appeared randomly, 50° to the right or to the left of

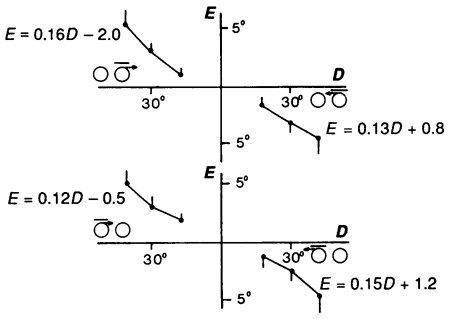



**Fig. 3.** Average error ($E$) as a function of ocular misalignment ($D$) for the right eye (**top**) and left eye (**bottom**). The targets were presented at the center and 12° to the right and to the left so that a 30° eye deviation with respect to straight ahead resulted in eye misalignments of 18°, 30°, and 42°. Vertical bars represent 1 SD.

the S, and then immediately began moving at 5° per second along a horizontal line crossing the digitizing table. The S told the experimenter when the target appeared to be straight ahead. The target was immobilized at that position. If that position did not appear to the S to be exactly straight ahead, the S could ask the experimenter to move it further to the right or to the left until the target was perceived as being straight ahead. This final position was recorded. Targets were presented first in a normal, monocular-viewing condition and then with the covered right eye deviated 30° to the right or to the left by means of the suction lens.

The Ss in this experiment were also tested with the paradigm from the first experiment in order to compare, in a single sitting in the same S, the perceived location of the centrally presented target as indicated by the hand and by verbal report (Fig. 4).

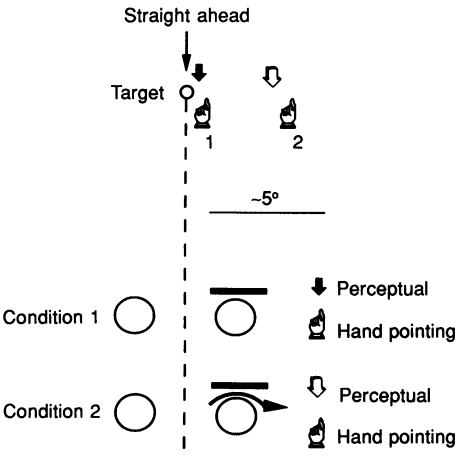



**Fig. 4.** Perceptual localization of a target as being straight ahead. In the normal condition, the target position was properly indicated by the hand (hand 1) and there was only a slight straight ahead position error (black arrow). With the right eye deviated 30° to the right, the Ss identified the position of a target presented straight ahead as being markedly to the right of the actual target position. The error of position indicated by the hand (hand 2) was slightly larger than the shift in perceptual straight ahead (white arrow). Hand, hand pointing localization; arrow, perceptual estimates of straight ahead.

In the normal, monocular-viewing condition, the hand-pointing marks and the indicated positions of the perceived straight ahead are close to each other. The mean pointing error was 1.25° ± 0.8° to the right of the target, whereas the mean perception of straight ahead was 1.6° ± 0.6° to the right of the midsagittal plane.

During sustained deviation of the covered right eye, 30° to the right, the Ss mislocated the target presented straight ahead by 4.6° ± 0.5° to the right. The average perceived straight ahead direction was likewise shifted to the right, by 6.1° ± 0.7°.

A sustained deviation of a nonviewing eye results in the displacement of the apparent position of a centrally presented target. Our results indicate that the sensing of target position was altered by a change in the position in the orbit of the nonviewing eye. The fact that the localization error was roughly the same amplitude, and in the same direction, whether the S was requested to indicate the target position with his hand or by verbal report, indicates that the effect is not specific to the hand motor control system (*8*). Since, in our protocol, mechanical deviation of the covered eye does not affect the eye muscle activation of either eye (by the law of equal innervation), we propose that the localization errors are the result of changes of ocular muscle proprioception. For example, when the right eye, covered, is deviated to the right, the only difference between that eye and the fixating eye relates to lengthening of the right medial rectus and shortening of the lateral rectus of the deviated eye. Consequently, we infer that proprioceptive information is used in the computation of the position of a target with respect to the body.

Most patients with naturally occurring strabismus mislocalize targets before or after surgery with the normal or the deviated eye. Some patients, when tested in a hand-pointing task, behave in a way suggesting that the nonfixating eye, whether it be the habitually straight or deviated eye, introduces a bias in the sensing of the position of a monocularly viewed target. Our data in normal humans subjected to an experimental stabismus complement these studies in patients (*4*).

These results lead to some speculation about ocular muscle proprioception and efferent copy. Both inflow and outflow models (*1*) have been proposed to describe object location perception. Our data support a model in which both inflow and outflow signals combine to encode the position of the eye in orbit. In our study, the major component for encoding the position of the eye in orbit seems to be outflow, but a nonnegligible portion is clearly of proprioceptive origin. For large imposed ocular deviations, ocular muscle proprioception may account for 32% (Eqs. 1 and 2 predict an error of 0.16$D$ for each eye, where $D$ is the angular misalignment) of the infc .na-tion used to sense eye position (*9*). Furthermore, the information from both eyes, whether or not they are both used to fixate the target, participates in the elaboration of the signal encoding eye position in the orbit.

## REFERENCES AND NOTES


1. When vision is not allowed, or when a small single dot target is present in total darkness, eye-in-orbit position is provided through nonvisual information. Such information may arise from a copy of eye muscle activation (efferent copy hypothesis or outflow theory) or from a measure of the muscle length or static tension (inflow or afference hypothesis) through sense organs located in muscles and tendons—or through sensors located around the globe. The efferent copy hypothesis has received considerable support, in particular in experiments dealing with space constancy (that is, the mechanism by which the visual environment appears stationary while we, or our eyes alone, move) [U. J. Ilg, B. Bridgeman, K. P. Hoffmann, *Vision Res.* **29**, 454 (1988); L. Stark and B. Bridgeman, *Percept. Psychophys.* **34**, 371 (1983)]. Moreover, no definite function has yet been attributed to ocular muscle proprioception [H. Von Helmholtz, in *Optique Physiologique* (Masson, Paris, 1867), pp. 111–182; H. Mittelstaedt, in *The Perception and Control of Self-Motion*, R. Warren and A. H. Wertheim, Eds. (Erlbaum, Hillsdale, NJ, 1989), pp. 3–23.
2. Afferents from the receptors contained in the eye muscles [C. S. Sherrington, *Brain* **41**, 332 (1918)] and tendons have been traced to all central structures involved in eye movement control including the cerebellar vermis involved with saccadic and smooth pursuit, and to the floccular lobe involved with eye movements induced by the vestibular system. Projections also reach the brainstem [M. Fillenz, *J. Physiol. (London)* **128**, 199 (1955)]; the visual cortex, the vestibular nuclei, and the superior colliculi [C. Batini and G. Horcholle-Bossavit, *C.R. Acad. Sci. Paris* **285**, 1491 (1977)]; the nucleus prepositus hypoglossi [J. A. Ashton, A. Boddy, I. M. L. Donaldson, M. L. Milleret, *J. Physiol. (London)* **376**, 376P (1986)]; and the oculomotor nuclei [J. A. Ashton, A. Boddy, I. M. L. Donaldson, M. L. Milleret, *ibid.* **382**, 74P (1987)]. Ocular muscle proprioception also projects to structures receiving afferents from the neck muscles [H. Barbas and B. Dubrovsky, *Exp. Neurol.* **74**, 67 (1981); J. D. Porter, *J. Comp. Neurol.* **247**, 133 (1986); D. Edney and J. D. Porter, *ibid.* **250**, 389 (1986); C. Milleret, E. Gary-Bobo, P. Buisseret, *Neurosci. Lett.* **22**, S298 (1985)].
3. Ocular muscle deafferentation results in the absence of maturation of orientation selective cells of the visual cortex [P. Buisseret and L. Maffei, *Exp. Brain Res.* **28**, 421 (1977)], alteration of depth perception [A. Fiorentini, L. Maffei, M. C. Cenni, A. Tacchi, *ibid.* **59**, 296 (1985)], and alteration of orientation in the cat [A. Fiorentini, N. Berardi, L. Maffei, *ibid.* **48**, 113 (1982)].
4. Twenty-seven of 43 strabismics (16 constant and 11 alternating strabismics) tested in a visual target localization task exhibited error systematically in the direction of the nonfixating eye, whether the fixating eye was the normal or the strabismic eye and whether the left or right hand was used to indicate the position of the presented target [G. M. Gauthier, P. V. Berard, J. Deransard, J. L. Semmlow, J. L.

Vercher, in *Adaptive Processes in Visual and Oculomotor Systems*, E. L. Keller and D. S. Zee, Eds. (Pergamon, New York, 1985)]. Proprioception in eye alignment and localization of visual targets has been demonstrated in strabismic patients [M. J. Steinbach and D. R. Smith, *Science* **213**, 1407 (1981)], whereas other authors [O. Bock and G. Kommerell, *Vision Res.* **26**, 1825 (1986)] with the same approach, obtained data that supported the outflow model.

5. The computerized system made use of a Summagraphics BITPAD 90 cm by 70 cm digitizing table connected through an electronics interface to an IMS 5000 microcomputer. The S was seated at the table, the head immobilized in a forward tilted angle by a bite bar covered with dental wax. A row of green light-emitting diode (LED) targets was positioned horizontally 60 cm above the table. A glass plate 1.5 mm thick was placed horizontally between the digitizing table and the row of LEDs at such a level that, as seen by the S, through the glass plate, the LEDs appeared as virtual targets exactly on the surface of the digitizing table. Five subjects ranging in age between 25 and 47 years were tested. Virtual targets were used to prevent Ss from using tactile cues to locate the targets. The LED targets had the same light intensity and appeared as green spots, about 2 mm in diameter.
6. Eye position is not consciously sensed [P. A. Merton, *Symp. Soc. Exp. Biol.* **18**, 387 (1964)]. In addition, in our experiments, the S's corneal afferents were desensitized by administration of local anesthetic.
7. The data are presented as "pointing maps" showing on a single graph all the pointing marks directed toward the three targets. The computer calculated the average pointing position for each set of five pointings directed towards a given target. A special representation was selected to visualize the data and provide an estimate of the data dispersion. For this, the regression line passing through each set of data points (five pointings towards a given target, in a given condition) was calculated. A new coordinate reference was defined with the abscissa parallel to the regression line and passing through the mean of the data. The ordinate was defined, perpendicular to the regression line, and centered on the mean of the data points. The location of each point and the data dispersions were calculated in the new coordinate system. An ellipse was drawn centered on the mean position of the points with its principal and minor axes oriented along the new axes. The lengths of the major and minor axes were equal to 2 SD centered about the mean of the data points, as calculated with respect to the new coordinate system. If one assumes a normal, homogeneous distribution for the data points, the probability for a given point to be within the ellipse is close to 36%.
8. Eye pulling could have had an effect on the sensing of hand position [T. A. Easton, *Brain Res.* **25**, 633 (1971); *Expl. Neurol.* **34**, 497 (1972); G. M. Gauthier, J. L. Vercher, F. Mussa-Ivaldi, E. Marchetti, *Exp. Brain Res.* **73**, 127 (1988); G. M. Gauthier, D. Nommay, J. L. Vercher, *J. Physiol. (London)* **406**, 24P (1988); R. C. Miall, D. J. Weir, J. F. Stein, *Neuroscience* **16**, 511 (1985); G. M. Gauthier and F. Mussa-Ivaldi, *Exp. Brain Res.* **73**, 138 (1988)]. No such interaction accounts for the mislocation errors we observed by pulling the covered eye of our Ss.
9. Our data seem in contradiction with the data of A. A. Skavenski, G. Haddad, and R. M. Steinman [*Percept. Psychophys.* **11**, 287 (1972)], since we show, in a somewhat simpler protocol dealing with the localization of a single target, that proprioception was involved. (In Skavenski *et al.*'s protocol, the role of inflow in the localization of target was studied by using a second target presented to the deviated eye, and correction had to be made for phoria and retinal error.) These authors concluded that "perception of direction is directly proportional to the magnitude of the outflow signal." Still, in the data from Skavenski *et al.*, proprioception may well explain the discrepancy between pure and only inflow information and actual data. Our data show that when one eye is deviated, the shift in localization of the target viewed by the other eye is about 16% of the angular deviation of the covered eye. On the average, the error between predicted pure inflow and actual data recorded by Skavenski *et al.* is in the range of error. Therefore, the data of Skavenski *et al.* essentially agree with ours.
10. We thank D. Zee for reviewing the manuscript. Supported by grants from C.N.R.S. Unité Associée 372 and INSERM 896007.

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# Mediation of Cardioprotection by Transforming Growth Factor–β

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**Myocardial ischemia causes heart injury that is characterized by an increase in circulating tumor necrosis factor (TNF), the local production of superoxide anions, the loss of coronary vasodilation (relaxation) in response to agents that release endothelial cell relaxation factor, and cardiac tissue damage. Ischemic injury can be mimicked by TNF. When given before or immediately after ischemic injury, transforming growth factor–β (TGF-β) reduced the amount of superoxide anions in the coronary circulation, maintained endothelial-dependent coronary relaxation, and reduced injury mediated by exogenous TNF. Thus, TGF-β prevented severe cardiac injury, perhaps by alleviating damage mediated by increases in circulating TNF.**

MYOCARDIAL ISCHEMIA AND REperfusion involves a critical sustained reduction in coronary flow followed by restoration of flow to the ischemic region of the heart. However, reperfusion results in dysfunction to the endothelium of the coronary vasculature as well as injury to the cardiac muscle cells (*1, 2*). Among the factors thought to mediate these damaging effects are the release of cytokines [for example, interleukin-1 (IL-1) and TNF] and oxygen-derived free radicals [for example, superoxide anions (*3, 4*)]. These humoral agents are produced by adhering neutrophilic leukocytes or by endothelial cells (*5, 6*) and are released upon reperfusion. Moreover, TNF concentrations are increased in humans after myocardial infarction (*7*). One means of counteracting these deleterious humoral agents is by addition of the naturally occurring growth factor, transforming growth factor–β (TGF-β).

TGF-β is a homodimeric protein with a molecular size of 25 kD originally defined for its ability to reversibly induce a transformed phenotype and anchorage-independent growth of normal fibroblasts (*8–10*). The most common form is TGF-$\beta_1$, which acts as a regulatory protein that modulates a variety of biological actions relating to developmental processes (*11*). Specific cell membrane receptors for TGF-β are present in many cell types. TGF-β also appears to act in a manner opposing actions of the cytokine TNF-α (*12, 13*). TGF-β is present in cardiac myocytes and coronary endothelial cells (*14*), but disappears after myocardial infarction, except at the border zone of injured myocardial tissue, where increased TGF-β occurs (*15, 16*). TGF-β appears to be angiogenic and inhibits neutrophil adherence to endothelial cells (*17*). TGF-β may therefore moderate the damaging consequences of reperfusion after myocardial ischemia. TGF-β could exert cardioprotection during acute myocardial ischemia by preventing endothelial cell–induced myocardial injury and by promoting healing of injured myocytes after their dysfunction.

We therefore tested the ability of recombinant human TGF-$\beta_1$ to prevent the loss of endothelium-dependent relaxation (EDR) in the coronary microvasculature soon after reperfusion of ischemic myocardium and to reduce myocardial injury 24 hours after myocardial ischemia and reperfusion when the infarction process is well under way. Certain vasodilators like acetylcholine (ACh) and adenosine diphosphate exert their vasodilation only in the presence of an intact endothelium, which is stimulated to release a substance termed endothelium-derived relaxing factor (EDRF) (*18*). If the endothelium is injured so that EDRF is not released, no vasodilation occurs to these endothelium-dependent agents. In contrast, several other vasodilators are endothelium-

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