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R. W. SPERRY

Department of Anatomy, The University of Chicago, Illinois

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ONTOGENETIC DEVELOPMENT AND MAINTENANCE OF COMPENSATORY EYE MOVEMENTS IN COMPLETE ABSENCE OF THE OPTIC NERVE[1]

R. W. SPERRY

Department of Anatomy, The University of Chicago, Illinois

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By delicate reflex regulation of the extrinsic ocular muscles, the eyes of most vertebrates automatically maintain a steady view of the visual field in the presence of disturbing movements of head and body. Head displacement that otherwise would alter orientation of the visual image on the retina tends to elicit compensatory conjugate movements of the eyes in the opposite direction with adjusted intensity such that the eyes tend to ride in their orbits in gyroscopic fashion with a fixed orientation.

The vestibulo-ocular reflex apparatus subserving these compensatory eye movements with its discrete sensory and motor nuclei, motoneurons without collaterals, accessible association tracts and other special features (17) possesses a number of anatomical and physiological advantages for experimental investigation of the central integrative phenomena involved. Perhaps more than in the case of any other reflex mechanism a concerted attack upon this system from all possible angles holds promise of revealing eventually a satisfactory picture of the central events involved in nervous coordination. The high complexity of the motor patterns required for these conjugate eye movements suggests, furthermore, that regulatory principles found here would have broad applicability to the general problems of central nervous coordination. A great number of studies are already available regarding the anatomy, function and development of the vestibulo-ocular apparatus (see 3, 5, 10, 12, 13-19, 21, 25, 33 for leading references). Analysis even of the central nervous mechanisms has been far advanced particularly, of late, through the work of Lorente de Nó.

Many problems remain unanswered, however, especially with regard to the selectivity of neuronal linkages between the various end organs of the labyrinth and the different extra-ocular muscles. How these selective central associations become established in ontogeny is likewise quite obscure. It is hoped that study of this developmental aspect of the vestibulo-ocular reflex system may furnish new leads to an understanding of the form and function of the adult system.

In approaching the problem of the ontogenetic establishment of selective neuronal linkages, a first important point that must be settled is that of the extent to which the neuronal associations are preformed directly in the growth process and the extent to which they are patterned by functional regulation through experience and training. Where functional regulation is indicated,

[1] This work was done while the author was a Research Fellow of Harvard University at the Yerkes Laboratories of Primate Biology, Orange Park, Florida.

further analysis will lead into the problems of the physiological basis of learning. Where inherent predetermination is indicated, further analysis will deal with the embryological and cytological problems of the growth, migration and differentiation of nerve cells and of their inter-reactions with each other and with their end organs.

That the essential reflex relations in the case of the compensatory eye movements may be laid down directly in development without practice is strongly suggested by the fact that in some vertebrates, including man (1, 7) the reflexes are already moderately well developed at birth. On the other hand the fact that the reflexes at birth are usually somewhat immature and improve rapidly with the onset of vision, and the fact that in other animals appearance of the reflexes is delayed after birth until the eyes have opened (6) imply that sight of the visual field may possibly have significant regulative influence in their organization. Variations in the degree of development of the reflexes at the onset of vision and in the extent to which the reflexes are controlled directly by visual stimuli makes generalizations from one species to another difficult at present.

It has been inferred by Lorente de Nó (13) that in the rabbit the compensatory ocular reflexes must be acquired by learning because they are abnormal at birth showing gradual improvement through the first few months of development, and especially because the mature eye movements show a remarkable constancy from animal to animal in the face of wide anatomical variations in the origin, insertion and size of the various ocular muscles as well as in the construction of the labyrinth. It has been reported by Nasiell (23), however, that rabbits which had been reared in the dark for almost three weeks had in that time developed normal compensatory eye movements. Mowrer (22) attacked the problem in pigeons. He tested optic and vestibular head nystagmus in birds which had been raised for five weeks with their eyelids stitched together to exclude vision and concluded that in the pigeon the coordinations of *optic* nystagmus are dependent upon learning but not those of *vestibular* nystagmus. Objection may be raised in regard to all the foregoing that observation of the compensatory eye movements has been made in the light with the pupils of the eyes uncovered. According to Marina (20), Bethe and Fischer (2), Goldstein (8) and others a few trials or even a single trial may be sufficient for adaptive functional organization of this type of response pattern. Although this contention has certainly been applied too broadly in some respects (32) it cannot be wholly ignored.

The present experiments were carried out on amphibians in which the problem is of especial interest due to the recognized advantages of these animals for embryological study and hence the possibility of investigating further the underlying morphogenetic factors responsible for the development and maturation of the central reflex patterns. The animals were frog tadpoles in which the eyes, in the course of experiments on a related problem, had been transplanted before the establishment of vision. The transplanted eyes developed normally in external appearance but in all the cases here reported they failed to form an optic nerve connection with the brain. There could thus be no question whatever of any visual regulation of the eye movements in these cases. Vision was conclusively eliminated during development and during the course of the tests as well. Not only were overt visual excitations ruled out in these experiments but also any implicit or spontaneous discharges of the retina and optic nerve which Herrick (11) has pointed out may conceivably play a role in the developmental organization of the nervous system. Furthermore the optic centers of the midbrain remained in an underdeveloped state due to the lack of ingrowth of the optic fibers.

METHODS

Transplantation of the right eye from donor animals into the left orbit of new hosts was carried out in embryos of *Rana clamitans* at stages corresponding to Shumway's (26, 27) stages 21–24 for *R. pipiens* at which time the cellular layers of the retina have only begun to differentiate. The contralateral intact eye was excised two days later in one group of animals at about stages 24 and 25 of Shumway's series when the rods and cones are beginning to undergo visible differentiation. In a second group the contralateral eye was not excised until about two months later when the animals had developed to approximately the larval stage XI of Taylor and Kollros (35) with an average length of 40 mm. About one-third of the cases were discarded because the transplanted eye had either not survived or its development had been obviously defective. Repeated tests for vision in the remaining animals indicated that 7 in the first group and 9 in the second group never acquired any vision in the transplanted eyes. Subsequent microscopic examination revealed that the optic nerve of the transplanted eyes in these 16 cases was either lacking or had failed to connect with the brain. Thus Group I had never experienced any vision whatever. Group II had experienced vision only through the contralateral eye previous to its extirpation at the end of two months.

By midlarval stages the transplanted eyes had come to resemble closely the normal in external appearance except for their orientation in the orbit. Because the polarity of the eyeball had evidently been established already at the time of transplantation and because right eyes were crossed to the left side, one axis of the eye, differing in individual cases, was necessarily inverted. The orientation of the eye in most cases was easily ascertained by a characteristic blood vessel and by the pigmentation of the eyeball. The inherent ventral pole of the globe developed a golden pigmentation and the inherent dorsal pole became black in the usual way though their actual positions in the orbit had been greatly altered or diametrically reversed.

Tests for compensatory movements of the blind transplanted eyes were made by placing the tadpoles on moist cotton on a small glass dish which was tipped and tilted back and forth in the three primary planes of the body. The eye responses in the meantime were watched through a dissecting microscope with a magnification of about ten times. The compensatory eye reflexes of the tadpole to tilting in the vertical planes are quite pronounced and easily observed. The eyeball riding in the transparent orbital jelly tips and turns in very delicate manner to compensate for imposed movements of the body. Because reactions to horizontal rotation were very slight and variable even in the normal cases of this batch, the horizontal component was not relied upon as a test of function. The responses of the experimental cases were compared with those of control animals which had developed normally until the time of testing when their optic nerves were severed to exclude any possible visual control. The compensatory eye movements to tilting and turning of the head are evoked mainly through labyrinthine stimuli in tadpoles and persist without noticeable defect after optic nerve section (31).

RESULTS

When the animals were tested about 40 days after operation, definite compensatory movements of the blind transplanted eyes were displayed by all cases of both groups with the exception of one animal in Group I. Good reactions in the proper direction to rotation in both vertical planes of the body were found to be present in five of the animals, 2 from Group I and 3 from Group II. Tilting the head downward to the left on its longitudinal axis caused the transplanted eye on the left side to deviate upward. When the head was tilted upward to the left, the eye rotated downward. Tipping the head on its horizontal transverse axis dorsally or ventrally caused the eye to rotate wheel fashion on its optic axis in the opposite direction, so that it tended in each case to maintain its original orientation with respect to the visual field. As far as could be determined with this method of observation the reflex reactions were all roughly similar to those of the control cases with respect to direction and also with respect to timing and intensity. The eyes not only responded in the correct directions to angular acceleration, but they also maintained the appropriate compensatory poses after movement had ceased.

In other animals defects in intensity of response of varying degree were found to exist in one or two of the primary planes of movement. Careful dissection under the microscope of four cases of this type following fixation in Bouin's solution revealed that the decreased intensity or lack of response was in each case correlated with very poor development or complete absence of the particular ocular muscles concerned or with insertion of the muscles more medially than usual on the eyeball so that their mechanical advantage was decreased. The single animal in Group I already mentioned which showed no eye rotations in any plane was found to possess only the superior oblique muscle and possibly a wisp of the retractor bulbi muscle. The superior oblique muscle in this case was not inserted at the dorsal pole of the eye in the usual manner but at the nasal pole in such a position that its contraction could merely pull the eye without rotation against the wall of the orbit. The nasal pole was the original or inherent dorsal pole due to disorientation of the eyeball.

In the remaining 4 animals, 2 in each group, there existed in addition to quantitative defects in intensity of reaction, qualitative abnormalities in the direction of response. For example, in two of these cases the eye responded consistently in approximately the horizontal plane when the head was tilted vertically on its longitudinal axis. In both of these animals the dorsoventral axis of the eyeball was displaced roughly 90 degrees so that the inherent ventral pole of the eye was in the temporal part of the orbit and the inherent dorsal pole was in the nasal position. Had the eye been properly oriented with respect to the dorsoventral axis, the reflex movements would have been directed correctly. The abnormality of the reactions in these particular cases could thus be explained on the assumption that the muscles had tended to insert on the eyeball according to its original or inherent polarity rather than according to its actual position, and furthermore that they had retained their usual central timing despite this peripheral alteration in mechanical relations. Support for this assumption was evident in the dissections which showed that the superior oblique and superior rectus muscles had definitely inserted on the inherent dorsal pole of the eye despite the fact that this pole was displaced nasalward almost 90 degrees.

In the remaining two animals both of which showed consistent directional errors in eye movements the abnormality of response was similarly correlated with a disorientation of the eyeball of approximately 90 degrees plus deficient and atypical development of the extraocular musculature. In these cases, however, the identity of individual muscles could not be determined with certainty. Furthermore in one case the reactions were exceptional in that the direction of response was not properly correlated with the direction of disorientation. This animal had only one large extraocular muscle which was inserted on the eyeball about half way between the normal insertions of the lateral and inferior rectus muscles. The eye regularly deviated toward this side even when the head was tilted in the same direction.

A 90 degree displacement of both the dorsoventral and nasotemporal axes seemed to be more conducive to abnormal development and insertion of the ocular muscles than having either axis correctly oriented and the other completely inverted 180 degrees. That the ocular muscles had a tendency to form insertions on the eyeball according to the inherent quality of the different quadrants of the globe regardless of their actual positions with respect to the orbit was indicated in some cases. This tendency if actually present, however, appeared to be definitely limited and was easily overridden when the quadrant of the eye concerned was far removed from its natural position. In one animal in which the dorsoventral axis of the eye was almost exactly reversed the horizontal rectus muscles were both lacking while the vertical rectus and oblique muscles were all well developed and effected compensatory reactions in the proper directions.

The development of consistently misdirected reactions correlated with disorientation of the eyeball and alteration in the insertion of the muscles as described adds to the evidence that the central reflex mechanisms are not patterned by training in accordance with any useful functional effects. Because the eyes are relatively large structures in the tadpole, it might conceivably be argued that their gyroscopic movements have a beneficial mechanical stabilizing effect registered through kinesthetic stimuli by which the central associations could be trained. Such an interpretation is ruled out, however, by the above systematic establishment of reflex movements in the wrong plane of the body.

The form and function of the eye muscles in Group II was on the whole slightly better than that of Group I despite the fact that there had been a tendency in first separating the two groups to choose the initially better-looking transplants for Group I. This suggested that the presence of the intact contralateral eye may possibly have had a beneficial influence on the development of the transplanted eye and its musculature. If such an effect actually existed, the question is open as to whether it was due entirely to embryological inductive actions of a chemical sort or whether function itself may have had at least an indirect role.

Tests of the ocular reflexes were repeated about once every two weeks during the following two and one-half months until the onset of metamorphosis. The general character of the reflexes persisted as described above without significant change. The excision of the normal right eye in the second group two months after operation was without noticeable effect on the reflex movements of the blind transplanted eye on the opposite side. One case from Group I and two from Group II were kept an additional 8 weeks without extra feeding in an aquarium with water plants at a temperature averaging approximately 10°C. They failed to metamorphose or to increase noticeably in size. The compensatory eye movements survived this period in all three cases without deterioration.

In summary, definite compensatory movements and postures of the blind transplanted eyes developed and persisted in 15 out of the 16 cases. The ocular responses to tilting of the head in the vertical planes in different directions were of normal character in the majority of instances. Absence or abnormality of response, where present, was clearly correlated with atypical development of the extraocular muscles concerned plus disorientation of the eyeball and therefore could not be ascribed to improper development of the central reflex mechanisms.

DISCUSSION

The results particularly from Group I in which the contralateral eye had been excised in the embryo show conclusively that in the tadpole visual experience and training are not necessary for development and maintenance of the compensatory ocular reflexes which aid in preserving a steady view of the visual field. The beneficial functional effect for which the reflexes are adapted never registered in the central nervous system in these animals and therefore could not have played any role in adjusting the central reflex associations. To assume that the movements of the blind eyes might have been trained through proprioceptive cues from the ocular muscles or that the reflex relations governing the eye movements might have been established as part of a larger motor pattern which itself was trained through useful functional effects has little explanatory value in either case since it is necessary under both conditions to have recourse in large measure to exactly the kind of phenomena which the assumptions attempt to avoid, namely, developmental organization in the vestibulo-ocular system by non-functional factors. That function of the intact contralateral eye in Group II may have aided in establishing proper central associations for the motor ocular nuclei of the opposite blind eye is not precluded by the evidence; but this too would necessarily involve the action of afunctional developmental agencies in effecting the transfer from one system of nuclei to the other and thus would not be in accordance at all with the contention that central synaptic associations in development are formed, reinforced, and discarded depending on the adaptiveness of their functional effects. The experiments strongly support the conclusion that the essential neuronal linkages of the vestibulo-ocular system like the basic integrative relations involved in swimming (4, 9) and in limb coordination (37) and in vision (28, 29, 30, 34) are organized directly in amphibians in the growth process without functional adjustment through conditioning or training.

With the learning process discarded as an important factor in the developmental organization of these reflexes, there remains the problem of accounting for the formation of the systematic sensori-neuro-muscular associations in terms of neuron growth and differentiation. Although the vestibulo-ocular reflexes appear at first glance rather simple, reference to the studies of Lorente de Nó will at once reveal the high complexity, precision, and plasticity of the integrative relationships involved and the extreme difficulty therefore of formulating any scheme by which the underlying structure for such intricate functional patterns might be pre-established in ontogeny. Nevertheless since some working hypothesis is necessary, and since oversimplified or even incorrect schemes may often have value in crystallizing the problems and in suggesting further research, the following conjectures on the matter may not be untimely.

Nerve connections between the fourth and sixth cranial motor nuclei and their respective muscles are apparently achieved by central differentiation of the nuclei followed by direct outgrowth of the motor axons into the proper discrete muscle primordia (24). How the various motor cells within the compound oculomotor nucleus, however, form appropriate connections both centrally and peripherally with the different muscle primordia of the first head myotome remains a problem. Nor is it clear how the sensory fibers of the various end organs of the labyrinth establish their selective relations in the vestibular nuclei of the medulla where the anatomical terminations are not topographically distinct but overlap diffusely (16). And finally in the development of the associations between the vestibular and motor ocular nuclei no obvious means is apparent by which the differentially adaptive relationships are attained.

According to the idea of peripheral regulation of central synaptic associations (28) the central relations acquired by the oculomotor axons of different muscles and the sensory fibers supplying different end organs might in each case be determined in a selective manner by qualitative biochemical specificities (36, 37) developmentally induced in the peripheral neurons by their various end organs. The systematic recovery of vestibular reflexes after centripetal regeneration of the vestibular nerve root (31) could be accounted for on this basis. It may be presumed that the association neurons of the vestibular nuclei become individuated according to contacts which they form downstream with the different motor ocular nuclei. Finally, the closing of the direct central arcs on the sensory side could be systematically completed according to the resultant differential affinities and incompatibilities between the invading sensory fibers and the cells of the vestibular nuclei. The self-reexciting circuits of the reticular formation superimposed upon the direct routes (17) are only a few degrees removed from the main line of induction. The fact that they manage to acquire systematic associations instead of becoming hopelessly intertangled in the diffuse reticular formation may be due to special affinities impressed upon them by their initial associations with the main reflex routes.

Development of differential reflex relations between the various end organs of the labyrinth and the different extraocular muscles of the two eyes could thus conceivably be regulated in a systematic manner by differential biochemical affinities among the peripheral and central neurons concerned. There is considerable experimental evidence (28, 29, 30, 31, 36, 37, 38) for the existence of refined neuron differentiation of this kind. Theoretically each neuron or group of neurons constituting a link in the reflex chain could undergo an independent self-differentiation predetermining the particular type of associations it could form. It seems more probable, however, that this differentiation begins at certain key points in the reflex circuit, particularly in the periphery, and is then extended serially by induction of indifferent neurons as they are brought into relationship with cells already specified.

Inherent central nervous organization is, of course, not presumed to be dependent entirely on refined inductive effects of this kind even in the simplest direct pathways. An extensive background differentiation of the motor and sensory columns, of the primary sensory and motor nuclei and of their neighboring structures which, along with mechanical, timing, and other factors, determines the general location of nerve nuclei and the course of the nerve tracts is also required in addition to the special effects mentioned above. The specific inductions postulated are presumed to be superimposed upon this background differentiation and to influence primarily the refined details of selective synaptic formations within a nucleus, for example, within the oculomotor, reticular, or vestibular nuclei.

In the vestibulo-ocular system afferent fibers entering the vestibular nuclei from the horizontal canals must, according to the foregoing, have a special predilection for those central vestibular neurons which connect with motoneurons of the proper horizontal rectus muscles. Similarly fibers from the vertical canals must have predilection for selective linkage with the appropriate vertical rectus and oblique muscles. The macula of the utriculus must be assumed to undergo in development a polarized differentiation somewhat as does the retina (28) in order that sensory fibers connecting with different macular regions may be distinguished from each other in the centers.

It must be emphasized that the foregoing is intended merely to suggest one conceivable plan along the general lines of which the complex reflex relationships subserving conjugate compensatory eye movements might be organized directly in development without aid of functional adjustment. An alternative scheme could be drawn up on the basis of the Resonance Principle of Weiss (36, 37) in which the specification of the nervous system is conceived to be such that it affects the excitation modes and receptive sensitivities of the nerve cells rather than the growth and maintenance of selective anatomical associations. Although further elaboration of either scheme in specific detail is feasible at present, it had better await the addition of further experimental evidence.

SUMMARY

The compensatory ocular reflexes which serve to maintain a steady view of the visual field in the presence of disturbing movements of head and body were found to develop in normal manner in frog tadpoles the eyes of which had been transplanted to the contralateral orbit in prefunctional stages and had never developed an optic nerve connection with the brain.

It is concluded that the reflex associations of the vestibulo-ocular system in these animals are not patterned by training but are laid down directly in growth in a predetermined manner. Some preliminary conjectures are offered regarding the general nature of the developmental processes which may be responsible for the orderly establishment of the intricate central reflex relations involved.

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