

Etiology of Heterophoria and Heterotropia

In heterophoria there is a relative deviation of the visual axes held in check by the fusion mechanism, whereas in heterotropia there is a manifest deviation of the visual axes. The relative position of the visual axes is determined by the equilibrium or disequilibrium of forces that keep the eyes properly aligned and of forces that disrupt this alignment. Clearly, the fusion mechanism and its anomalies are involved in some manner in producing comitant heterotropias. To understand the etiology of neuromuscular anomalies of the eyes, therefore, one should also gain an insight into other factors that determine the relative position of the visual axes.

First, there are *anatomical factors*, which consist of orientation, size, and shape of the orbits; size and shape of the globes; volume and viscosity of the retrobulbar tissue; functioning of the eye muscles as determined by their insertion, length, elasticity, and structure; and anatomical arrangement and condition of fasciae, ligaments, and pulleys of the orbit.

Second, there are *innervational factors*, that is, all the nervous impulses that reach the eyes. These factors include the co-movements of extraocular muscles with intrinsic ocular muscles, psych-optical reflexes (fixation reflex, fusional impulses), influences of the static apparatus on extraocular muscles and their tonus (endolymph, vestibular system, reflexes from neck muscles), and influences of the several nuclear and supranuclear areas that govern ocular motility.

Factors Responsible for the Manifestation of a Deviation

Abnormalities of Fusion Mechanism

DEFECT OF MOTOR FUSION IN INFANTILE ESOTROPIA. Motor fusion in patients with heterophoria is adequate to maintain a proper alignment of the eyes. This does not mean that patients with a heterophoria necessarily have normal sensory fusion. In those with higher degrees of heterophoria, suppression and a high stereoscopic threshold may be present, but motor responses are sufficient to keep the eyes aligned. In heterotropia this is not the case. These circumstances have led to a theory of the etiology of strabismus developed by Worth in 1903 in his famous book on squint.¹⁵⁶ His theory was that the essential cause of squint is a defect of the fusion faculty^{156, p. 55} and indeed is a congenital total absence of the fusion faculty.^{156, p. 61} Worth did not make a distinction between sensory and motor fusion.

Worth's theory has had an enormous influence on the thinking about strabismus, especially about essential infantile esotropia, but objections to it have been raised. In fact, Chavasse,²⁴ in editing the seventh edition of Worth's *Squint*, went so far as to say

We need no longer vainly genuflect before the fireless altar of "defect of the fusion faculty"; anymore than we need be content to regard lameness (with which strabismus has so much in common) as a defect of the

walking faculty [p. 2] . . . To many it will be a relief to see the exposure . . . of “congenital defect of fusion faculty” as a superstition which may have had its uses in the past [p. viii].

The comparison with lameness limps, as do most comparisons. Lameness may result from many causes, among them a defect in the “walking faculty,” that is, incoordination of the impulses to muscle, as in tabetic ataxia, or from paralysis of a muscle with contracture of the antagonist. In most instances, however, lameness has little in common with comitant strabismus.

To assess what Worth meant, one must reread what he wrote. He stated that when the fusion faculty is inadequate “the eyes are in a state of unstable equilibrium, ready to squint either inwards or outwards on slight provocation.”^{156, p. 55} Precipitating factors may be hypermetropia, anisometropia, motor anomalies, specific fevers, violent mental disturbances, injury during birth, occlusion, and hereditary factors. In other words, Worth makes no claims other than that the factors that lead to a latent deviation become manifest in the absence of a proper fusion mechanism. By general agreement, this is how heterophoria and heterotropia are defined.

One must admit that Worth’s proof for his concept of a *congenital* weakness of the fusion faculty^{156, p. 61} is not conclusive. He cited the example of a young patient with alternating esotropia and normal vision in each eye, no refractive error, and no detectable motor anomalies. Hypermetropia and mechanical elements therefore are excluded as etiologic factors. When tested with the amblyoscope, the patient suppressed the image from one eye and no amount of exercise enabled him to fuse the two images. The esotropia, Worth reasoned, must be the result of a congenital total absence of the fusion faculty when, in fact, this patient’s inability to fuse probably resulted from a well-established suppression mechanism rather than from a primary fusion defect. Indeed, considering that Worth, as stated above, did not make a distinction between sensory and motor fusion, one could conceive here that the original problem was in the motor fusion mechanism and that suppression took place as a consequence of the loss of ocular alignment. Another finding difficult to reconcile with a primary sensory fusion defect is the observation that some patients with essential infantile esotropia show a remarkably high degree of sensorimotor binocular cooperation (*subnormal binocular vision*)¹¹⁰ after surgical alignment of the eyes (see Chapter 16).

Modern psychophysical research in infants^{5, 134} has made it possible to add to the rather ancient theory of Worth. It has become evident that motor and sensory components of binocular vision such as visual acuity,⁶⁶ contrast sensitivity,^{8, 11} stereopsis,^{7, 68} and retinal disparity sensitivity (vergences)⁶⁷ are incompletely developed at birth (see also Chapter 11). The infantile visual system appears especially vulnerable to destabilization during this state of visual immaturity. The absence of a strong vergence control mechanism in the presence of a weak sensory input may explain the high prevalence of transient esotropias or exotropias in infants that later develop normal binocular vision.^{54, 109} With maturation of motor fusion, stabilization of ocular alignment occurs. However, if development of motor fusion is delayed or if motor fusion (i.e., the vergence system) is primarily defective, perhaps from genetically determined factors, esotropia may develop under the influence of a variety of strabismogenic causes.¹¹⁰ These may include excessive tonic convergence, hypermetropia, anisometropia, anomalies of the neural integrator for vergence movements, and other factors still unknown. Held,⁶⁷ who proposed a similar working hypothesis for the etiology of essential infantile esotropia (see also Helveston⁶⁹), points out that this theory, while speculative, has the advantage of being testable with available methods. Further reference to this theory is made in Chapter 16.

SENSORY OBSTACLES TO FUSION. Observations in older patients leave no doubt that interference with fusion may precipitate a manifest deviation in predisposed patients. The interference may be of peripheral or central origin and produce sensory or motor obstacles to fusion. Among the peripheral sensory obstacles are conditions that materially reduce the vision in one eye or the patching of either eye. A result of patching is well illustrated by the following example.

CASE 9-1.

A 14-year-old boy had a large chalazion of the right lower lid. After removal of the chalazion, he wore a bandage over the eye for 2 days. When the bandage was taken off he complained of diplopia. He now had an alternating esotropia of 40°. The visual acuity was 6/6 in each eye and a hypermetropia of +5.0 sphere D was present OU. He was given the refractive correction which he had never worn before and

fit-over base-out prisms that restored single binocular vision. The strength of the prisms was reduced every 2 or 3 days. After 2 weeks the manifest deviation had entirely disappeared, but an esophoria remained for distance of about 20^Δ, with correction. Both with and without correction, the boy had excellent fusional amplitudes and full stereopsis. The patient refused to wear his refractive correction. Since his vision was excellent, he had no symptoms and the glasses were in his way. Throughout 2 years of observation the condition remained unchanged. It should be added that the boy's older brother had been operated on for esotropia.

In essence, Case 9-1 demonstrates that a peripheral sensory obstacle, in this instance brief occlusion of one eye, is capable of precipitating a large manifest deviation when ordinarily a well-functioning fusion mechanism would prevent such an anomaly. A similar problem may also be caused by centrally acting factors, as shown by the following cases.

CASE 9-2.

A 17-year-old girl was thrown from her bicycle when it struck a tree. She sustained bruises and was somewhat dazed, but there were no serious injuries. As soon as she recovered from the initial shock, she noted diplopia. Examination on the day of the accident revealed standard visual acuity in each eye with her correction for myopia, no sign of a paresis or paralysis of an extraocular muscle, and an alternating exotropia of 18^Δ for distance. Single vision could be readily obtained with prisms. After a few days, spontaneous single binocular vision with good amplitudes and stereopsis was reestablished, but an exophoria of 15^Δ was evident on dissociation of the eyes.

CASE 9-3.

A 72-year-old woman began seeing double during an attack of pneumonia 10 years before being examined and had seen double thereafter. According to the ophthalmologist whom she consulted at the time and others who saw her subsequently, there was no evidence of a paralysis of an extraocular muscle. Examination revealed standard visual acuity in both eyes, a minimal refractive error (+0.25 sphere D OU), an alternating esotropia of 20^Δ without any sign of an inveterate paralysis, and good fusional amplitudes and stereopsis on the synoptophore. An operation was performed that relieved

the patient of the diplopia. Two years later she had an esophoria of 2^Δ for distance and 8^Δ of exophoria for near, with correction. Binocular cooperation was normal.

Cases 9-2 and 9-3 are examples of transient or permanent impairment of the fusion mechanism from traumatic or toxic causes. Toxic causes also may be the precipitating factors in heterotropias of childhood, although it is difficult to prove this point. In a significant number of cases it can be established only by the history. Parents are known to be prone to attribute an ocular deviation in their children to an incidental cause—a fall or disease. Yet, knowing how severe the toxic effect of diseases such as measles or whooping cough may be on the central nervous system, it is not unreasonable to formulate the hypothesis that these conditions may precipitate heterotropia in some children. This question will be brought up again in the discussion of the etiologic role of brain damage (see p. 141).

A more permanent interference with the fusion mechanism may cause *sensory heterotropia* in children and adults. There is controversy in the older literature at what age eso- or exotropia develops when there is visual loss in one eye as a consequence of, say, a congenital or traumatic cataract. We found that eso- and exotropia occur with equal frequency when the onset of unilateral visual loss occurs between birth and 5 years of age.¹³³ After that age, sensory exotropia predominates, and both sensory eso- and exotropia may be accompanied by a dissociated vertical deviation.^{15, 89} The reason a blind eye becomes esotropic in some patients and exotropic in others is not clear. Jampolsky⁷⁷ postulated that tonic divergence triggered by blurred peripheral and macular images in one eye relative to the other eye causes the eye with poor vision to diverge. This theory does not explain the mechanism of sensory esotropia. Other authors have blamed the degree of loss of visual acuity¹⁸ or the type of underlying refractive error^{24, p. 172} for the direction of the deviation. However, we were unable to establish a correlation between these factors and the occurrence of sensory esotropia or exotropia.¹³³

COMITANT STRABISMUS AS A RESULT OF HORROR FUSIONIS AND DIPLOPIAPHOBIA.

Horror fusionis is a term used by Bielschowsky^{16, p. 72} for a specific phenomenon—avoidance of bifoveal stimulation. Historically, this subject

was dealt with first by von Graefe in 1854,⁶⁰ when he introduced the term “reluctance to see singly” (*Widerwillen gegen Einfachsehen*) and was later mentioned by Javal who, in 1896, spoke of “repulsion of images.”⁷⁹ The term *horror fusionis* should not be loosely applied to other forms of absent or deficient sensory fusion. The phenomenon can be observed when images presented to the eyes are moved slowly toward each other by means of a haploscopic arrangement or rotary prisms. One eye maintains fixation while the image in the fellow eye is moved across the retina closer to the fovea. The distance between the two images is gradually reduced until the image in each eye is close to or on the fovea. At that moment the two images separate more widely, and no amount of manipulation of the devices brings about a superposition of the two foveal images. The patient rejects bifoveal stimulation whenever it is attempted. Bielschowsky^{16, p. 72} ascribed the change in distance of the double images to variations in the deviation. He thought that two images localized in the same direction without being fused caused a feeling of discomfort that the patient instinctively endeavored to avoid by changing the angle of squint. Bielschowsky^{16, p. 73} also believed that horror fusionis might be caused by defective development of sensory connections in the visual cortex.

There is little doubt that horror fusionis is caused by a change in the angle of strabismus, and in our experience the condition is quite rare except when elicited artificially. For instance, many orthoptists are acquainted with what they call “chasing,” that is, the continual increase in deviation in tests with a major amblyoscope whenever the stimulus in the deviated eye is placed on or near the fovea in the deviated eye. This phenomenon could also be attributed to some sort of anomalous disparity-induced vergence mechanism and be identical or at least similar to the “eating up” of prisms.²¹

Avoidance or active rejection of bifoveal stimulation may not be achieved solely by changes in the deviation. Bielschowsky’s definition of horror fusionis may be enlarged by including deepening of suppression and changes in the mode of localization whenever bifoveal stimulations are attempted. The clinical aspects of horror fusionis were discussed in a monograph by Hamburger.⁶⁴

The possibility has been mentioned in the older literature that this aversion to bifoveal stimulation conceivably is an etiologic factor in strabismus.

Horror fusionis would then belong to the group of etiologic factors that produce what has been called a *purposive strabismus*,^{24, p. 125} comparable to the *diplopiaphobia* of van der Hoeve.¹⁵⁰ Van der Hoeve reasoned that if a child did not have a strong fusion mechanism, the result would be double vision. Because diplopia is most disturbing, the child would soon instinctively find it less annoying if one eye were turned so as to bring the image of the fixated object on a more peripheral retinal area of low visual acuity. As a result, the child would acquire a constant strabismus, having followed an active separatist policy, as Chavasse^{24, p. 125} so colorfully described it. A similar active policy may arise from a horror fusionis, but the likelihood of this being the case is remote.

Reflexologic Theories

The concept of fusion does not mean the same to all authors. To some, fusion is preformed anatomically and physiologically as a constitutional characteristic of the individual. To others, fusion is acquired by usage. To those who hold this latter view, the concept of a congenitally defective or absent fusion mechanism is not acceptable. To Chavasse,^{24, p. 80} fusion was an overt motor response of the eyes based on conditioned reflexes and as such was acquired by usage. Sensory fusion, distinct from motor fusion, was not recognized by him. Chavasse believed that peripheral or central interference with development of binocular reflexes causes an anomaly of these reflexes, expressed in a relative deviation of the visual axes. If the interference lasts beyond the plastic stage in development of a child, proper reflexes can no longer be acquired by therapy. Nonsurgical, orthoptic treatment aimed at restoration of binocular vision is useless once the child is no longer in the plastic stage. This type of reasoning has widespread appeal. One may hear it said, for example, that a functional cure was achieved because of late onset of the deviation and that the child had an opportunity to gain binocular experience.

Another strongly reflexologic view was championed by Keiner,⁸¹ who believed the causative factor in strabismus to be a disturbance of the optomotor reflexes, following the teaching of Zeeman.¹⁵⁷ Keiner stated that optomotor reflexes determine relative position of the eyes in the course of postnatal development. He recognized a monocular duction reflex grafted on the proprioceptive

reflex pathway, a binocular reflex for versions grafted on the vestibular reflex pathway, and a convergence reflex also grafted on the proprioceptive reflex pathway. According to Zeeman and Keiner, the position of the eyes in the orbit during fetal life depends on stimuli originating chiefly in the proprioceptive and enteroceptive fields and the labyrinths. With birth comes light—a powerful conditioning stimulus that determines the function of the foveae and the cooperation of the homonymous halves of the retinas through development of optomotor reflexes. After a short transitional period (during which the eyes of all infants have only dissociated movements), the optomotor reflexes supersede older subcortical reflexes and soon take precedence in determination of the position of the eyes in space (binocular reflexes) or in the orbit (monocular reflexes). The directing and coupling process, initiated by optomotor reflexes, eventually leads to full motor and sensory coordination of the eyes; in the infant, eyes change from a state of dissociation to a state of association. The abnormal position of eyes in convergent strabismus is a consequence of abnormal development of optomotor reflexes and consists of a predominance of monocular adduction reflexes over those for conjugate movements and abduction.

Keiner⁸¹ concluded from his studies that all neonates are potential squinters and that this universal disposition is offset in the first 18 months of life unless interfered with by endogenous or exogenous factors. Keiner thought that the cause for disturbance of development of optomotor reflexes might be a delay in the process of myelination of pathways, a possibility that had been alluded to as early as 1897 by Steffan.¹³⁹ These thoughts are not entirely at odds with our current thinking on the etiology of infantile esotropia according to which a delay in the development of motor fusion, which could conceivably be caused by a delay in the myelination of the pathways for vergences may be responsible for this condition (see p. 135) Lang⁹² also blames a delay of myelination or difficulties in coordination between ocular and vestibular influences on a nasal fixation bias which in turn causes infantile esotropia.

Factors Causing the Underlying Deviation

Mechanical (Muscular) Theories

At the beginning of scientific ophthalmology, the first theories were that mechanical or muscular

malfunction caused comitant strabismus. They superseded earlier physiologically oriented theories, which were largely speculative and even fantastic. The mechanical theories arose largely because of the development around 1840 of an operative procedure for successfully correcting horizontal deviations. Since deviations could be corrected by mechanical means, it seemed reasonable to assume that mechanical factors were responsible for them. These mechanical factors were held responsible for anomalies affecting the action of antagonistic muscles due to disproportions in their structure, length, cross section (mass), and elasticity, or to anomalies of the insertions. Structural anomalies of the orbits and orbital tissues were also taken into consideration.

In subsequent years the foremost exponents of the muscular theory of the etiology of comitant strabismus have been Scobee¹³¹ and Nordlöw.^{113, 114} Scobee was of the opinion that in 90% of patients with heterotropia there is an underlying anatomical cause for the deviation. He observed anomalies of the check ligaments that consisted of thickening, fusion, and posterior extension on the muscles and supernumerary muscle slips and footplates on otherwise normal-appearing insertions. These footplates were described as attaching the muscle to the globe anywhere from 2 to 7 mm behind its insertion. They corresponded in all probability to structures described much earlier by Motais¹⁰⁰ (see p. 40). Scobee pointed out that the effect of these anomalies was to prevent relaxation of the antagonist of the affected muscle, and he believed that existence of the anomalies had a bearing on the type of operation to be performed. Since anatomical anomalies cannot be detected during preoperative examination of the patient, Scobee suggested that the decision about the type of operative procedure should be made while the patient is on the operating table following a forced duction test by which the passive mobility of the globes can be determined.¹³¹ It is of interest that the concept of etiologic significance of primary structural alterations in the extraocular muscles of strabismic patients is upheld by contemporary authors. Domenici and coworkers⁴³ described alterations of both contractile structures and mitochondria, more pronounced at the scleral myotendinous junction than in the actual muscle belly, in patients with infantile esotropia. Corsi and coworkers²⁹ reported on alterations of extraocular muscle proprioceptors in this patient group.

In most patients it is impossible during an

office examination to establish the presence or absence of anatomical abnormalities, but certain important facts can be uncovered about functioning of the muscles. In many patients with heterotropia, varying degrees of excessive or defective excursions of the globe can be observed. The extent to which the eyes are capable of rotating is important not only in determining the best operative approach but also has a bearing on the etiology of strabismus.

The first to take into account the behavior of the rotations, that is, the extent and position of the monocular and binocular field of fixation in strabismus, was von Graefe.⁶¹ He stated that in comitant strabismus the amplitudes of the excursions were normal in extent but that their midpoint was displaced nasalward in esotropia and templeward in exotropia. In this von Graefe saw support for his muscular theory of strabismus. According to this theory strabismus is caused by disproportion in the mean length of the different extraocular muscles. Landolt⁹¹ also emphasized the importance of determining the amplitude of the horizontal excursions, but he⁹⁰ and other supporters of the accommodative theory of strabismus believed that displacement of the excursions was secondary, occurred gradually under the influence of convergence and accommodation, and resulted eventually in contractures of the muscles.

The most exhaustive studies of the horizontal excursions were made by Hesse⁷² and by Nordlöw.¹¹³ Hesse confirmed von Graefe's theory⁶¹ regarding the horizontal excursions in esotropia and exotropia and found that in 70% of the cases there was agreement between the displacement and the angle of squint within the limits of error of the method (5°). Hesse did not evaluate his material from the point of view of etiology. He was interested in the changes in position of the midpoint of the excursions following operative procedures.

Nordlöw,¹¹³ on the other hand, undertook his painstaking study with special regard for the etiology of comitant esotropia. He investigated statistically the visual acuity, refraction, angle of squint, horizontal excursions, fusional amplitudes, retinal correspondence, and depth perception in a group of normal subjects and in a group of squinters. Nordlöw found in the normal subjects no statistically significant difference in horizontal excursions between the right and left eyes or between adults and children. For each subject there was good agreement between the heterophoric position

and displacement of the midpoint of horizontal excursion of the eyes. Nordlöw considered this displacement to be an expression of the heterophoric position. A nasal displacement of horizontal excursions of normal amplitude could only be explained on the basis of mechanical factors. Nordlöw concluded from his study that at the time of onset of a constant esotropia mechanical factors are present that produce a strabismus even if the fusion mechanism is normal. In constant strabismus the refractive factor plays a subordinate role.

One of the main arguments of Scobee¹³¹ and Nordlöw¹¹⁴ in favor of mechanical (muscular), possibly hereditary, causes of strabismus is the frequency with which onset of esotropia occurred at birth or in early infancy. Curiously, this same observation convinced Keiner that mechanical factors could not be held responsible. The diametrically opposed inferences drawn by these authors from the same premise would indicate that there is no conclusive evidence for either theory.

Structural Anomalies of Extraocular Muscles

A discussion of mechanical theories would be incomplete without reference to the fact that congenital or acquired anomalies of extraocular muscles or adjacent orbital structures may cause strabismus. Among these anomalies are acquired myopathies, acquired and congenital fibrosis, fractures of the orbital bones, Brown syndrome, and many others that are discussed in detail in the appropriate chapters of this book. Systemic diseases such as sarcoidosis^{28, 137} or tumor metastases^{13, 59} may affect extraocular muscle and produce manifest strabismus.

Congenital absence (agenesis) or anomalous insertion of one or several extraocular muscles is described in Chapter 3. This anomaly, often unsuspected by the ophthalmologist during preoperative evaluation of the patient, may not become apparent until the time of surgery and a swift decision may then be required by the surgeon regarding alternative surgical approaches. If muscle surgery is contemplated in a patient with Crouzon's disease, agenesis or anomalous insertion of extraocular muscles must always be suspected because these variations are very prevalent in such cases.^{40, 136}

Role of Accommodation and Refraction in Comitant Strabismus

When Donders⁴⁴ discovered the close relationship between accommodation and convergence, he also

provided the means for understanding a frequent cause of heterotropia. This relationship was treated in detail in Chapter 5. The reader will recall that whenever a given amount of accommodation is exerted, a well-defined amount of convergence (called *accommodative convergence*) is coupled with it. An excessive amount of accommodation, required to clear the retinal image at a given fixation distance, generates an excessive amount of accommodative convergence. This occurs, for example, in the uncorrected hypermetrope. Accordingly, one generally finds an esophoria present in uncorrected hypermetropes and an exophoria in uncorrected myopes; however, neither excessive nor deficient convergence impulses *in themselves* lead to esotropia or exotropia. The vast majority of people have adequate motor fusion and therefore are not heterotropic; but if the fusional amplitudes are inadequate or if the fusion mechanism is impaired by some sensory obstacle, the eyes may deviate. Once fusion has broken down, all other etiologic factors (mechanical and innervational as well as accommodative) gain free rein and a heterotropia is established. At first it may be intermittent, but in time it will become constant.

Refractive errors, through their effect on accommodation, are without doubt one of the prime causes of misalignment of the eyes. Removal of the deviation by corrective lenses in one third of the patients with comitant esotropia is simple and direct evidence for this.

To be sure, Donders's theory⁴⁴ since its inception has found critics who demonstrated that there are esotropes who are emmetropic or even myopic and exotropes who are hypermetropic. Other critics have pointed out that there is no correlation between the amount of the refractive error and the size of the deviation. All this is quite true, but it does not affect the soundness of Donders's theory. First of all, there is a group of patients who have an esotropia that is not accommodative in origin to which Donders's theory does not apply, but there remain two thirds to whom it does apply. Furthermore, the amount of deviation induced by accommodation depends on the individual's responsiveness, that is, his or her accommodative convergence/accommodation (AC/A) ratio (see Chapter 5). If the AC/A ratio is high or very high, large deviations will occur regardless of the refractive error. Also, patients with moderate hypermetropic errors (2D to 3D) frequently have a high AC/A ratio, whereas patients with high

hypermetropia (5D or more) frequently have a low AC/A ratio.¹¹²

All these matters must be understood to evaluate Donders's theory in the somewhat expanded form presented in this chapter. Solidly based on physiologic facts and clinical observations, his remains the best-substantiated theory of the cause of certain types of strabismus (see also Chapter 16).

Fixation Disparity

The possibility that a relationship exists between fixation disparity (p. 21) and heterophoria was suggested many years ago by Ames and Gliddon⁴ who used the term "retinal slip" to describe what is now known as *fixation disparity*. They found fixation disparity associated with heterophorias, but exceptions were observed in patients with exophoria or esophoria in whom disparity was not noted.

Jampolsky and coworkers⁷⁸ investigated the possibility of quantitatively expressing the relationship between fixation disparity and heterophoria. They found that while the direction and magnitude of the disparity in esodeviations correlated well with the direction and magnitude of the heterophoria, such a relationship could not be established for exophorias. In fact, in many patients, exophoria was associated with esodisparity.

Crone³⁰⁻³³ also implied a close relationship between fixation disparity and heterophorias. Using the technique of Ogle and coworkers¹¹⁵ he demonstrated that esodisparity is present in patients with esophoria and exodisparity with exophoria. However, using an experimental method that interferes only minimally with the condition of casual seeing (phase difference haploscopy), Palmer and von Noorden¹¹⁷ showed that small degrees of heterophoria do not necessarily produce fixation disparity and that fixation disparity does not necessarily sustain heterophoria.

The possible role of fixation disparity in the etiology of heterophorias is far from being settled. Convincing data are lacking that indicate a consistent qualitative and quantitative relationship between fixation disparity and heterophorias in all directions of gaze as well as the absence of fixation disparity in orthophoric subjects. Far-reaching and in our opinion often unsupported conclusions have been drawn with respect to the etiology of heterophoria from an experimental situation in which the fusible material in the central or periph-

eral field of vision of an observer was artificially reduced or in which fixation disparity was artificially provoked by stressing motor fusion with prisms or lens-induced vergences. The available evidence is insufficient to establish that fixation disparity is anything more than a physiologic variant of normal binocular vision. This should not distract from the value of lens-induced fixation disparity as a laboratory method for determination of the AC/A ratio (see Chapter 5).

Other Innervational (Neurologic) Factors in Comitant Strabismus

Innervational causes have been implicated in the etiology and pathogenesis of strabismus ever since the inception of scientific ophthalmology. They were recognized in general terms as early as 1855 by Mackenzie,⁹⁸ who stated that

The cause of strabismus should be sought elsewhere than in the muscles of the eyes, elsewhere than in the retina; that is to say in the brain and nerves, organs which preside over the association of acts of the muscles of the eyes.

Donders's theory suggests that a specific innervational mechanism exists for esotropia. Adler³ found that one third of the patients with comitant esotropia fit Donders's theory and fell into the purely accommodative class. In another third the accommodative element was more or less prominent. The nonaccommodative element in this latter group and in the remaining one third, in whom no contributing accommodative element is found, requires an explanation. It is to these patients that musculomechanical interpretations of the deviation have been applied by some workers. Others also have alleged innervational causes for the nonaccommodative factor of the deviation.

PARETIC ELEMENTS. Snellen¹³⁵ held that nonaccommodative comitant heterotropia in all cases should be considered paralytic in origin in the absence of a better explanation of its pathogenesis. Since Snellen, several investigators have concurred with his opinion.

Paresis of an extraocular muscle may lead to paralytic strabismus. With diminution of the paresis, the paralytic strabismus tends to acquire characteristics of a comitant strabismus, and this is known as *spread of comitance* (see Chapter 18). There is no doubt that a certain number of cases of strabismus that are connatal or appear in early infancy are indeed parietic in origin because of a

paresis of a horizontal rectus muscle. However, one should not unduly stretch this hypothesis to cover all cases of infantile nonaccommodative strabismus.

A vertical deviation also may reasonably be assumed to be the immediate cause of a horizontal strabismus. A paresis or paralysis of a vertically acting muscle is a gross obstacle to fusion, and one almost invariably finds that in an adult with acquired paralysis of such a muscle a horizontal deviation is also present because the preexisting heterophoria has become manifest.

ANOMALIES OF THE BRAINSTEM. The intriguing possibility has been raised that infantile strabismus may be caused by a congenital defect in neural wiring of the brain stem that could impede the function of recently discovered integrating systems.⁹⁵ These systems include the nucleus prepositus and interneurons of the abducens nucleus which connect the pontine horizontal gaze center with the motor neuron of the medial rectus muscles. The nucleus prepositus receives visual input as well as information on eye position and movement. It acts as an interface between the vestibular nuclei and the cerebellum. Although there is no evidence to implicate the nucleus prepositus, it could be functionally capable of initiating events that lead to ocular misalignment.¹⁰

ANOMALIES OF CONVERGENCE AND DIVERGENCE. An excess of convergence or divergence innervation from anomalies of the subcortical centers and pathways for convergence and divergence have been implicated as a cause of strabismus by prominent authors of the past.^{1, 118} The clinically useful classification of horizontal strabismus into convergence and divergence excess and insufficiency by Duane⁴⁵ (see Chapter 8) has similar connotations. The high probability cannot be denied that certain forms of esotropia, for instance, hyperaccommodative, hypoaccommodative, and nonaccommodative convergence excess (see Chapter 16), or the nystagmus compensation syndrome (see Chapter 23), are caused by an excess of convergence or that divergence insufficiency (see Chapter 22) is caused by a lack of divergence innervation. However, there is little to support the notion that other forms of esotropia or exotropia are caused by similar mechanisms. For this reason, as well as to avoid any false etiologic implications, we believe that the terms *esotropia* and *exotropia* employed in English are preferable to *convergent*

or *divergent strabismus*, as used in the European literature.

VESTIBULAR SYSTEM. Doden⁴¹ studied spontaneous nystagmus and optokinetic and postrotary vestibular nystagmus and found abnormalities in about 40% of patients with comitant strabismus. Salman and von Noorden¹²⁷ reported abnormal responses to caloric stimulation in children with dissociated vertical deviations, congenital esotropia, or both. These anomalies consisted of postcaloric nystagmus of irregular amplitude and frequency, vestibular hyperexcitability, and irregular eye movements with the eyes closed and at rest. According to Doden, a primary disturbance in optomotor coordination exists in these children. He sought the cause of the primary motor incoordination in children with genetically determined or acquired abnormalities and found birth injuries to be predominant among the acquired abnormalities. A normally developed sensory system can compensate for the deficiency of motor coordination. When accessory factors (hypermetropia, reduced fusion ability caused by general weakness of the patient, and anatomical anomalies) are present, a manifest deviation develops.

Hoyt⁷⁵ reevaluated the vestibular system in strabismic children by studying the vestibulo-ocular response in congenital esotropia. He described this response to be consistently abnormal in these patients, which is in contrast to the normal response obtained from children with the nystagmus blockage syndrome (see Chapter 23). However, these findings do not necessarily indicate that dysfunction of the vestibular system is a primary cause of infantile esotropia.

Safran and coworkers¹²⁶ described an “ocular tilt reaction,” which occurs in a number of clinical conditions that are believed to be related to alterations in the otolithic or vertical semicircular canal pathway, or both. This type of strabismus shows a prominent vertical component associated with a change in the perception of verticality, conjugate cyclotorsion of the eyes, and a head tilt.

ANOMALIES OF THE VISUAL PATHWAYS. In normal subjects optokinetic nystagmus is elicited with equal facility, regardless of whether the optokinetic targets move in a nasotemporal or temporonasal direction. In esotropes, patients with dissociated vertical deviations, and occasionally in exotropes, the optokinetically elicited pursuit movement is either absent or abnormal when the stimulus moves in a temporal direction (optoki-

netic asymmetry.^{36, 103, 143–152} This finding has been interpreted as being indicative of anomalies involving the visual motion processing centers of the primary and extrastriate cortex, which, in turn, are responsible for the strabismus.^{144, 147} We¹¹¹ and others¹³² have proposed a different mechanism and suggested that this asymmetry, which is a normal finding in visually immature infants,^{6, 108} is the consequence of disruption of normal binocular vision early in life, rather than the manifestation of a primary structural anomaly of the brain. The absence of normal binocular input during infancy disrupts maturation of the visual pathways, and the immature stage of the optokinetic response, with its nasotemporal asymmetry, persists. This view is supported by the establishment of a direct relationship between the presence of optokinetic asymmetry and the age at which the strabismus becomes manifest³⁶ (see also Chapter 16). Another reason we think that optokinetic asymmetry is the consequence of strabismus rather than the manifestation of a primary anomaly of the motion-processing ability is the finding that this asymmetry also occurs in nonstrabismic children who lose sight in one eye prior to the sixth month of life.⁶³

Kommerell⁸⁵ suspects a common mechanism for the optokinetic asymmetry and manifest-latent nystagmus in patients with infantile esotropia (see Chapter 16) He believes that cortical binocularity is impaired in such patients, either because of a primary defect or as a consequence of the esotropia. Reduced binocularity prevents signal transmission from the visual cortex to the brain stem as evidenced by maldevelopment of slip control of the retinal image. This slip explains the defective optokinetic response to monocularly viewed and temporally directed visual targets. This asymmetry is also evident in the latent nystagmus with a tonic preponderance directed nasalward with reference to the fixating eye. The adduction preference of the fixating eye is said to be due to a superimposed gaze innervation with the purpose of dampening the nystagmus. However, the question remains open why manifest-latent nystagmus occurs only in some patients with infantile esotropia, whereas optokinetic asymmetry is a consistent feature of this condition.

The demonstration of abnormal visually evoked responses (VERs) by some authors⁵¹ (unconfirmed by others¹⁰²) have added further to speculations that some patients with strabismus have structural anomalies of the brain. This notion has gained additional support because of the association of

optokinetic asymmetry and strabismus with misdirection of the retinogeniculate pathways in patients with albinism.^{27, 38} However, some persons with albinism have the capacity for binocular visual processing, as well as for fusion and global stereopsis, despite misrouted temporal retinal fibers.

Tychsen¹⁴⁵ described marked reduction of the connections between neighboring cortical dominance columns in macaque monkeys with a naturally occurring esotropia that resembled human infantile esotropia in many respects. He believes that these changes may actually be the cause of the motor signs of infantile strabismus. However, he also deems it possible that these anomalies are purely secondary and the result of abnormal binocular experience during visual infancy. *There are no convincing data at this time to link primary structural anomalies of the brain with the etiology of essential infantile esotropia.*

Lang⁹² believes that manifest-latent nystagmus and infantile esotropia have a common etiologic denominator. He stated that the nystagmus is driven by a functional preponderance of the nasal half of the retina because of prematurity, birth trauma, or from "other causes." This functional nasal preponderance of the retinas is said to be reminiscent of a phylogenetically and ontogenetically older visual system with uncrossed fibers. It causes children to take up fixation with either eye in nasally eccentric areas shortly after birth. During the first few months the fixation area then moves toward the foveola but the tendency for the image to drift nasalward persists, causing latent nystagmus during monocular viewing. In discussing this theory Kommerell⁸⁵ pointed out that it is difficult to explain why the slow drifts of the nystagmus are toward the allegedly functionally superior nasal half of the retina when the opposite (a fast corrective saccade) should actually be expected. To this we add our concern about the difficulties involved in determining nasally eccentric fixation reliably in an infant. The observations that infantile esotropia is rarely present at birth (see Chapter 16) but typically develops during the first trimester is also difficult to reconcile with this hypothesis. The pronounced nasotemporal asymmetry of differential light threshold in patients with infantile esotropia (see Herzau and Starc⁷⁰), favoring the temporal hemifield, must be considered as a consequence of abnormal visual experience early in life rather than as a evidence

for a primary functional preponderance of the nasal retina.

Brain Damage

Doden⁴¹ suggested that the etiology of strabismus should be clearly distinguished from its pathogenesis, that is, from mechanisms immediately responsible for this anomaly. In his view, disturbance of the optomotor coordination is the pathogenetic factor, whereas birth injuries and other endogenous or exogenous influences are etiologic factors.

This theory, then, relates strabismus to brain damage. With regard to brain damage there are two opposing camps. Bielschowsky^{16, p. 59} did not think enuresis and left-handedness were more frequent in strabismic than in nonstrabismic children. This opinion was based on a study by his pupil Lippmann,⁹⁷ who made a detailed analysis in 2086 cases of "stigmata of degeneration" and laterality in their significance for strabismus. On the other hand, Lessel⁹⁶ (see also Firth⁴⁹), who reported in more recent studies an increased prevalence of left-handed and ambidextrous persons in an esotropic population, felt that brain asymmetry or anomalous wiring of the visual system may be the cause of esotropia in some patients. Burian and coworkers,²⁰ in studying the higher visual functions in patients with amblyopia, and Burian,¹⁹ in investigating the relation of eyedness and handedness in amblyopic patients, did not find evidence that these patients belonged in the class of brain-damaged persons. A recent review¹²³ of studies conducted between 1934 and 1986 showed that the average percentage of right-handedness in the strabismic population was 73.8% and of right-eyedness, 46.9%. Both of these percentages are considerably lower than in the general population and the author of this review offered the hypothesis that reduced right dominance in the strabismic population may result from dysfunction of the otoliths or their higher brain stem pathways, or of both.¹²³

One could cite the high prevalence of strabismus associated with mental retardation and especially with Down syndrome to make a point for brain damage as a contributing factor to the etiology of strabismus. Fisher⁵⁰ reported a prevalence of 22% of mental retardation associated with *infantile esotropia* without indicating, however, how many of the retarded children had Down syndrome. According to other authors the prevalence

of strabismus in Down syndrome ranges between 21%¹⁴ and 57%.²²

Vontobel¹⁵³ pointed to the high prevalence of hypermetropia in Down syndrome, compared with the frequency of hypermetropia among institutionalized mentally defective patients.⁸⁷ The same point was made by other authors who emphasized that inhibition of growth of the eye, to which they ascribed the hypermetropia, is in accordance with the generalized inhibition of growth in children with Down syndrome. The high incidence of hypermetropia in brain-damaged children and in educationally subnormal children has also been emphasized by other authors.^{48, 57, 80} In contrast to these findings, Caputo and coworkers²² found an about equal distribution of hypermetropia and myopia in 187 patients with Down syndrome.

Unger¹⁴⁹ believed that a general motor retardation, found in a large number of strabismic children, was the most convincing expression of early brain damage and that this damage was mainly attributable to exogenous causes. Prominent among these causes were birth injuries following complicated births, in which he reported 45% of 300 patients as being strabismic. A high incidence of strabismus among children who had sustained a birth trauma was also reported by other authors.^{65, 71, 125, 130, 142}

In marked contrast to these data are the figures of Richter,^{124, p. 72} who found among 542 mothers of strabismic children only 5.9% with a history of abnormalities of pregnancy and 9.4% with a history of complicated deliveries. In a control series of 53 mothers of children without strabismus who were seen for external eye diseases or ocular injuries, the corresponding figures were 7.5% and 11.7%, respectively. Richter concluded that the frequency of exogenous factors to which strabismus might be attributed is no greater in these children than in nonsquinting children.

Gardiner and Joseph⁵⁸ reported an interesting association between congenital heart lesions and eye defects. Of 85 children, all over 6 years of age, examined by these authors, 12 (14%) had strabismus. It is significant that of the cyanotic group (tetralogy of Fallot) 24% were so affected, whereas in the noncyanotic group only 12% were heterotropic. In any event, the frequency of strabismus in this population is four to six times higher than in the general population. It is difficult not to attribute to this nonhereditary factor a causative role in the appearance of the strabismus.

In further support of the etiologic role of brain

damage as a cause of certain forms of nonhereditary strabismus is the high prevalence of strabismus in children with cerebral palsy and premature birth. Numerous studies, quoted in a review by Hiles and coworkers,⁷³ cite the prevalence of strabismus in patients with cerebral palsy as ranging from 15% to 62%, with a 44% average in the 1953–1965 surveys. Esotropia occurred about three times more often than exotropia in these patients. A peculiar fluctuation between esotropia and exotropia, which is not seen in the neurologically “normal” strabismic population, may appear in these children and must be taken into consideration when planning surgical therapy.¹²⁸

Gallo and Lennerstrand⁵⁵ reported a prevalence of strabismus of 9.9% in 528 premature children as compared with a prevalence of 2.1% in 1047 full-term children. Excluding those with severe regressed retinopathy of prematurity (ROP) and reduced visual acuity, the prevalence was 8.5% and 11%.^{56, 82} Esotropia occurred about twice as frequently as exotropia, and the prevalence of refractive errors and of nystagmus was also higher than in normal subjects.⁵⁶ Including children with retinopathy increased the prevalence to 14.7% in the first year of life in another study of 3030 premature infants enrolled in the Multicenter Trial of Cryotherapy for Retinopathy of Prematurity.¹⁷ There was a correlation between the seat and stage of ROP, which indicates that the strabismus was sensory in some patients and thus only indirectly related to ROP. A high prevalence (20.7%) of strabismus in children with very low birth weight was also noted by Pott and coworkers.¹²¹ However, the *infantile esotropia* syndrome occurred in only 1.9% of this group, which is not more frequent than what has been reported in normal children and indicates that brain damage does not play an important role in this particular condition. These findings are in contrast with another study in which infantile esotropia occurred more frequently in children with low birth weight and prematurity than in normal controls.¹⁰⁵

Brain injuries also may affect the centers for motor fusion and cause strabismus. Such patients become incapable of single binocular vision for any length of time. After momentary superimposition of the double images, the eyes will begin to drift into a position of small angle esotropia or exotropia and diplopia will occur. Fusional amplitudes are severely reduced or absent altogether. Jaensch⁷⁶ first described this condition in 1935, and several other studies were published later.^{42, 122, 138}

We have found this disorder in patients who had suffered head trauma, usually followed by periods of unconsciousness, and refer to it as *post-traumatic fusion deficiency*.⁹ The clinical features of this condition are discussed in Chapter 22.

The common association of latent and manifest-latent nystagmus and *infantile esotropia* (see Chapters 16 and 23) may also be interpreted as evidence for primary brain dysfunction. However, Kommerell⁸⁴ pointed out that latent nystagmus and optokinetic asymmetry may occur also as a consequence of strabismus⁸⁵ and the occurrence of manifest-latent nystagmus is not limited to esotropic patients.

As discussed, there is sufficient evidence that strabismus occurs with increased frequency in a population afflicted with brain damage. However, care must be taken to not imply to parents that children with strabismus who are apparently normal in all other respects are “brain-damaged.” This may evoke unfounded parental anxiety or guilt feelings. Unless more becomes known about the nature of the disturbance causing the strabismus in Down syndrome, mental retardation, or prematurity, it suffices to mention the frequent association of these conditions with strabismus.

Embryopathy

In view of the high prevalence of ocular and systemic malformations associated with Duane’s syndrome (see Chapter 21) it has been surmised for some time^{34, 86} that certain forms of strabismus may be caused by a teratogen. This theory has found firm support in the findings of a high prevalence of Duane’s syndrome in *thalidomide embryopathy*.^{104, 141} Since this entity may also be associated with Möbius syndrome, isolated lateral rectus palsy, or horizontal gaze paresis, Miller¹⁰⁴ suggested that certain forms of incomitant horizontal strabismus may result from a developmental disturbance beginning early in the fourth week of gestation and extending over the next 4 to 5 days.

In a recent multidisciplinary and multi-institutional study²⁵ the risk factors for esotropia and exotropia were examined in a cohort of 39,227 children, followed from gestation to the age of 7 years. The incidence of esotropia was 3% and of exotropia 1.2%. Maternal *cigarette smoking* during pregnancy and low birth weight were independent and important risk factors for both esotropia and exotropia. There was a clear correlation be-

tween the number of cigarettes smoked per day and the risk of developing horizontal strabismus. The types of strabismus (e.g., accommodative vs. nonaccommodative, infantile vs. late acquired strabismus) were not further identified and the etiologic connection remains unclear at this time.

A high prevalence of strabismus in children afflicted by the *fetal alcohol syndrome* has also been noted.^{23, 140}

Facial and Orbital Deformities

The common association of horizontal or cyclovertical strabismus with craniofacial dysostoses (oxycephaly, Crouzon’s disease, plagiocephaly)⁶² or the association of certain forms of A- or V-pattern types of strabismus with anomalies of the lid fissures clearly implicates anomalies of the bony orbit in the pathogenesis of certain forms of strabismus. The role of desagittalization of the oblique muscles in patients with plagiocephaly and hydrocephalus causes dysfunction of the oblique muscles and may result in cyclovertical strabismus (see Chapter 19). Rotation of the entire orbit along with the globe or *heterotropia of muscle pulleys* (see Chapter 3) will change the action of the extraocular muscles as will be discussed in connection with apparent dysfunctions of the oblique muscles (see Chapter 18) and A- and V-pattern strabismus (see Chapter 19). Orbital lesions, for example, fibrous dysplasia,¹⁰⁶ may push on the globe, restrict ocular motility, and cause strabismus. Enlargement of the globe itself in high myopia will limit rotation of the eye because its posterior pole collides with the orbital walls or the paths of some muscles has been altered³⁷ (see Chapter 21).

Genetics of Comitant Strabismus

Every ophthalmologist is aware that strabismus often affects more than one member of a family. This observation goes back to antiquity. Indeed, Hippocrates wrote: “We know that bald persons descend from bald persons; blue-eyed persons from blue-eyed persons, and squinting children from squinting parents”⁷⁴ An amusing though quite chauvinistic account of how the causes of congenital strabismus were viewed over 400 years ago is found in the first printed textbook of oph-

thalmology published in 1583 by G. Bartisch¹² (Fig. 9-1).

The incidence of hereditary strabismus in a strabismic population has been estimated as 30% to 70%. In spite of the seemingly obvious hereditary nature of strabismus and the vast literature on the subject, fully reported in the volumes of François,⁵³ Waardenburg,¹⁵⁴ p. 1009 and Klein and Franceschetti,⁸³ the mode of inheritance is by no means clear because of the nature and frequency of the condition and the methods used to study the pattern of its inheritance. Almost without exception, writers on the subject have attempted to find the mode of inheritance of manifest deviation.

There is no reason to believe that the manifest deviation as such is heritable. What very likely is heritable is the condition underlying the deviation,

the cause of the "disease" strabismus, which, depending on circumstances, may or may not lead to a manifest deviation.

To be sure, it is impossible to look for the cause of strabismus, as there is no single cause for all forms. We know that a variety of causes, singly or combined, may lead to a deviation, manifest or otherwise. Mechanical (musculofascial) anomalies, paretic factors, anomalies in the version system and in the systems for convergence or divergence connected or not connected with the function of accommodation and refraction of the eyes, other anomalies in the optomotor system, and anomalies in the sensory system are all more or less well-documented factors in the cause of strabismus.

In spite of these and many other factors identi-

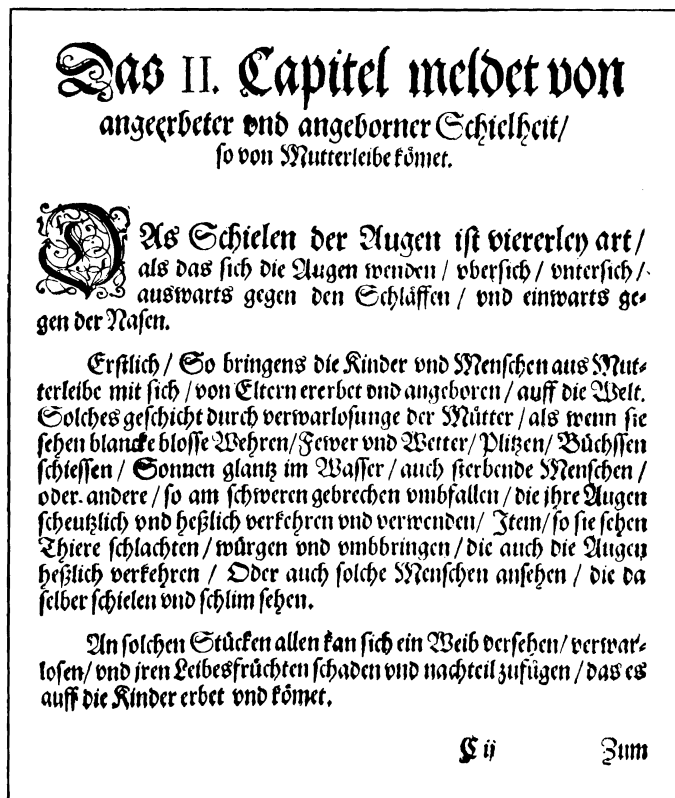


FIGURE 9-1. "The second chapter describes inherited and congenital strabismus/as it is passed on from the mother's womb. There are many forms of strabismus/as the eyes may turn/upward/downward/outward toward the temples/and inward toward the nose. First/it is passed on to children and people from their mother's womb/inherited from the parents and inborn. Such may be caused by negligence of the mothers/as when they look at shining armor/fire and storm/lightning/gunfire/the sun reflecting in water/also at dying people/or others/collapsing from severe infirmity/who twist and contort their eyes in a hideous manner/likewise/when they watch the slaughter of animals/choked and killed/who will also contort their eyes in agony/or look at people who are squinting themselves and don't see well. Through all this carelessness/a woman will become slovenly/cause damage to the fruit of her womb/so that it is then passed on to the children." (Author's translation from Bartisch G: Augendienst (Oftalmoleia). Dresden, 1583, p 14. Facsimile reprint, London, Dawsons of Pall Mall, 1966.)

fied as causing strabismus, this etiologic heterogeneity is mostly neglected by geneticists. Probably as a result of this neglect, there is a wide diversity in the reported mode of inheritance. Some authors concluded from their studies that strabismus was *recessively* transmitted,^{26, 35, 132} whereas others stressed the *dominant* mode of inheritance.^{53, 54, p. 1014}

Dufter and coworkers⁴⁶ studied the inheritance in 195 unselected patients with strabismus, separating them into alternating strabismus without amblyopia (presumably esotropia), alternating strabismus with amblyopia, and accommodative strabismus with a high AC/A ratio. This family study and the complex segregation studies show that the hypothesis of *dominant autosomal* inheritance with *incomplete penetrance* is the most probable of the three types.

Maumenee and coworkers¹⁰¹ studied pedigrees of probands with *infantile esotropia* and the absence of significant degrees of hypermetropia. These authors employed the method of segregation analysis for best fit to different models of mendelian inheritance. A best fit was obtained with a model of codominant inheritance, with a high probability of being affected for homozygotes carrying a relatively common allele. Since standard errors from this analysis are large, the transmission probability for this codominant model differs significantly from mendelian expectations. This suggests the existence of etiologic heterogeneity among the 173 families studied by Maumenee and coworkers, which could have resulted from a major admixture of autosomal recessive, some dominant, and even some nongenetic cases.

Twin studies are of value in investigations of the genetics of strabismus as in all other heritable condition.⁹⁴ Here the concordance of the trait in monozygotic twins as opposed to dizygotic twins

is of particular importance, since a prevalence of the former would indicate the heritable nature of the trait under consideration. Waardenburg^{154, p. 1018} did indeed find such a prevalence in monozygotic twins, as did Richter,^{124, p. 38} and de Vries and Houtman,³⁹ whereas Weekers and coworkers¹⁵⁵ and François⁵³ did not (Table 9-1). Indeed, Weekers and coworkers concluded that, strictly speaking, strabismus (i.e., the manifest deviation) is not genetic. They stated that it is a facultative complication of an ametropia, which alone is genetically determined.¹⁵⁵ This is in marked contrast to Waardenburg's opinion^{154, p. 1017} that both hypermetropia and esotropia are separately inherited and to Lang's⁹³ finding that 10 of 24 monozygotic twins had *essential infantile esotropia*, a condition which we know to be independent of ametropia.

Richter^{124, p. 75} found no evidence for autosomal recessive inheritance of strabismus and cautioned about the assumption of autosomal dominant inheritance with incomplete penetrance. Instead, a multifactorial system of inheritance was held responsible for the fact that fewer members in kindred of the proband exhibited the trait than would be expected. She considers the assumption unproven that sensory anomalies in strabismic patients are the consequence of the abnormal relative position of the eyes. She claims that these sensory anomalies (anomalous correspondence, amblyopia) are inherited traits. This view is supported only by the frequency of their appearance in strabismic families and has no support other than the opposite view held strongly by even such enthusiastic geneticists as Waardenburg.^{154, p. 1014} Clearly, the enormous amount of work expended by Richter has still not brought us nearer to the solution of the problem.

To demonstrate how widely some authors may differ in their opinions, even when reached on the basis of very similar material, the conclusions

TABLE 9-1. Twin Studies in the Investigation of the Genetics of Strabismus

Study	Monozygotic Twins		Dizygotic Twins	
	Concordant	Discordant	Concordant	Discordant
Waardenburg ¹⁵⁴	11	0	4	13
Weekers et al. ¹⁵⁵	3	4	6	2
François ⁵³	2	4	—	—
Richter ¹²⁴	11	1	7	20
de Vries and Houtman ³⁹	8	9	—	—
Lang ⁹³	8	4	—	—
Totals	43	22	17	35

drawn by Schlossman and Priestley¹²⁹ from a rather large group of patients are quoted:

Hyperopia alone was not the cause of convergent squint. Hyperactivity of the center of convergence, defective fusion faculty and obvious anatomic malformation, although important, were not major inherited factors except in a small percentage of the families. . . . There are probably two types of inheritance: (a) a defect in the ectoderm involving the nerve tissues, and (b) a defect in the mesoderm, involving such structures as muscles, check ligaments and fascial attachments. Anisometropia is a relatively unimportant factor in the etiology of familial esotropia. Amblyopia and abnormal retinal correspondence are not inherited. By use of the a priori method, it was found that the data fit a 3:1 ratio, indicating a recessive inheritance for both esotropia and exotropia. There was a certain lack of penetrance in both the families with convergent and the families with divergent strabismus. Convergence is dominant over divergence. About 1 of every 4 persons is a carrier of the gene for strabismus.^{129, p. 20}

In a study of 32 patients with Williams syndrome (mental retardation, short stature, aortic stenosis, "elfin" facies, and associated ocular anomalies) Esswein and von Noorden⁴⁷ found a prevalence of strabismus of 78% (25 of 32 patients) which, with the exception of two patients, consisted of *infantile esotropia*. Others have reported that patients with Williams syndrome without measurable strabismus may have a primary microtropia.¹¹⁶ This extraordinarily high association of Williams syndrome with *infantile esotropia*, unmatched by any other medical condition known to us, strongly suggests a genetic linkage between the two diseases.

Summary

The study of the literature of genetics in strabismus¹¹⁹ gives an impression of considerable confusion. One cannot help but feel that most workers in the field have looked in the wrong place, taking certain motor and sensory manifestations (deviation, amblyopia, and anomalous correspondence) to be the trait that is inherited rather than the underlying condition to which these traits are owed. Richter^{124, p. 70} believed that these conditions are not accessible to measurement. This view can be challenged. There are functions that can be quantitatively characterized and their distribution in strabismic and nonstrabismic families established. In relation to the deviation, such functions are the AC/A ratio,¹⁰⁰ optomotor responses (e.g., fusional amplitudes,⁹⁹ but also responses of the optovestibular system), and, in the families of

patients with an A or V pattern of fixation, the configuration of the lids and structures around the eyes. Instead of looking for an inheritance pattern of amblyopia and anomalous correspondence, one should investigate quantitatively retinal rivalry, the readiness to suppress, and other similar functions. One could even conceive of an ophthalmologist well versed in biochemistry who would test the hypothesis of Keiner,⁸¹ that a heritable metabolic factor is at the root of the presumed retardation of myelination of the visual system.

Most of the work on the genetics of strabismus was done 30 or more years ago. With the advent of molecular biology and in view of the rapid advances in gene identification in recent years, it is hoped that strabismus once again catches the interest of geneticists so that the pattern of inheritance can be firmly established. The frequent association between Williams syndrome and infantile esotropia⁴⁷ (19 of 32 patients) mentioned earlier in this chapter should provide fertile ground for further investigation with modern methods of genetic research.

Accurate knowledge of the inheritance of strabismus (in the broadest sense, not in the sense of the deviation as such) would be of utmost practical use. Suppositions would no longer have to be relied on to answer the question of whether sensory anomalies are cause or sequelae. Such information might help to explain why certain patients do and others do not respond to treatment.

The frequent occurrence of sensorimotor anomalies in the pedigrees of strabismic probands¹²⁰ obliges the conscientious ophthalmologist to insist on an examination of all siblings of a strabismic child to rule out the presence of neurosensory anomalies of the eyes. Such anomalies may be subtle and thus may have escaped the attention of parents. Abrahamson and coworkers² identified a positive family history of strabismus and hypermetropia in excess of +3.00D as risk factors for the development of strabismus. Children with these characteristics were four to six times more likely to develop strabismus than normal controls.

Concluding Remarks

In strabismus, the deviation, even if comitant, is caused by a variety of etiologic factors. Each author lays the greatest stress on those factors that he or she finds most appealing on the basis of theoretical concepts, personal clinical experience,

or individual research direction. A unitary theory of the pathogenesis of strabismus is then developed in terms of mechanical anomalies or innate paralysis and the admission that accommodation, refraction, or other innervational factors may also play a role is made almost grudgingly. The evidence that a normal sensorimotor mechanism can overcome remarkably severe anatomical and mechanical obstacles is neglected. Others to whom strabismus is a purely innervational anomaly consider it naive to allow mechanical factors to be involved. From some writings the impression is gained that nervous impulses act almost in a vacuum. To those who attribute a preponderant role to the fusion mechanism or to toxic influences, both mechanical and refractive elements are secondary, if they are acknowledged at all. And so it is with all other theories.

As has been pointed out repeatedly in this chapter, all elements listed contribute in varying degrees to the appearance of a deviation. Some authors have recognized this, and their number is increasing. Foremost among them was Bielschowsky,^{16, p. 51} who distinguished two groups of causes of comitant strabismus—static causes and anomalies of the sensorimotor system. Van der Hoeve¹⁵¹ also stated explicitly that strabismus is neither a purely static nor a purely sensorimotor or psychic problem but a combination of all of them. Many modern authors have expressed themselves in a similar vein.

For the practicing ophthalmologist the truth, in an academic sense, about the etiology of strabismic deviations is of small importance. However, it is necessary to be well acquainted with the multiplicity of causes that may lead to a deviation, for a rational treatment is possible only if the cause is understood.

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