Congenital eye defects in rats following maternal folic-acid deficiency during pregnancy

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Malformations of fetal rat eyes result from a variety of maternal vitamin deficiencies employed either transiently or continuously during pregnancy. Thus, eye defects have been produced in rat fetuses as a result of maternal deficiencies of vitamin A (Wilson, Jordan & Brent, 1953), pantothenic acid (Lefebvres-Boisselot, 1951; Nelson, Asling & Evans, 1957), niacin (Chamberlain & Nelson, 1963) and pteroylglutamic acid (PGA or folic acid) (Evans, Nelson & Asling, 1951; Nelson, Asling & Evans, 1952; Giroud & Boisselot, 1951; Giroud, Lefebvres & Dupuis, 1952; Giroud, Delmas, Lefebvres & Prost, 1954).

Previous studies on the teratogenic effects of PGA-deficiency on the developing rat eye, although informative, have been concerned mainly with stages after the 15th day of pregnancy (the day of finding sperm in the vagina is considered to be day zero). However, since the eye begins forming between the 9th and 10th days of gestation, it was felt that a study embracing both early and late stages of ocular development in rat embryos from mothers maintained on a PGA-deficient regimen for different lengths of time during gestation would be of more value in understanding the genesis of certain ocular abnormalities. The following account concerns such an investigation and describes the abnormalities encountered in the visual system.

MATERIALS AND METHODS

Rat fetuses were obtained from mothers maintained on the PGA-deficient regimen from the 7th to 9th, 9th to 11th, or 11th to 21st days of gestation; details of the diets employed will be found in Nelson et al. (1952). Autopsies were performed beginning with the 9th, 10th and 11th days of pregnancy respectively and continued on each successive day for all experimental groups through to term. Fetuses were fixed in Bouin’s solution, embedded in paraffin, serially

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sectioned at 10 μ and stained with hematoxylin and eosin. Control fetuses of corresponding age maintained on a stock diet or a PGA-supplemented diet were treated similarly and previous studies have shown that there are no significant differences between the embryos of these two groups. Eyes from a total of 230 embryos were studied of which 90 were obtained from mothers PGA-deficient on days 7–9 of gestation, 50 from mothers PGA-deficient on days 9–11, and 20 from mothers PGA-deficient on days 11–21; there were 70 controls. In addition, 16 eyes were obtained from rats aged 1, 5, 21, 45, 60 and 90 days post partum in order to observe eye development after birth; these eyes were embedded in nitrocellulose, sectioned at 10 μ, and treated with hematoxylin and eosin or with Mallory’s connective tissue stain. Eyes from comparable PGA-deficient young, however, were not obtainable as the experimental fetuses were incapable of postnatal existence.

RESULTS

At 9½ or 10 days in control embryos two outpouchings from the lateral walls of the diencephalon denote the anlagen of the optic vesicles. At this stage the anterior and posterior neuropores are widely open although the neural tube is closed in its mid-portion. The outpouchings consist of two to six layers of neuroectodermal cells while one or two layers of mesodermal cells intervene between them and the surface ectoderm (Plate 1, fig. A).

Embryos from PGA-deficient mothers are indistinguishable from control embryos until the 11th day of gestation when those subjected to maternal PGA-deficiency from the 7th to 9th days of pregnancy show evidence of general retardation. Microphthalmia is a common feature in all groups of PGA-deficient embryos (i.e. the embryos from PGA-deficient mothers) in the later stages of development.

Defects of closure of the neural tube were frequently observed in the 7th to 9th day and 9th to 11th day PGA-deficient embryos but were rarely seen in the 11th to 21st day PGA-deficient embryos. In two anencephalic 21-day embryos from mothers on the PGA-deficient regimen from the 7th to 9th days of gestation the pituitary stalk was absent; in one the entire posterior lobe was also missing while in the other it was present but small in size. Abnormalities of the skeletal elements of the skull were common especially when PGA-deficiency was established early in pregnancy.

Further observations on PGA-deficient and control embryos will be considered in terms of the structural organization of the eye.

Eyelids. In control fetuses the eyelid folds are distinguishable at day 15 and hair follicles and glandular elements are present by day 17. On day 18 the free edges of the eyelids fuse and remain so until the 14th day after birth (Plate 1, fig. E).

Marked retardation of eyelid formation occurred in fetuses from mothers in all three PGA-deficient groups. However, it was especially pronounced in the
offspring of mothers PGA-deficient from days 9 to 11 and days 11 to 21 of pregnancy. In these two groups several fetuses showed 'open eye' due to failure of fusion of the eyelids.

**Cornea and sclera.** Corneal formation is evident in control embryos at day 14, by which time the lens vesicle has separated from the surface ectoderm and the latter has resealed to form the epithelial layer; a cord of mesoderm then migrates between the epithelium and the lens and forms the corneal stroma. Distinct epithelial and stromal layers of the cornea are present by day 16 and a cleft between it and the lens demarcates the anterior chamber (Plate 1, fig. D). Just after day 17 scleral condensation becomes apparent and the corneoscleral junction is distinguishable. By day 18 the endothelial layer of the cornea has appeared and subsequent development continues slowly during the remainder of pregnancy. Descemet's membrane does not appear until after birth and Bowman's membrane does not form in the rat. Progressive stratification of the corneal epithelium and considerable increase in collagen deposition in the corneal stroma and sclera occur in the early stages of post-natal development.

In some 7th to 9th day and 9th to 11th day PGA-deficient fetuses the cornea shows areas of thickening in its mesenchymal (stromal) layer with occasional deposition of a fibrillar material which gives it an irregular and disorganized appearance. In the case of 11th to 21st day PGA-deficient fetuses the cornea and sclera have a normal topography although their differentiation is retarded.

**Lens.** The optic vesicle contacts the surface ectoderm at day 11 and shortly afterwards the latter thickens to form the lens plate which presents a slight external depression, the fovea lentis (Plate 1, fig. B). By day 12 the lens plate becomes the lens vesicle which initially remains connected to the surface ectoderm although no longer communicating with the exterior. At day 13 the cells of the posterior wall of the vesicle differentiate into primary lens fibers extending almost to the anterior epithelium while equatorially the cells become more compact, indicating preparation for differentiation into secondary lens fibers. The cells of the anterior epithelium now become more cuboidal in shape although their nuclei remain stratified; the tunica vasculosa now forms on the posterior surface of the lens.

Separation of the lens from the surface ectoderm has usually occurred by day 14 when primary lens fibers obliterate its original cavity. Between days 15 and 17, secondary lens fibers form and numerous mitotic figures appear in the anterior epithelium which consists of a single layer of cuboidal cells. Suturing of secondary fibers at the posterior lenticular pole commences about day 16 (Plate 1, fig. D) and distinct sutures at both anterior and posterior poles are present on day 17; one day later the lens capsule begins to form and is noticeably thickened on day 20. In the newborn the lens is more spherical in shape and often shows fine vacuolation in its central portion (Plate 1, fig. F).

After birth there is further addition of secondary lens fibers but at a rapidly decreasing rate. One day post partum the tunica vasculosa lentis begins to
atrophy and in 21-day-old rats its degeneration is complete. The suspensory ligament of the lens was first observed in the 60-day-old rat.

In some 7th- to 9th-day PGA-deficient embryos the lens was absent and this was associated with failure of the optic outgrowth to reach the surface ectoderm; in others, microcilia were present. Herniation of lens fibers through the anterior epithelium (Plate 3, fig. J), as well as vacuolation (Plate 3, fig. K), similar to that occurring in maternal PGA-deficiency from the 9th to 11th days of pregnancy, was occasionally observed.

When maternal PGA deficiency is instituted on the 9th to 11th days of gestation, general retardation of about 12 h is noted at day 12 in that the eye anlage consists of a poorly defined optic cup and lens plate. Often, at this stage, the inner layer of the optic cup is unusually thick so that the depth of the cup is decreased. Most lens abnormalities encountered in this group appeared to result from a primarily malformed retinal anlage. Lenses, in addition to being smaller than those of corresponding controls, are displaced anteriorly and laterally and sometimes rotated through a right angle by the pressure of various diverticula from the wall of the malformed optic cup. Other anomalies observed less frequently were: lens vacuoles, a condition resembling ‘posterior lentiglobus’ in man, and rupture of the anterior lens epithelium leading to lenticular tissue herniating into the anterior chamber; these abnormalities, however, seem unrelated to retinal malformation.

Lenses from 11- to 21-day PGA-deficient fetuses show numerous vacuoles

**Plate 1**

Abbreviations. ac, Anterior chamber; ce, corneal epithelial layer; cp, ciliary processes; cs, corneal stromal layer; el, eyelids; em, external eye muscle; ha, hyaloid artery; lp, lens plate; of, optic nerve fibers; ov, optic vesicle; pc, posterior chamber; pm, pupillary membrane; pv, post-lental vessels; sf, secondary lens fibers; tc, transitory layer of Chievitz.

Fig. A. Day-10 control embryo showing optic vesicles, in the inner walls of which are numerous mitotic figures. × 72.

Fig. B. Day-11½ control embryo showing invaginating optic vesicle and lens plate. × 310.

Fig. C. Day-14 control embryo in which the hyaloid artery and post-lental vascular plexus are well formed. The cells are more compactly arranged at the equator of the lens. × 70.

Fig. D. Day-16 control embryo. The cornea shows epithelial and stromal layers and the anterior chamber is present. Secondary lens fibers are forming with suturing at the posterior pole. Optic nerve fibers stream into the optic stalk. External ocular musculature is appearing. × 75.

Fig. E. Day-19 control embryo in which the eyelids (epithelial layer removed) are fused and the conjunctival sac is apparent. The lens capsule is thickening and the pupillary membrane is thinning in its central portion prior to disintegrating. The sclero-choroidal elements are evolving. The transitory layer of Chievitz is distinguishable in the sensorial retina. × 35.

Fig. F. Day-21 control embryo showing the ciliary processes and the anterior and posterior chambers. The line of fusion of the eyelids is recognizable and hair follicles and glandular elements are well shown. The lens is more spherical in shape and there are numerous small vacuoles in its central portion. The pupil is now established. × 20.
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(Plate 3, fig. O) of varying sizes which are usually centrally disposed. These vacuoles are first observed on day 14 and contain a frothy-appearing substance as seen in ordinary histological preparations. No other lenticonular anomalies were observed in this particular group.

**Choroid, iris and ciliary body.** The choroidal anlage can be observed as early as day 12 in the form of a layer of capillaries developing externally to the outer layer of the optic cup. This vascular network becomes increasingly complex during later prenatal stages and by day 21 large blood vessels and a few chromatophores have appeared. No distinct layers can be determined prenatally. However, 5 days postnatally the suprachoroid, the blood vessel layer and the choriocapillaries become distinguishable. Chromatophores continue to increase in number up to the 21st day after birth.

The iris is recognizable on day 17 with the appearance of the pars iridis retinae, which is invaded by blood vessels from the choroid on day 18. On the latter day the pupillary membrane is established but this begins to break down on day 19 when a definite stroma in the iris is discerned (Plate 1, fig. E). The ciliary body now forms and 1 day post partum ciliary processes are visible. The sphincter pupillae muscle appears 5 days after birth; the dilator pupillae muscle is much more difficult to distinguish and was not observed clearly until 90 days post partum.

In the PGA-deficient fetuses the choroid, iris and ciliary body show no malformation in the absence of other eye aberrations. In the presence of severe lenticonular malformations their degree of differentiation varied from simple retardation to complete absence.

**Retina.** The optic vesicles (retinal anlagen) appear on day 9½ as two diencephalic outpouchings; on the 11th day they have increased in size and are almost in direct contact with the overlying surface ectoderm (Plate 1, fig. A). Invagination of each optic vesicle occurs about 12 h later, resulting in the optic cup, which is lined by a thick layer of cells, the neural retinal rudiment. During

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**Plate 2**

*Abbreviations. gc, Ganglion cell layer; il, inner limiting membrane; im, inner molecular layer; in, inner nuclear layer; lr, layer of rods; nf, nerve fiber layer; ol, outer limiting membrane; om, outer molecular layer; on, outer nuclear layer; pc, pigment cells; tc, transitory layer of Chievitz.*

Fig. G. Day-16 control embryo. The sensorial and pigmented layers of the retina are shown. In the former the nerve fiber layer and the inner and outer nuclear layers are distinguishable. × 330.

Fig. H. Day-19 control embryo. The transitory layer of Chievitz is now apparent between the inner and outer nuclear layers. The separation of the pigmented and sensorial layers is an artifact. × 375.

Fig. I. Retina 60 days postnatally. The definitive layers of the sensorial retina can be distinguished. Rods are present but not cones. × 420.
the 12th day the optic cup deepens and is intimately related to the lens plate, only a few cytoplasmic fibrils and mesenchymal cells intervening between them. On the same day the hyaloid artery traverses the choroidal fissure and a small channel indicating the annular vessel is recognizable at the cranial border of the optic cup. Pigment granules first appear in the outer layer of the optic cup on day 13. The hyaloid artery lies deep in the optic stalk by the 14th day and the retinal vessels are established (Plate 1, fig. C). Two zones are now distinguishable in the inner layer of the retina, an inner anuclear zone and an outer nuclear zone.

In the sensorial retina on day 15 nerve fibers can be traced from the anuclear zone of the retina to the optic stalk and a structure resembling the internal limiting membrane is observed near the fundic area. Some of the innermost cells of the nuclear zone apparently have differentiated into primitive ganglion cells and are giving rise to nerve fibers; other cells of this zone are differentiating into nuclei of the fibers of Müller. On day 16 the innermost nuclei of the retina-nuclear zone are round or oval in shape and show a lighter chromatin pattern and a looser arrangement than the outermost nuclei of the same layer; the latter are elongated, have a dense chromatin pattern, and are more compactly arranged (Plate 2, fig. G). The fibers of Müller and the internal limiting membrane which is closely related to the central retinal vessels are now more evident, and the choroidal fissure has begun to close.

By day 17 closure of the choroidal fissure is complete and the external limiting membrane has appeared. Continued differentiation in the nuclear zone of the sensorial retina is apparent by day 19 and a narrow fibrillar layer resembling the transitory layer of Chievitz, as described in the human retina, separates the nuclear zone into primitive inner and outer neuroblastic layers (Plate 2, fig. H). The nuclei of the inner neuroblastic layer are still round or oval in shape, while those of the outer are elongated. By the 20th day the fibrillar layer separating the neuroblastic layers has increased in width and a primitive inner molecular layer is appearing; it is now difficult to determine whether the transitory layer of Chievitz is present or not. On the 21st day, however, seven retinal layers are distinguishable: internal limiting membrane, nerve fiber layer, inner neuroblastic layer, inner molecular layer, outer neuroblastic layer, external limiting membrane, and pigment epithelium.

Differentiation of the retina is both rapid and extensive after birth (Plate 2, fig. I). In the 5th day rods appear and the ganglion cell layer differentiates; on the same day the formation of an outer molecular layer begins to divide the outer neuroblastic stratum into inner and outer nuclear components. All ten layers of the retina are distinguishable on the 21st day post partum, by which time the pigment epithelial cells are completely filled with granules.

In fetuses from mothers maintained on a PGA-deficient regimen from the 7th to 9th days of pregnancy retarded development of the optic vesicle was frequently seen between the 13th and 15th days of gestation. In one 15-day PGA-deficient embryo of this group, the lens was quite well-developed yet the optic cup was
Ocular abnormalities in rat embryos following various periods of maternal PGA deficiency during pregnancy. Figs. J-L: PGA deficiency from days 7 to 9; Figs. M, N: PGA deficiency from days 9 to 11; Fig. O: PGA deficiency from days 11 to 21.

Abbreviations. a, Anterior epithelium of lens; c, small optic cup; d, retinal diverticulum; h, anterior herniation; n, optic nerve fibers; v, lens vacuolation.

Fig. J. Day 14; anterior herniation of lens. × 260.
Fig. K. Day 15; small optic cup. × 95.
Fig. L. Day 16; marked reduction in optic nerve fibers entering optic stalk. × 100.
Fig. M. Day 15; retinal folding producing double optic cup. × 90.
Fig. N. Day 20; retinal diverticulum. × 30.
Fig. O. Day 21; vacuolation of lens. × 35.
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much reduced in size (Plate 3, fig. K) while in several 16-day embryos the choroidal fissure was still present. The most unique abnormality in this group of PGA-deficient embryos, however, was observed in five embryos (days 16 and 17) where the optic stalk was narrowed or discontinuous and the optic nerve fibers either greatly reduced in number or absent (Plate 3, fig. L). In such instances the general appearance of the eye seemed normal although cellular differentiation in the retina was retarded.

Fetuses from mothers subjected to PGA-deficiency from days 9 to 11 of gestation often exhibited primary retinal defects associated with secondary malformation of the lens. These aberrations first appear on day 12 when thickening of the inner layer of the optic cup and masses of neuroectodermal cells project from its periphery to give the cup an irregular shape (Plate 3, fig. M). With continuing development these distortions lead to the formation of diverticula (Plate 3, fig. N), in some cases so marked that a ‘double optic cup’ results; other diverticula occupy the anterior chamber while some arising centrally cause displacement and rotation of the lens. A ‘double optic cup’ was almost always accompanied by retinal coloboma or by retinal eversion. Several cases of retinal folding with or without eversion were noted which could not be clearly attributed to diverticula of the optic cup. Extensive folding of the neural retina was in some instances accompanied by cysts and rosettes. In all cases where the neural retina was primarily affected, the pigment epithelium and the optic nerve were grossly malformed.

Retinal malformations were not observed when maternal PGA deficiency was from the 11th to 21st days of gestation.

DISCUSSION

1. Controls

Whereas differentiation of the human eye is almost complete in the newborn except for the presence of the fovea centralis retinae (Mann, 1957), the rat eye is quite immature at birth and continues to develop markedly for another 2–3 weeks post-natally; in addition, the eye of the rat seems to grow during most of its life in contrast to man where growth is negligible after 5 years (McLaren, 1963). In control rats of the present study separation of the eyelids was delayed until the 13th and 14th days post partum, and photoreceptor cells (rods) did not appear until the 4th or 5th day after birth, findings which are in agreement with Detwiler (1932). Structures such as Bowman's membrane, the fovea centralis, and cones, commonly present in the eyes of higher mammals, are absent in the rat eye, and while Walls (1942) has claimed that a few rudimentary cones are found in the rat retina, no support for this concept was found in this study.

The vascular pattern of the rat eye also differs from that of man. As Janes & Bonds (1955) noted, in the former the sclera is avascular and the iris and ciliary body have a common blood supply; according to these authors the sclera receives
nutrients from the choroid by diffusion. The present study confirms the avascu-
larity of the sclera although the detailed blood supply of the iris and ciliary body
was not investigated. Again, in the rat, although the ciliary processes become
highly differentiated in the adult, only a few strands of ciliary muscle are ever
present (Woolf, 1956). In most other respects development of the rat eye
resembles that of man as described by Mann (1957).

2. PGA-deficient fetuses

Embryos from PGA-deficient mothers were always smaller and less advanced
in development than the corresponding controls, indicating retardation of both
growth and differentiation. In addition, embryos of the PGA-deficient groups
exhibited some degree of microphthalmia frequently accompanied by marked
abnormality of the lens, retina, or of the entire ocular system. Microphthalmia
was also a common feature of the PGA-deficient embryos studied by Giroud &
Boisselot (1951), Giroud et al. (1952, 1954), and by Nelson et al. (1952).

Many of the abnormalities observed in this study have been described pre-
viously in older rat fetuses as a result of treatment with various teratogenic
agents and procedures. However, in none of these has there seemingly been any
attempt to follow the sequence of events leading to malformation in embryos at
different stages of development.

Delayed fusion of the eyelids in 21-day rat fetuses was reported by Nelson
(1957) when maternal PGA-deficiency was induced from the 9th to 11th days of
gestation, and the present investigation confirms this finding. In addition, it has
shown that retarded eyelid development also may result when PGA deficiency
is instituted on the 7th to 9th or 11th to 21st days of pregnancy.

Disorganization of the corneal layers, especially of the stroma, has been
described previously in PGA-deficient rat fetuses (Nelson, 1957) and in rat
fetuses exposed to intra-uterine injections of urethane (Hall, 1953). In the PGA-
deficient embryos of the current study primary corneal or scleral lesions were
not encountered at any stage of development. Nevertheless, both the cornea and
sclera were grossly disorganized and showed fibrillar deposits when the entire
ocular system was malformed in fetuses from mothers deficient in folic acid from
the 7th to 9th or 9th to 11th days of gestation, but not when PGA deficiency was
induced from the 11th to 21st days of gestation. Thus it would seem that
disturbance of corneal differentiation occurs secondarily to gross retinal and
lenticular defects following maternal PGA deficiency during the early stages of
ocular development.

The types of lens defects also vary with the time of institution of maternal
PGA deficiency. Thus, in the present study with PGA-deficiency from days 7
to 9, the lens appeared to escape gross malformation with the exception of
rupture of the anterior lens capsule as reported by Nelson (1957) for the identical
period of PGA deficiency. The same lenticular malformation was also observed
in an embryo from a mother PGA-deficient from days 9 to 11 of gestation.
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Giroud et al. (1954) described a similar abnormality in PGA-deficient embryos and attributed it to delayed separation of the lens vesicle from the surface ectoderm; he also noted that in such instances the lens fibers were swollen and considered that this may cause the capsule to rupture. The fact that posterior lentiglobus was also seen in the eye of the PGA-deficient (9th to 11th day) fetus with rupture of the lens capsule anteriorly may indicate concomitant stress on the posterior part of the capsule as well. Posterior lentiglobus has also been observed in rat fetuses following intra-uterine injections of urethane (Hall, 1953). Frequently the anterior epithelium did not surround the excrescence completely but was interrupted where it communicated with the lens proper.

In fetuses from mothers subjected to PGA deficiency from the 9th to 11th days of pregnancy, the majority of lens abnormalities were either rotations or displacements (ectopia lentis) apparently secondary to pressure from diverticula of the optic cup. The latter may arise as early as the 12th day of gestation and may be centrally, caudally, or peripherally located; the last-mentioned usually occupy the anterior chamber. Minute vacuoles were observed in a number of lenses of otherwise normal appearance in this same group of fetuses.

When PGA deficiency began on the 11th day of pregnancy, lenses showed vacuolation as early as day 14. These vacuoles were noted previously by Nelson (1957) in 21-day PGA-deficient fetuses, and by Gillman & Gilbert (1954) in the offspring of rats injected with trypan blue. Maternal PGA deficiency from days 11 to 21 of gestation usually affected only the lens and no other part of the eye.

A striking anomaly occurred in several 16- and 17-day PGA-deficient (7th to 9th day) embryos, in which the optic nerve was absent or represented by only a thin strand of fibres; it has been encountered only in this group of PGA-deficient fetuses. Dysgenesis of the outgrowth of axons from the ganglion cells of the retina into the optic stalk is an interesting delayed effect of this particular PGA-deficient regimen; a somewhat similar occurrence has been reported by De Meyer & Issac-Mathy (1958) and by Tuchmann-Duplessis & Mercier-Parot (1958) in rat fetuses following maternal administration of sulfamide.

The consequence of failure of optic nerve fibers to develop was clearly seen in one 17-day embryo of the same PGA-deficient group in which the optic stalk was discontinuous and the eye separated from the central nervous system. Such eyes must either fail to grow or undergo degeneration, resulting in microphthalmia or anophthalmia respectively by time of birth. Although these abnormalities are often assumed to be the result of dysgenesis or agenesis of the optic vesicle, it is quite evident that they may also arise from disturbance in the later stages of eye development. A somewhat similar situation has been observed in rat fetuses from chlorambucil-treated mothers in which absence of the kidney in older fetuses was not the result of agenesis but of degeneration of the kidney in later pregnancy following abnormality of the Wolffian duct (Monie, 1961).

Retinal coloboma, eversion, and folding, similar to that observed in the PGA-deficient (9th to 11th days) fetuses have been reported in rat fetuses following
maternal PGA deficiency by others (Giroud et al. 1954; Nelson, 1957). Coloboma was also described in rat fetuses as a result of X-irradiation (Wilson, 1954), and folding of the retina following maternal injections of trypan blue was reported by Gillman & Gilbert (1954).

In the most severe sensorial retinal defects the formation of pigment epithelium was retarded and atrophic. This is found especially in coloboma, eversion, and duplication of the optic cup. Giroud et al. (1954) attributed many retinal abnormalities to retarded development of this layer. However, the results of the present study indicate that many malformations of the sensorial and pigment layers of the retina, as well as of the lens, can also be attributed to abnormality of formation of the primitive retinal anlage (optic cup) as early as the 12th day of gestation. These early aberrations always seem to involve the inner layer of the cup or the future sensorial retina primarily.

**Summary**

1. The development of the Long-Evans rat eye follows a pattern similar to that of the human eye. However, in the rat a considerable part of morphogenesis occurs postnatally. Bowman’s membrane, the fovea centralis and retinal cones, present in the human eye, are absent in that of the rat.

2. The effect of maternal folic acid (pteroylglutamic acid or PGA) deficiency on eye differentiation in rat fetuses at various stages of gestation was observed in three groups of fetuses, from mothers maintained on a PGA-deficient regimen from the 7th to 9th, 9th to 11th or 11th to 21st days of pregnancy.

3. Malformations of the eyes of PGA-deficient fetuses included anophthalmia or microphthalmia, reduction or absence of the optic nerve fibers (days 7–9), duplication of the optic cup, retinal folding, retinal coloboma and eversion, rupture of the anterior lens capsule and posterior lentiglobus (days 9–11), and lens vacuolation (days 9–11 and days 11–21).

4. Ocular abnormalities induced by PGA deficiency appear to result from several developmental mechanisms. PGA deficiency from the 7th to 9th days of pregnancy retarded the formation of the optic cup in some instances while in others it produced little disturbance of the configuration of the eye but retarded or suppressed the outgrowth of axons from the ganglion cells of the retina. On the other hand, PGA deficiency from the 9th to 11th days of gestation resulted in abnormal growth of the retina with secondary effect on the lens. With maternal PGA deficiency from the 11th to 21st days of pregnancy, vacuolation of lens fibers was the only ocular abnormality encountered.
**Résumé**

**Anomalies congénitales de l’œil, chez des rats, consécutives à une déficience maternelle en acide folique au cours de la gestation**

1. Le développement de l’œil chez le rat Long–Evans, suit une voie similaire à celle de l’œil humain. Cependant chez le rat une part importante de la morphogenèse a lieu après la naissance. La membrane de Bowman, la fovée centralis et les cones de la rétine, présent dans l’œil humain, sont absents dans celui du rat.

2. L’effet d’une déficience maternelle en acide folique (acide pteroylglutamique ou PGA) sur la différenciation de l’œil du fœtus de rat, à divers stades de la gestation, a été observée dans trois groupes de fœtus, provenant de mères soumises à un régime déficient en PGA des 7ème au 9ème, 9ème au 11ème, ou 11ème au 21ème jour de la gestation.

3. Les malformations des yeux des fœtus en cause, correspondent aux caractères suivants: anophthalmie ou microphthalmie, réduction ou absence des fibres du nerf optique (jours 7 au 9), duplication de la cupule optique, plissement rétinien, colobome rétinien et éversion, rupture de la capsule cristallinienne antérieure et du globe cristallin postérieur (jours 9 au 11), vacuolisation du cristallin (jours 9 au 11 et jours 11 au 21).

4. Les anomalies oculaires induites par une déficience en PGA apparaissent comme la résultante de plusieurs mécanismes du développement. La déficience en PGA du 7ème au 9ème jour de la gestation entraîne un retard dans la formation de la cupule optique dans quelques cas, cependant que pour d’autres, elle cause peu de trouble dans la configuration de l’œil, mais retarde ou supprime la croissance des axones des cellules ganglionnaires de la rétine. D’autre part, la déficience en PGA du 9ème au 11ème jour de la gestation a pour conséquence croissance anormale de la rétine, suivie d’un effet secondaire sur le cristallin. Pour la déficience maternelle en PGA du 11ème au 21ème jour de la gestation, la vacuolisation des fibres du cristallin est la seule anomalie oculaire observée.

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