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## Blindness and Menarche

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**I**N HUMANS, as in other polyestrous mammals, the neuroendocrine mechanisms which eventually will control ovulation do not become functional until a characteristic age is reached. Sometime before the first ovulation, the human female experiences her first vaginal bleeding (menarche); after cyclic ovulation begins, the release of an ovum is usually followed in about 2 weeks by menstruation. In the polyestrous rodents most often used to study reproductive mechanisms, the impending maturation of the neuroendocrine axis is indicated not by vaginal bleeding but by spontaneous rupture of the vaginal membranes, and ovulation is followed not by menstruation but by characteristic changes in the cellular composition of the vaginal epithelium (the vaginal estrous cycle).

There is considerable evidence that en-

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vironmental lighting exerts important effects on the age at which sexual maturation occurs in birds,<sup>15, 18</sup> monestrous mammals (i.e., the ferret<sup>3</sup>), and polyestrous rodents.<sup>5</sup> If weanling rats are housed under continuous illumination, spontaneous vaginal opening occurs prematurely.<sup>5</sup> Subsequently, the animals ovulate prematurely, the ovaries become heavier than normal,<sup>5, 19</sup> and the anterior pituitary gland contains abnormally large amounts of luteinizing hormone.<sup>10</sup> However, these effects are transient: Within a few weeks rats which have been kept under continuous illumination stop ovulating or ovulate only infrequently. This "persistent estrous syndrome" is associated with ovaries that are smaller than normal and contain few corpora lutea;<sup>5</sup> the level of luteinizing hormone in the pituitary is depressed.<sup>10</sup>

Conversely, rats which have been made blind or have been kept in continuous darkness from an early age suffer a delay in sexual maturation; eventually, however, cyclic ovulation is attained, and the ovaries reach the same weight as those of littermate animals housed under normal lighting (i.e., 12 hr. of light per day).<sup>4, 5</sup>

While there is considerable anecdotal indication that environmental lighting influences human sexual development and behavior, we are not aware of any experimental studies of the effects of light on human sexual maturation. Since it is obviously impractical to maintain human subjects in continuous light or darkness long enough to perform such experiments, we have tried using a "natural experiment" (i.e., blindness) to study the relationship between light stimulus and human sexual maturation.

In 1962 we initiated a study to determine whether early blindness influenced the timing of sexual maturation, as manifested by the occurrence of menarche.<sup>25</sup> To preclude the possibility that the agent which caused the blindness might also influence sexual development, we limited our study to girls whose blindness was clearly the result of orbital pathology and was not, so far as we could determine, associated with neurologic or neuroendocrine disorders. The blind population admitted to our preliminary study consisted mostly of girls suffering from retrolental fibroplasia (RLF),<sup>16</sup> an eye disorder found primarily in prematurely born children of low birth weight who had been exposed postnatally to high concentrations of supplementary oxygen.<sup>8, 9, 14, 23</sup> Many of these subjects were born in 1952 or 1953, when RLF reached its peak incidence;<sup>24</sup> thus, they had not yet attained menarche at the time of our preliminary investigation. If the mean age at menarche had at that time been calculated for those girls who *had* experienced menarche, the result would have been biased in favor of a falsely lower mean menarcheal age. In order to give a realistic representation of menarche among our blind and nonblind subjects, we examined our data by means of a life-table analysis.

We observed that blindness was associated with precocious menarche and that the magnitude of this effect appeared to be proportional to the degree of loss of light perception. Girls whose blindness was compounded

by a total absence of light perception underwent menarche earlier than blind girls in whom some light perception was preserved and much earlier than girls with normal vision.<sup>25</sup>

All of the blind and nonblind girls included in our original population have by now attained menarche. Hence, we are able to determine the mean age at menarche and to estimate its variance for the blind and nonblind groups. In confirmation of our previous findings, the present report shows that the absence of the retinal response to light is associated with an acceleration of menarche in proportion to the degree of loss. In blind girls with no light perception, menarche occurred an average of 7 months earlier than in the nonblind controls, while blind girls able to perceive light experienced menarche 4–6 months earlier.

#### METHODS

The data for this report were obtained from 960 blind and nonblind girls. There were 557 subjects (58%) who were questioned directly by personal interview or questionnaire; the data for the remaining 403 (42%) were obtained by examination of medical records. The girls were then grouped.

#### *Group I: Prematurely Born Blind*

Of 270 prematurely born girls made blind by RLF\* during the first few months of life,

\* Thirty-six girls were born at the Boston Lying-In Hospital, 17 were in King's RLF series,<sup>7</sup> and 217 were or had been pupils in various resident schools for the blind (Arizona State School for the Deaf and Blind; Arkansas School for the Blind; California School for the Blind; Colorado School for the Deaf and Blind; Diamond Head School, Honolulu; Iowa Braille and Sight-Saving School; Kansas School for the Blind; Nebraska School for the Blind; New York State School for the Blind; Ohio State School for the Blind; Oregon State School for the Blind; Tennessee School for the Blind; and the Virginia State School). Thirty-seven (14%) girls were interviewed personally; data from the remaining 233 were obtained by questionnaire.

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138 had light perception; the remaining 132 had none.

### *Group II: Prematurely Born Nonblind*

One hundred eight prematurely born girls with normal vision\* were studied.

### *Group III: Term Blind*

Of 254 girls born at full term, who were blind at birth or became blind during the first year of life,† 214 had light perception; the remaining 40 had none. All but 9 of the latter group were excluded from the study for reasons given below. Since the remaining sample was inadequate for statistical analysis, only full-term blind girls with light perception were considered in the study.

### *Group IV: Term Nonblind*

A total of 328 girls born at term with normal vision‡ were studied.

Blindness, for the purpose of this study, was defined as visual acuity of 20/200 or less for both eyes. Since term blind as well as prematurely born blind girls were included in the study, it was possible to identify the

\* These were girls with normal vision born at the Boston Lying-In Hospital during the same years as the girls in Group I.

† These girls were or had been pupils in the schools for the blind listed above. The causes of blindness were: absence of macula; aniridia; anophthalmia; aphakia; coloboma of the iris or lens; microcornea; microphthalmos; congenital amblyopia; cataracts; glaucoma; lens dislocation; nystagmus; optic nerve defects; extreme hyperopia, myopia, or strabismus; cortical or optic nerve atrophy; injury to the visual centers (e.g., birth injuries, cerebral palsy, hemorrhage); albinism; choroiditis; chorioretinitis; endophthalmitis; optic neuritis; retinitis pigmentosa; sympathetic ophthalmia; uveitis; malignant tumors; retinoblastoma; VanRecklinghausen's disease; amblyopia exanopsia; macular degeneration; nerve head cyst; phthisis bulbi; retinal detachment; maternal rubella; meningitis; Still's disease; syphilis; toxoplasmosis; tuberculosis of the optic nerve.

‡ At the time of our original study, these girls were students at the schools of nursing of the Massachusetts General Hospital, the Beth Israel Hospital, or the Children's Hospital Medical Center, Boston, or were students at Webster College, St. Louis, Mo.

effects of blindness on sexual development, as distinguished from possible effects of premature birth or the excessive use of oxygen therapy.

To avoid the possibility that the process which caused the blindness might also have influenced sexual maturation by a mechanism unrelated to the visual defect, we retained in the study only those blind girls whose cause of blindness was known and whose pathology was believed to be limited to the orbit and unrelated to central nervous system or neuroendocrine disorders. Furthermore, any blind or nonblind girls found to have any of the disorders listed below\* were excluded from the study. No girl younger than 110 months of age was admitted to the study; all subjects were born between 1938 and 1954 (Table 1).

Of the 960 girls concerning whom data were obtained, 600 (62.5%) were retained in the study; 313 (32.5%) did not meet our stated criteria and were excluded. Contact could not be maintained with 47 of the group which had not yet attained menarche at the time of our original report. The number of girls excluded or lost from each group is shown in Table 1.

In the questionnaires, in our personal interviews, and in our instructions to cooperating schools, we requested that, if the exact age at menarche could not be given, the inexactness should be indicated (e.g., by stating "almost 12," "just 13," "almost 12½"). Approximately 60% of the respondents in each group gave the age at menarche to the nearest month, or even more precisely. In the remaining 40%, when menarcheal age

\* Nonorbital or multiple developmental abnormalities, blindness of a heredity or familial nature, albinism, neurologic disorders, deafness, migraine, neonatal trauma or hemorrhage, neoplasms, toxoplasmosis, chorioretinitis of unknown etiology, orbital infection, subnormal intelligence, emotional problems which required hospitalization, and specific medical entities such as tuberculosis, rheumatic fever, diabetes, and the Stein-Leventhal syndrome.

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TABLE 1. DISTRIBUTION OF SUBJECTS IN BLIND AND NONBLIND GROUPS

Group	Total in study	Excluded		Lost		Included		Year of birth
		No.	%	No.	%	No.	%	
I (premature, blind)	270	45	17	33	12	192	71	1938-1949
II (premature, nonblind)	108	10	9	0		98	91	1938-1949
III (term, blind)	254	165	65	14	5.5	75	30	1938-1954
IV (term, nonblind)	328	93	28	0		235	72	1940-1946

was given in years only, 6 months were added in each instance in an effort to distribute the possible error (i.e., "12 years" was taken to be 150 months).<sup>11</sup>

Data were analyzed statistically for means and standard errors.

RESULTS

In confirmation of our previous observations,<sup>25</sup> blindness was found to be associated with an acceleration of menarche (Table 2). Prematurely born girls made blind by RLF (Group I) and unable to perceive light experienced menarche 7 months earlier than the prematurely born girls with normal vision in Group II ( $p < 0.01$ ). Those in Group I with some light perception experienced menarche at an intermediate age, which was also significantly lower than that of girls with normal vision ( $p < 0.01$ ). In the group of

blind girls born at term (Group III), it was not possible to relate the presence or absence of light perception to age at menarche, because the sample of girls without light perception was too small to permit statistical analysis. However, those with light perception first experienced vaginal bleeding 4 months earlier than term normal subjects ( $p < 0.05$ ). Prematurity in the absence of blindness had no effect on age at menarche; both premature and full-term girls with normal vision underwent menarche at a mean age of 150 months.

DISCUSSION

The data presented in this report indicate that the neuroendocrine mechanisms responsible for sexual maturation in humans, like those which operate in polyestrous rodents, are dependent upon perceived environmental lighting. The effect of photic deprivation upon humans appears to be the opposite of that seen in rats: Blind rats undergo spontaneous vaginal opening later than normal animals,<sup>4, 5, 18</sup> while blind humans experience their first episode of vaginal bleeding earlier. This difference may be related to the fact that the rat is a nocturnal animal, while the human is active diurnally: Previous studies on other neuroendocrine responses to light (i.e., the effect of light on the synthesis of pineal hormones) have suggested that there is a fundamental difference in the way nocturnal and diurnal species utilize their photic input.<sup>1, 2, 18, 20</sup>

The neuroendocrine pathways which mediate the effects of blindness upon human sexual development are not known. In the

TABLE 2. EFFECTS OF BLINDNESS ON AGE AT MENARCHE

Group*	No.	Mean age (months)	S.D.	S.E.
IA (premature, blind)	85	143.0	14.5	1.6†
IB (premature, blind)	107	144.0	14.3	1.4†
II (premature, nonblind)	98	150.8	16.1	1.6
III (term, blind)	68‡	146.0	14.6	1.9§
IV (term, nonblind)	235	150.5	10.2	0.7

\* Girls in Group IA had no light perception; those in Group IB had some light perception.

† Differs from Group II,  $p < 0.01$ .

‡ The 9 subjects without light perception were not included in the study.

§ Differs from Group IV,  $p < 0.01$ .

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rat the photoreceptor which converts environmental lighting into biologic signals resides within the retina.<sup>13, 18, 21, 22</sup> Light, or its absence, generates nerve impulses which are carried to the brain along the optic nerves. Just beyond the optic chiasm, that portion of the photic input which is destined to influence gonadal (and pineal) function leaves the main optic tract to travel with the inferior accessory optic tract.<sup>13</sup> This tract, which terminates at the junction of the hypothalamus and the mesencephalon, runs within the medial forebrain bundle and thus is able to provide signals both to the neurons in the medial hypothalamus which control pituitary function and to the central adrenergic areas which regulate synthesis of pineal hormones. The effects of light deprivation on the human ovary might be mediated by the hypothalamo-hypophyseal system, the organ, or both.

The fact that menarche occurs prematurely in blind women does not in itself indicate that the time of the first ovulation is also accelerated or that the mechanism responsible for cyclic ovulation is in any way abnormal. Our data do suggest, however, that studies designed to examine reproductive function in blind women might uncover useful information. The role of light in the mechanism which generates cyclic ovulation in humans also remains to be established. In the rat, ovulation occurs once every 4 or 5 days. The time of day that this event takes place appears to be regulated by the environmental lighting cycle: Ovulation usually occurs 3 or 4 hr. after the onset of darkness.<sup>6</sup> If the daily light-dark cycle is shifted by 12 hr., a corresponding shift soon occurs in the hour of spontaneous ovulation. Daily rhythms in body temperature, urinary norepinephrine concentration, the rate of cortisol secretion, and a large number of other phenomena in humans are produced, or at least synchronized, by the light-dark cycle.<sup>12, 18</sup> Although ovulation in humans may also occur at a characteristic light-dependent time of day,

it has not yet been possible to obtain evidence for this relationship, partly because of the absence of a simple, reliable indicator of human ovulation.

Thomas and Pizzarello<sup>17</sup> compared 22 blind subjects (whose causes of blindness were not given) resident in one institution with 69 nonblind girls (also of undescribed diagnoses) who resided in a different institution. These authors found no difference between the mean ages of menarche of the two groups. We are unable to interpret this result, since their report did not note how many of the blind subjects suffered from diseases (e.g., congenital syphilis, anencephaly, toxoplasmosis) which not only cause blindness but might also affect the neuroendocrine axis. They also failed to specify the degree of blindness among their subjects and gave no explanation of why the nonblind subjects were institutionalized.

### SUMMARY

Information about age at menarche was obtained from 524 blind and 436 nonblind girls; 557 subjects were questioned directly by interview or questionnaire, and the data for the remaining 403 were obtained by examination of medical records. Any blind girl whose blindness could not be attributed solely to known orbital pathology was excluded from the study, as were blind and nonblind girls with systemic diseases. The age at menarche of the 270 blind girls suffering from retrolental fibroplasia (RLF) was compared with that of 108 girls with normal vision born prematurely at the same hospital and during the same years. The age at menarche of the remaining 254 blind girls (born at term) was compared with that of 328 subjects with normal vision born at term.

Blindness was found to be associated with an acceleration of menarche. This effect was unrelated to the cause of blindness but may be related to the extent of loss of light perception. Girls with normal vision underwent menarche at a mean age of 150 months,

whether they were born at term or prematurely. Prematurely born blind girls lacking light perception experienced their first episode of vaginal bleeding 7 months earlier ( $p < 0.01$ ); those with RLF who had some light perception underwent menarche 6 months earlier than normal girls ( $p < 0.01$ ). Blind girls with some light perception who were born at term experienced menarche 4 months earlier than normal girls ( $p < 0.05$ ). These data indicate that the maturation of the human neuroendocrine axis, like that of other polyestrous mammals, is influenced by environmental lighting.

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