

Holoprosencephaly: A Mythologic and Teratologic Distillate

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This review of holoprosencephaly provides a mythologic and teratologic distillate of the subject under the following headings: Babylonian tablets; Greek mythology; pictures from the 16th through the 20th Centuries; 19th Century teratology; history of more modern concepts and their terminologies; and ocean-going ships named "Cyclops." © 2010 Wiley-Liss, Inc.

KEY WORDS: teratology; Babylonian tablets; Arimaspi; Greek mythology; Polyphemus; cyclopia; proboscis; cyclocephalians; otocephalians; ethmocephalus; cebocephalus; edocephalus (penis head); cyclopic animals; arhinencephaly; holotelencephaly; USS Cyclops

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INTRODUCTION

The history of teratology through the centuries is rich in texts, documents, tables, diagrams, drawings, engravings, art forms, and pictures. Here, only a distillate of topics dealing with holoprosencephaly can be discussed. I have written about holoprosencephaly *in extenso* elsewhere [Cohen and Gorlin, 1969; Cohen et al., 1971; Cohen, 1989a,b, 2003, 2006, 2009a,b; Cohen and Sulik, 1992; Cohen and Shiota, 2002]. A monograph on holoprosencephaly is also available [Siebert et al., 1990].

Most of the mythology of holoprosencephaly centers on cyclopia. Ideas about one-eyed people have been found in many lands throughout the ages.

Although many of these myths are quite fanciful, it seems reasonable to assume that observation of cyclopic infants and perhaps cyclopic animals may have left vivid impressions that underwent mythical transformation [Cohen and Sulik, 1992].

BABYLONIAN TABLETS

Babylonian tablets housed in the British museum relate a story about a one-eyed monster who would bring calamity to the country. The Arimaspi were said to be a one-eyed people who lived in the Altai mountains of northeast Scythia. They were known to be rich in gold that they stole from the griffins—fantastic

beasts with the heads and wings of eagles and the bodies of lions. The story of the Arimaspi is also found in writings of Heroditus, Pliny, St. Augustine, and was also known to poets from Aeschylus to Milton [Ballantyne, 1904; Esser, 1927; Warkany, 1971].

GREEK MYTHOLOGY

Homer's *Odyssey* narrates the lifestyle and behavior of the Cyclopes, who were normal in size except for Polyphemus, who was a giant dwelling in a separate cave from the other Cyclopes [Bazopoulou-Krykanidou, 2005]. The occasional newborn of a diabetic mother can have both cyclopia and macrosomia—conditions that may have served as the basis for the mythical cyclopean giant Polyphemus [Cohen and Sulik, 1992].

PICTURES FROM THE 16th THROUGH THE 20th CENTURIES

Figure 1 shows an old demon mask from Sri Lanka with single, centrally located eye. In Reisch's *Margarita Philosophica* of 1508, five malformed figures are presented; the second figure from the left pictures a woman with a cyclopic eye and a normal nose below it instead of a proboscis above it [Reisch, 1508] (Fig. 2).

This publication "Holoprosencephaly: A Mythologic and Teratologic Distillate" has been written in honor of Erich Roesler, M.D., Ph.D. for his molecular publications on holoprosencephaly and in honor of Ute Moog, M.D., Ph.D. for her publications on genetic disorders with mental retardation.

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Figure 1. Old demon mask with a single centrally located eye from Sri Lanka. From Cohen and Sulik [1992].

A more accurate rendition of cyclopia is found in Licetus's *De Monstrorum Natura, Caussis, et Differentiis*, published in 1634 (Fig. 3). A single median eye is shown with a proboscis, which Licetus compared with a penis, located above the eye. Occipital defects include an eye in the back of the head, surely based on the imagination, and a scalp defect, possibly like those in trisomy 13 [Siebert et al., 1990; Cohen and Sulik, 1992].

In the *Records of the Colony and Plantation of New Haven from 1638 to 1648*, a cyclopic pig—not rare in the species (Fig. 4)—was born in 1641. It was described as having “but one eye in the middle of the face” Above the eye

In the Records of the Colony and Plantation of New Haven from 1638 to 1648, a cyclopic pig—not rare in the species—



Figure 2. Cyclopic woman (second malformed figure from the left) with a normal appearing nose. From Reisch's *Margarita Philosophica*, 1508. Appeared in Cohen and Sulik [1992].



Figure 3. Three views of a cyclopic infant from Licetus's *De Monstrorum Caussis*, 1634. Appeared in Cohen and Sulik [1992].

was born in 1641. It was described as having “but one eye in the middle of the face”

“a thing of flesh grew forth and hung downe . . . like a mans instrum” of “gen’ation.” The cyclopic pig was thought to have arisen from interspecies fertility. This resulted in the trial and execution of George Spencer, a one-eyed servant with a cataract in his bad eye, who was convicted of an “unnatureall spell and abominable filthynes” [Warkany, 1971].

Smiling Cyclops from 1883 and *Cyclops* from 1914, both by Redon, are shown in Figure 5. *The Difficult Crossing*, a fascinating oil painting by René Magritte in 1963, appears in Figure 6. Amazingly, the entire head is a single eyeglobe.



Figure 4. Cyclopic pig. Engraved by N.F. Regnault in *Morceau de la Sarthe*, 1808. Appeared in Cohen and Sulik [1992].

NINETEENTH CENTURY TERATOLOGY

The 19th Century produced a great many teratological works that contained valuable information about holoprosencephaly. Contributions were made by Etienne Geoffroy Saint-Hilaire and his son Isidore Geoffroy Saint-Hilaire [1832], Vrolik [1834], Hannover [1884], and Taruffi [1891], among others. In the early 20th Century, Ballantyne's *Manual of Antenatal Pathology and Hygiene* (Volume 2, *The Embryo*) appeared in 1904.

In his three volume treatise on anomalies, Isidore Geoffroy Saint-Hilaire [1832] grouped cyclopia with ethmocephalus and cebocephalus, coining the latter two terms. He also coined other terms, such as rhinocephalus to indicate cyclopia with proboscis formation and stomacephalus to indicate cyclopia with a small mandible and an abnormal mouth. His classification of what he called cyclocephalians is

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summarized in Table I. Saint-Hilaire also classified what he called the otocephalians (Table II). In this classification he retained the term sphenoccephalus used by his father Etienne Geoffroy Saint-Hilaire. In Isidore Geoffroy's classification he also used the term edocephalus,



Figure 5. Two artistic renditions of a Cyclops by Odilon Redon. **Left:** Smiling Cyclops, 1883. Museum of Fine Arts, Boston. Appeared in Cohen and Sulik [1992]. **Right:** The Cyclops, 1914. Oil on Canvas, Museum Kroller-Mueller, Otterlo, The Netherlands.

which means penis head because of the presence of a proboscis accompanying a cyclopic eye [Saint-Hilaire, 1832].

The otocephalian classification of Isidore Geoffroy was criticized by Taruffi [1891] who thought too much attention was paid to the ears, but not enough to the mandible. He made other changes to Saint-Hilaire's classification, coining the term hypoproso-aplasia, which was subdivided into hypomicrognathus (small mandible) and hypoagnathus (absent mandible). He also used cyclops hypoagnathus (cyclops with absent mandible) and aprosopus (absent eyes, nose, and mouth).

The extent to which cyclopia was reported in the 19th Century can be gauged by the 368 tabulated by Hann-

over [1884] and by the 184 tabulated by Taruffi [1891] (Table III).

Dareste [1891] produced cyclopia and other malformations experimentally by using varnished eggs, refrigeration, electricity, magnetism, and various chemicals.

HISTORY OF MORE MODERN CONCEPTS AND THEIR TERMINOLOGIES

Kundrat [1882] coined the term "arhinencephaly," emphasizing absence of the olfactory tracts and bulbs. In 1959, in his monumental work "Pathoarchitectonic Studies of cerebral malformations,"

Yakovlev used the term "holotelencephaly" to emphasize failure of the prosencephalon to be transformed into cerebral hemispheres with separate lateral ventricles [Yakovlev, 1959]. In 1963, DeMyer and Zeman proposed the term "holoprosencephaly" which more accurately describes this malformation sequence.

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They noted that the term "arhinencephaly" placed undue stress on only one of many defects in the condition. Likewise, the term "holotelencephaly" failed to reflect any of the anomalies of diencephalic tectogenesis, such as incomplete "cleavage" of the thalami, colobomas, or "anophthalmia" [Cohen and Sulik, 1992]. DeMyer and Zeman [1963] classified the brain as alobar, semilobar, and lobar types. The alobar type can be further subdivided into the pancake, cup, or ball types, depending on the degree to which the dorsal lip of the holotelencephalon rolls over to cover the membranous ventricular roof [Cohen, 1989b].

Parts of the scheme put forth by DeMyer and Zeman [1963] and by



Figure 6. The Difficult Crossing, a fascinating oil painting by René Magritte, 1963. Appeared in Cohen and Sulik [1992].

TABLE I. Isidore Geoffroy Saint-Hilaire's Cyclocephalians, 1832

Two closely-set orbital fossae	
Ethmocephalus	Two closely-set but distinct eyes, atrophic nasal apparatus, proboscis above the eyes
Cebocephalus	Two closely-set, distinct eyes, atrophic nasal apparatus, absence of a proboscis
Single orbital fossae	
Rhinocephalus	Two fused eyes or one double eye in the midline, atrophic nasal apparatus, proboscis present
Cyclocephalus	Two fused eyes or one double eye, atrophic nasal apparatus, absent proboscis
Stomocephalus	Two fused eyes or one double eye, rudimentary mandible very abnormal or absent mouth

From Siebert et al. [1990].

TABLE II. Isidore Geoffroy Saint-Hilaire's Otocephalians, 1832

Group I	
Sphenocephalus	
Ears approximated or fused in the midline	
Rudimentary mandible	
Distinct mouth	
Two separate eyes	
Group II	
Otocephalus	
Ears approximated or fused in the midline	
Rudimentary mandible	
Mouth present	
Cyclopic eye	
Edocephalus	
Ears approximated or fused in the midline	
Rudimentary mandible	
Absent mouth	
Cyclopic eye	
Nasal proboscis	
Opocephalus	
Ears approximated or fused in the midline	
Rudimentary mandible	
Absent mouth	
Cyclopic eye	
Absent proboscis	
Group III	
Triocephalus	
Ears approximated or fused in the midline	
Rudimentary mandible	
Absent mouth	
Absent eyes	
Absent proboscis	

From Siebert et al. [1990].

DeMyer [1977] have been criticized by several authors [Probst, 1979; Yokota et al., 1984; Leech and Shuman, 1986]. Leech and Shuman [1986] proposed a model for midline cerebral dysgenesis that included holoprosencephaly, aprosencephaly, commissural plate agenesis, septo-optic dysplasia,¹ agenesis of the

¹Although septo-optic dysplasia is not a true dysplasia, the condition is so well-known by this term that I have elected to continue its use in this article.

TABLE III. Reported Cases of Cyclopia in the Nineteenth Century

	Hannover [1884]	Taruffi [1891]
Humans	103	61
Calves	30	10
Lambs	51	28
Pigs	130	47
Puppies	22	11
Kittens	12	7
Foals	10	12
Kids	9	7
Rabbits	3	—
Deer	1	—
Asses	—	1
Total	368	184

From Cohen and Sulik [1992].

septum pellucidum, and agenesis of the corpus callosum. Probst [1979] divided the holoprosencephalic spectrum differently, using the dorsal sac to define the most severe malformation. Since the dorsal sac is found in both alobar and semilobar types, Probst's categories overlap with those of DeMyer and Zeman [1963]. Their classifications are compared in Table IV, and the reader is referred to the major work of Probst for more detailed discussion. Yokota et al. [1984] indicated that not all dorsal cyst malformations represent holoprosencephaly and advocated a new system of



Figure 7. USS Cyclops (1910–1918) anchored in the Hudson River on October 3, 1911. U.S. Navy Photo. General characteristics: Class and type: Proteus-class collier; displacement: 19,360 tons full; length: 542 ft; beam: 65 ft; draft: 27 ft 8 in; speed: 15 knots (17 mph); complement: 236 officers and enlisted; Armament: 4 × 4 in guns. The USS Cyclops was lost at sea in the “Bermuda Triangle” in 1918 with all 306 crew and passengers without a trace. Courtesy of the US Navy.

classification: prosencephalic, interhemispheric, and porencephalic types of dorsal cyst malformations.

OCEAN-GOING SHIPS NAMED “CYCLOPS”

Four English ships were named HMS Cyclops and two American ships were named USS Cyclops [Cohen, 2009b]. The most bizarre incident involved a collier type ship, which carried bulk coal for use in coal-fired warships in the early part of the 20th Century. The “USS Cyclops” (Fig. 7) was launched in 1910,

TABLE IV. Comparative Classifications of Holoprosencephaly*

DeMyer and Zeman [1963]	Probst [1979]
Alobar, with sac	1. Dorsal sac A
Alobar, without sac	2. Intermediate A
Semilobar, with sac	3. Dorsal sac B
	4. Dorsal sac C
Semilobar, without sac	5. Intermediate B
	6. Intermediate C
Lobar	7. Pseudohemispheric

*Numerical designations indicate progression toward “more normal development” in each classification. Because the classifications are not in complete agreement, the DeMyer and Zeman [1963] classification is sequential and although the Probst [1979] classification is nonsequential, it does match the equivalent category of DeMyer and Zeman [1963]. From Cohen [1989b].

was commissioned into World War I in 1917, and disappeared in the “Bermuda Triangle” in 1918 with all 306 crew and passengers without a trace. The disappearance of the “USS Cyclops” is likely the most investigated case by the US Navy, taking about 10 years. The ship still remains the largest Navy ship to be lost at sea without leaving the slightest clue about its disappearance and the number of deaths remains the largest number of men lost at sea except in areas of combat [Cohen, 2009b].

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