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Historical Review

Human Anotocephaly (Aprosopus, Acrania-Synotia) in the Vilnius Anatomical Collection

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A genetic theory of "multifactorial" malformations, i.e., anomalies of blastogenesis or organogenesis, involving polygenic predisposition with morphogenetic threshold effect, was developed by Sewall Wright in the 1920s and remains an essential basis of birth defects biology. Because of the phenomenon of *universality*, i.e., the deployment of identical inductive, or pattern-forming, upstream molecular mechanisms during the earliest stages of mammalian morphogenesis, Wright's work on guinea pig otocephaly is highly pertinent to "corresponding," i.e., homologous malformations in humans. This concept is illustrated on the hand of a human fetus in the Vilnius (Lithuania) Pathological Museum with anotocephaly, i.e., anencephaly and otocephaly so severe as to correspond to Wright's guinea pig otocephaly grade 11 or 12. The observation also supports our apology for old museums and old books as repositories for anomalies, no less important for their rarity. © 2001 Wiley-Liss, Inc.

KEY WORDS: malformations; otocephaly; anencephaly; Sewall Wright; guinea pigs; genetic predisposition; threshold effect; aprosopus

INTRODUCTION

In 1579, Stephen Batory, King of Poland and Grand Duke of Lithuania, and Valerian Protasewicz, Bishop of Vilnius, founded the University of Vilnius. The medical faculty, however, was not established until November 24, 1781 [Česnys, 1997]. During the initial stages of the *Collegium Medicum*, general pathology was taught together with other medical subjects. As of 1784, a separate course of general pathology was taught by the Viennese Joseph Langmajer of the Department of General Pathology (1784–1803). He taught until 1799, mostly along the lines of Boerhave's pathology; Langmajer was succeeded by August Becu who taught until his death in 1824. In 1803 the school was reorganized into the Vilnius Imperial University with 4 faculties [Kazakevičius, 1999]. Becu's department was one of 7 departments of the Medical Faculty and his course covered classification and natural history of diseases as correlated with age, sex and climate, and causes of disease with emphasis on environmental factors (temperature, humidity, air, food, immobility, insomnia [Kazakevičius, 1979]. After Becu's death general pathology, semiotics and epidemiology were taught by Adolf Abicht who published his lectures (*Praelectionum pathologiae generalis libri duo*, 1831) in 8 volumes covering pathology, causes, pathogenesis, and symptomatology [Kazakevičius, 1981] at the accepted international level reflecting the achievements of medical science of that time.

After the Polish-Lithuanian insurrection of 1830–1831 Tsar Nicholas I closed the University of Vilnius (1832); thereafter the medical faculty reorganized itself into the Medical-Surgical Academy and continued teaching, including pathology [Biziulevičius, 1997].

The beginning of pathology teaching in the old Vilnius University coincided with the founding of an anatomical pathology museum by Jacob Briotet in 1785, the demonstration of macroscopic changes in disease by Adam Belkevičius, the teaching of independent courses in anatomical pathology by Ludwick

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Fig. 1. View of the Vilnius Anatomical Collection. Medical Faculty of Vilnius University, 2000.

Sevrukas in 1835, and nosological pathology by Felix Rimkevičius in 1837. Arriving in Vilnius in 1777, Briotet had worked in Paris with famous anatomists and surgeons and was responsible for many macroscopic preparations that formed the core of the anatomical-pathological collection. Subsequently, Professors Stephen Lauryn Bisio, Joseph Frank, and especially Johannes Lobenwein played a strong role in the development of the museum. In 1812, it experienced a setback when Napoleon's army destroyed many of the preparations and some of the soldiers drank the alcohol in which the specimens were preserved. After 1815, the museum flourished again, enhanced, in part, by purchases from abroad and gifts from the Vilnius Medical Society [Biziulevičius, 1997]. After the closure of the Vilnius Medical-Surgical Academy in 1842 the greater part of the exhibits and other treasures of the museum were moved to Kiev.

After a 79-year hiatus (1842–1921) it was reestablished as the Stephen Bathory University (in honor of its founder) by Poland; however, during these inter-war years it did not serve the cultural needs of Lithuania. Nevertheless, the medical faculty was an important scientific institution that contributed greatly to public health and hygiene in the city and all of southeast Lithuania. A Department of General Pathology was founded in 1922 directed initially by Stanislav Tszebinski, from 1926 by Stanislav Sziling-Siengalevicz, and from 1930 by the distinguished Kazimierz Pelczar who was killed by the Nazi Germans in 1943 [Kutorga et al., 1981]. The Department was active in teaching, encouraged research in pathology, and re-established a museum incorporating, in part, the teratological and anatomical preparations of the Vilnius Medical Society [Siudikas et al., 1980]. More recently, pathology in the Medical Faculty of Vilnius is taught in two courses; the museum and its specimens have been renovated and restored and contain about 900 specimens (Fig. 1).

CLINICAL REPORT

Specimen 516 (part of the original Vilnius Anatomical Collection) (Fig. 2A,B) is a fetus that was initially fixed in 70% ethanol and later in 4% formaldehyde. We assume that this specimen was obtained during the time of Stephen Bathory University (1922–1939). Thus, we estimate the fetus is about 60–70 years old. No history or medical records on this fetus are preserved. It was also not possible to remove the fetus from its container to do further anatomical studies or to obtain radiographic images.

Grossly, this near-term male fetus manifested two major, clearly contiguous malformations, the first being meroacrania (anencephaly), which Van Allen postulated to result from failure of closure site 2 of the neural tube [Van Allen, 1996]. The fetus also lacked eyes, nose and mouth, instead had synotia (otocephaly), the 2 auricles being fused anteriorly in the midline and apparently replacing maxilla and mandible. The neck was thick, but apparently of normal length. There are 5

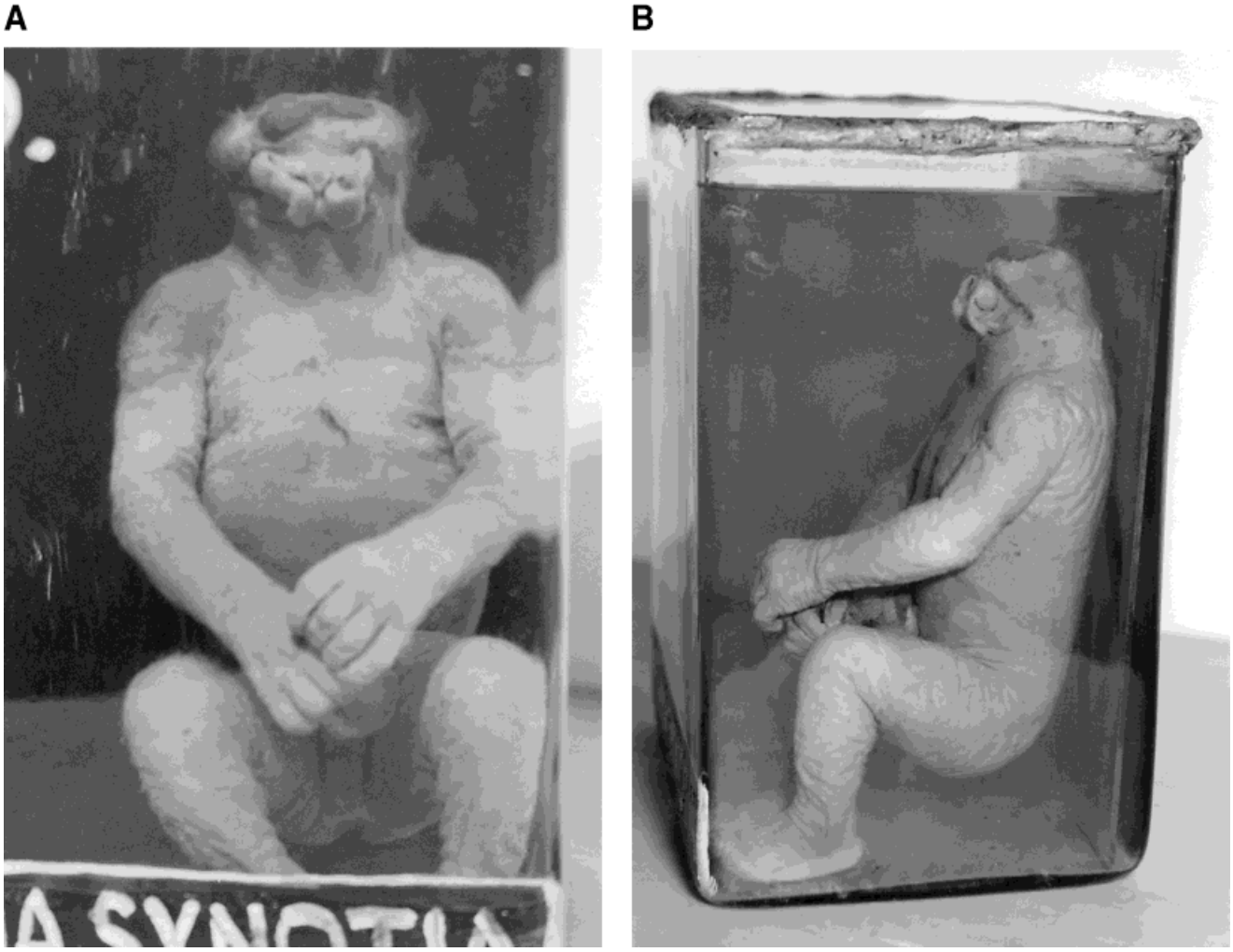

Fig. 2. **A:** Frontal view of the fetus, showing acrania and synotia; **B:** lateral view of the fetus.

digits on each limb, back is unremarkable, nipples appear somewhat low set, and no other gross malformations or deformities are evident.

DISCUSSION

Why should old museums and old books be of interest to the modern scientist? We think some anomalies are so rare that only one or a few specimens have been adequately described [Beckwith, 1998]. In this respect, Europe is far more fortunate and more enlightened than the United States in its several magnificent anatomical collections (e.g., Vienna, [E. Hausner, personal publication, 1998] Amsterdam, [Baljet and Oostra, 1998], Vilnius or the Virchow Museum of Berlin (what is left of it) [Krietsch and Dietel, 1996] to which spatial and financial resources are allocated presently unimaginable in North America.

A careful perusal of the classic morphology resources available to us shows only few examples of anotocephaly. *Planche VII* (Plate 7) of Isidore Geoffroy St.-Hilaire's epochal "*...Traité de Tératologie*" (1837) illustrates a "*chat opocéphale*", i.e., a cat with apparently normal neck, synotia with an apparent midline eye as the only other head rudiment, and a "*chien triocéphale*", i.e., a dog without a neck, a separation of a few centimeters between the ears, and only a small round mass to indicate a cranial rudiment.

According to Taruffi [1891] "Stefano" (he meant Etienne) Geoffroy St-Hilaire, in a discussion of this anomaly, coined the term *triencéphale* to refer to a head with the *tri*ple deficiency of oral, nasal and visual structures. A later writer, however, thought the term might suggest the presence of three brains when, in fact, only one was present; therefore he (Dugès) introduced the term *aprosopus*. Notwithstanding, when Etienne's son Isidore wrote his magisterial text on malformations (in which he coined the term teratology) he remained loyal to his father's legacy amending only slightly in preference for the term *triocephaly*, considered *poco felice* by Taruffi (lacking in felicity). In his detailed review of the subject to date Taruffi [1891] lists

Fig. 3. Wright's otocephalic guinea pigs. **Top:** A normal guinea pig and an otocephalic guinea pig from strain 2. All others with increasing grades of this malformation. Reproduced with the gracious permission of Wiley-Liss Inc. publisher of *The American Journal of Medical Genetics* where this figure was reproduced [Wright, 1984].

only seven well-documented human cases beginning with that of Vicq d'Azyr (physician of Queen Marie Antoinette) of 1776, and including that of Pokorny of 1863 (Fig. 4). He cites 76 observations in animals beginning with De Graaf [1672] of a dog and including 27 goats, 17 dogs, 12 piglets, 11 cats, and 5 calves. Taruffi was unable to refer to a first-hand copy of Regnault's *Les écarts de la nature* [1775], but quotes Gurlt's text of 1832. Plate 12 of Regnault [1775] (Fig. 5A) portrays an aprosopus dog, Plate 22 (Fig. 5B) an aprosopus pig, and Plate 28 (Fig. 5C) a cyclopic dog similar to that quoted by I. Geoffroy St-Hilaire as *chien triocéphale*. By far the most spectacular animal example of this malformation was noted and illustrated by Gurlt [1877] on his Plate XVII, Figures 106–110 (Fig. 6). It shows two pig fetuses conjoint in a frontal plane but with the "facial" aspect laterally, at 90° to the fontal plane showing identical bilaterally symmetrical aprosopus faces. This anomaly was designated "octopus janus aprosopus" and documents in a particularly

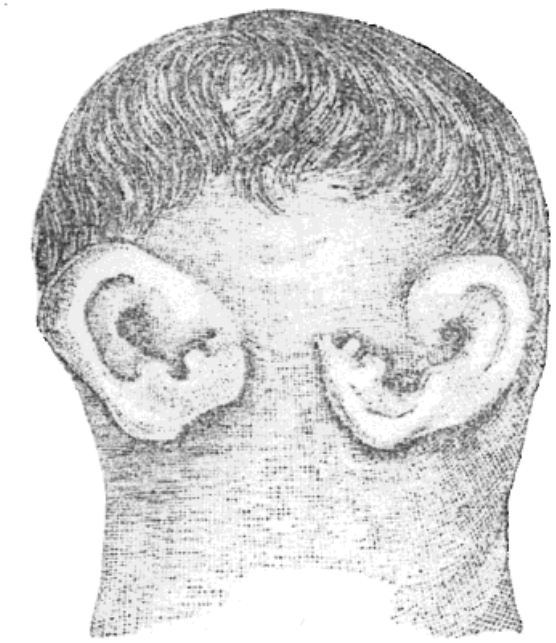

Fig. 4. Human "aprosopus" of Pokorny, illustrated by Taruffi [1891].

impressive manner how anomalies of earliest blastogenesis (i.e., conjoint twinning) may be associated with other grave defects of blastogenesis.

Another such combination of defects of blastogenesis (acrania, cyclopia and agnathia) in humans was illustrated in Förster's [1861] compendium of human malformations in Plate XIII, Fig. 23; this fetus was first observed and illustrated by Vrolik [1849] Plate XXVI (Fig. 7) and also had a large abdominal wall defect with ectopia of stomach, spleen, liver and gut with a severe torsion of the lower vertebral column and rotation of the lower body.

The very rare concurrence of otocephaly and cyclopia in humans is illustrated by Marx [1911] in Schwalbe's *Morphologie der Missbildungen des Menschen und der Tiere* (q.v. Fig. 387, p. 615). Thus, this combination of contiguous malformations can be a single (polytopic) field complex on the basis of: 1) occurrence in different animals (mice, rabbits, guinea pigs, dogs, pigs, cats, calves, goats, etc.), and 2) causal heterogeneity ("multifactorial" trait in guinea pigs, teratogenically produced by X-irradiation in mice, and by streptonigrin in rats) [Warkany, 1971]. Otocyclopia in humans was also published by Mollica et al. [1979] and Gaba et al. [1982]. Thus, in humans the combination of apparent anencephaly and otocephaly remains a rare anomaly.

In guinea pigs, however, this anomaly was studied systematically by Sewall Wright in the 1920s and 1930s [Wright and Eaton, 1923; Wright and Wagner, 1934; Wright, 1934, 1960] and reviewed in 1984 [Wright, 1984] when he was in his 95th year of life. He uses I. Geoffroy St-Hilaire's term otocephaly, and notes that all except for the least severely affected were born dead. He ordered degrees of severity in 12 grades based on external appearance (Fig. 3). The only defect notable in grade 1 is shortness of the mandible with only one or no lower incisors. In grade 2 the animals lacked a lower jaw. The ears were separated on the throat by hairy skin. In grade 3 they were separated slightly by bare skin. Grade 4, with only a single ear opening, was much the most numerous. Grade 5 showed, in addition, defects of the upper jaw. Grade 6 was characterized by a single nostril and in grade 7 the eyes were united below a proboscis (synotoprosencephaly). In grade 8 there was a single cyclopean eye below the proboscis, and those of grade 9 had no nasal proboscis. Animals of grade 10 lacked the eye. The ear opening on the throat was lost in grade 11. There was only a small median ear in grade 12. The forebrain became a single ventricle in all animals of grade 6 and the brain became reduced progressively in the "higher" grades until nothing was left but medulla in grades 11 and 12 (q.v., the brain anatomy in the conjoint piglets of Gurlt [1877] (Fig. 6).

In our "patient" it is difficult to determine whether there was an external auditory meatus or not; however, it is probably safe to say that the condition in this fetus is so severe as to constitute the equivalent of either grade 11 or 12 of Wright's otocephalic guinea pigs.

Occurrence of affected animals with normal sibs and parents in Wright's data suggested segregation of an autosomal recessive lethal. The genealogical data, however, clearly dispelled this notion. The animals were maintained in a strict brother-sister (or in one case parent-offspring) mating. In 14 strains no otocephalics occurred in over 24,000 recorded young; eight produced 19 in about 25,000 offspring (0.08%), 32 produced nine in 2,700 (0.33%), and strain 13, on the whole the most vigorous, produced 50 in about 3,500 young (1.54%). Six large branches, all tracing to one mating in the 7th generation, produced otocephalics in frequencies ranging from 0.7–2.3% (average 1.3%) indicating that the founding mating of this branch had acquired a genetic constitution "much more conducive to this type of abnormal development than the founding mating of the strain as a whole" [Wright, 1984]. A mating (13-13-1) in the 13th generation initiated a branch (soon the entire strain, maintained for some 30 years) in which otocephaly occurred with a constant frequency of 5.5%, indicating that the pertinent gene(s) had become homoallelic in the founding mating, 13-13-1, and had persisted as such (to generation 38). *The phenotypically normal and abnormal animals were of the same genotype*. Analysis of outcome of matings producing litters with affected pups demonstrated convincingly to Wright that individual embryos were determined as affected or not, "almost wholly independently, as accidents of implantation or establishment of good nutrition, or developmental accidents in general." Wright concluded that otocephaly was almost a pure threshold phenomenon based on accidental causes.

In the descendants of mating 13-19-1, however, six generations after fixation occurred in mating 13-13-1,

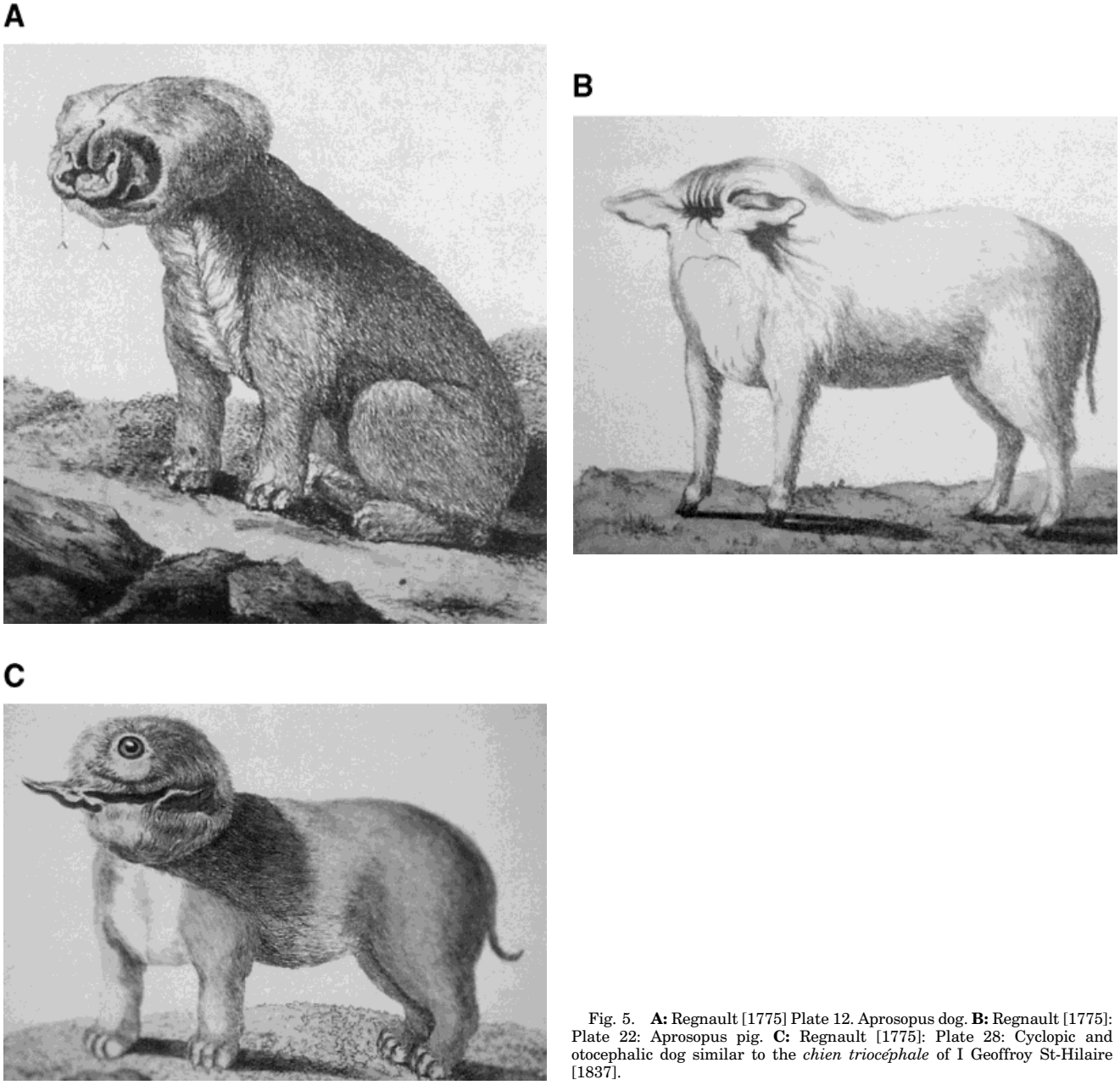

Fig. 5. **A:** Regnault [1775] Plate 12. Aprosopus dog. **B:** Regnault [1775]: Plate 22: Aprosopus pig. **C:** Regnault [1775]: Plate 28: Cyclopic and otocephalic dog similar to the *chien triocéphale* of I Geoffroy St-Hilaire [1837].

the situation was quite different. Mating 13-19-1 itself produced 2 affected among 10 and purebred descendants produced 212 otocephalics in 1168 young (18.2%) over 15 years; omitting some who relapsed to lower frequencies, the descendants of 13-19-1 produced about 28% affected otocephalics. Wright thought the simplest hypothesis was that a mutation had occurred in the homoallelic line that increased the probability of becoming otocephalic to about 0.20, but to 1.00 (always lethal) when homozygous. He thought a hypothesis of environmental causation in his guinea pigs could be dismissed because the factors that precipitated otocephaly were not, to any appreciable extent, common to littermates, and because the results of differential matings contradicted predicted outcomes. Unfortunately, these guinea pig strains to which Wright devoted so much effort and were last kept at the University of Chicago are now extinct; so it will be impossible to check on the developmental fate of homozygous embryos or to repeat any of Wright's work,

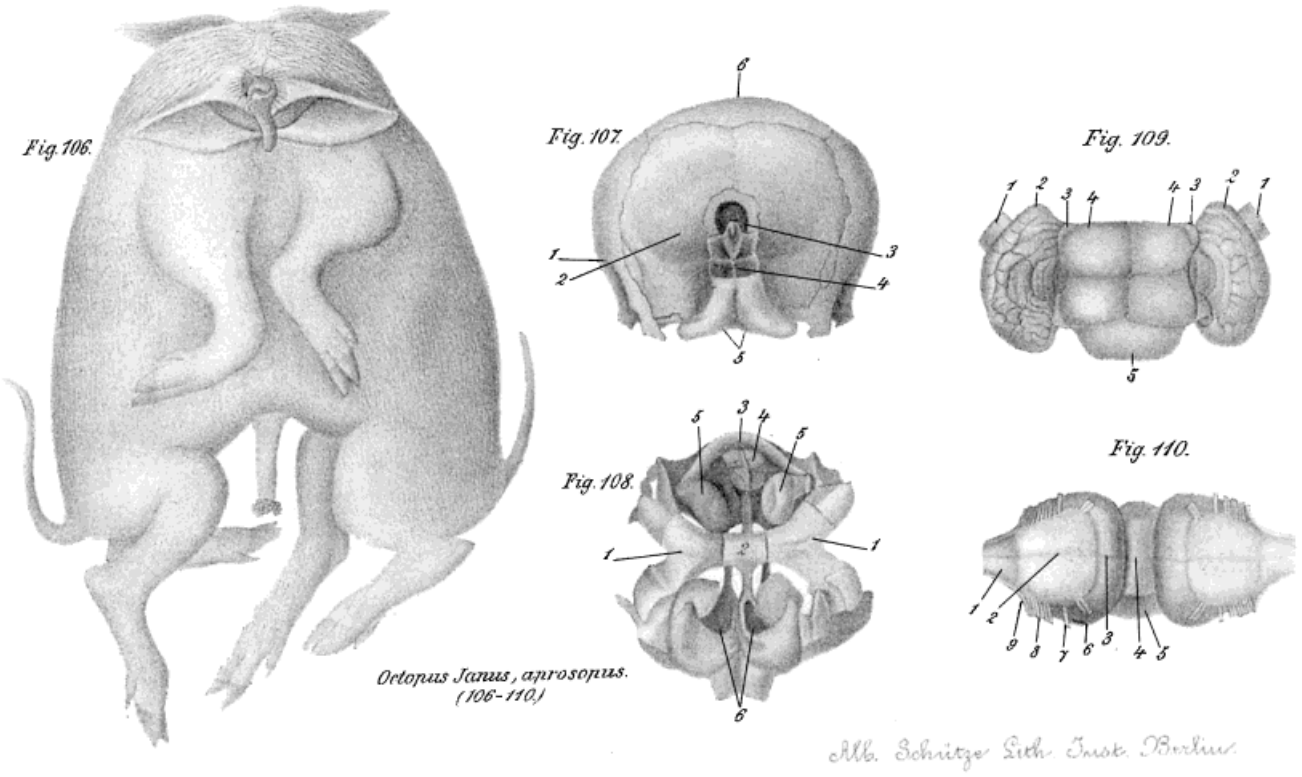

Fig. 6 . Gurlt's [1877] illustration of aprosopus conjoint pigs. Translation of legend: 106. Octopus janus aprosopus, piglet with 8 legs without face, ventral view. Half natural size. 107. Skull of this malformed piglet, in the same position as the head in Fig. 106. Natural size. 1. Occipital bone. 2. Parietal bone. 3. Rudiment of the frontal bone with a small orbital cavity. 4. The two external auditory canals. 5. The fused tympanic bones. 6. Single parietal bone of the posterior part of the head. 108. The same skull, ventral view. Natural size. 1,1: The two occipital bones. 2. Sphenoid bone (Keilbein). 3. Fused tympanic bones. 5.5 Petrous bones (ridges) of the temporal bone. 6. Separate tympanic cavities. 109. The double brain of the piglet(s), seen from above. Natural size. 1.1 The spinal cords. 2.2. The cerebella. 3.3 Posterior, 4.4 anterior pairs of the corpora quadrigemina 5. Fused optic nerve eminences. 110. The same brain; ventral view. 1. Spinal cord. 2. Elongated spinal base (medulla) 3. Hirnknoten. 4. Fused Hirnschenkel of both brains. Fused optic nerve eminence. 6. VII and VIII cranial nerves. 7. IX. 8 X, 9 XI cranial nerves.

this time with the molecular aspects of craniofacial development dominating the research agenda.

COLOPHON

In humans, otocephaly is a rare anomaly and anotocephaly (aprosopus) virtually unprecedented. When in 1979, John M. Opitz was leaving the University of Wisconsin, Sewall Wright, who had been a gracious, extraordinarily helpful, and collegial but quiet coworker in the Department of Medical Genetics for many years after his retirement from the University of Chicago, came to his going-away party. There he was able to see for the first time in his long life a human infant stillborn with otocephaly at an affiliated teaching hospital in Madison. He concurred that the recurrence risk for the parents of this infant probably was negligibly low (probably true also in the case of our Lithuanian fetus) and marveled at the close anatomical correspondence to the anomaly of the animals he had begun to study over a half century earlier. He would have been equally astonished at the close correspondence between the present fetus and his grade 11 or 12 guinea pigs, in modern terms a wonderful confirmation of the concepts of universality and phylogeneity [Opitz and Rauch, 1999].

Wright is far better known, however, for his massive seminal and original contributions to evolutionary theory finally distilled in book form beginning at age 70, the fourth volume appearing when he was 88 years old, and then living to see Halley's comet a second time in his life [Gould, 1998]. He wrote his first book at age 7 on the "Wonders of Nature," recounting that "One night when we had company, we had chicken pie. Our aunt Polly cut open the gizzard, and in it we found a lot of grain and some corn." [Provine, 1986].

The present fetus survived the catastrophes of the last 70 years of Eastern/Baltic European history to provide a rare but important insight into human developmental biology validated and made intensely relevant to the evolutionary aspects of all human formation and malformation through the studies of Sewall Wright, a truly great man who was also humble and generous.

Fig. 7. Vrolik's [1899] illustration of multiple defects of blastogenesis including abdominal wall defect, otocephaly and cyclopia with proboscis.

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