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CC/NUMBER 32
AUGUST 8, 1988

Walker B E & Fraser F C. Closure of the secondary palate in three strains of mice. *J. Embryol. Exp. Morphol.* 4:176-89, 1956.
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Previous evidence on the physiology and morphology of palate closure in mammals had been incomplete; this study of normal palate development in three strains of mice attempted to provide a standard for comparison with spontaneous and experimentally induced palate abnormalities. [The *SCI*® indicates that this paper has been cited in over 235 publications.]

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January 27, 1988

Bruce E. Walker was an undergraduate student at McGill University who came to take his PhD with me shortly after Ted Fainstat and I had discovered (more or less by accident) that cortisone, when injected into pregnant mice, could produce cleft palates in the offspring.[1] There were indications of strain differences in the frequency of cleft palate so induced;[2] this was the first example of a drug-induced malformation and of genetic differences in susceptibility to a teratogenic drug. We wondered whether to extend the genetic analysis or to look at what the cortisone was doing to interfere with palate closure. When I suggested to Bruce that he might start by looking at how the palate closes, he asked (quite rightly), "Why should I do that?" I had no better answer than N.J. Berrill's aphorism—"If you sit and look at an embryo long enough, it'll talk to you." So he did, and they did.

There was very little information available about the morphology of palate closure, and Bruce's studies of embryo heads fixed during closure, of histological sections, and in the living embryo provided the first definitive description, in dynamic terms, of palate closure. He identified an intrinsic force in the palatal shelves that causes them to bulge into the space above the tongue, retracting ventrally, until they displace the tongue downwards and meet in the midline to form the roof of the mouth.

When palate closure was divided into seven arbitrary stages to make statistical analysis easier, he noted differences in the age at which closure occurred between different strains, but there was considerable variation in palate stage at a given chronological age, even within litters. This variation was greatly reduced when embryos were classified by their developmental rather than chronological age, using a scoring system based on the external characteristics of the embryo—a "morphological rating." When palate closure was scored against the morphological rating, the strain differences in stage of closure became much more apparent. In a companion paper[3] we showed that cortisone caused cleft palate by delaying shelf movement and that there was more delay in the late-closing and susceptible (A/J) strain than the earlier-closing and resistant (C57BL/6) strain. The correlation between late closure and susceptibility was confirmed in various genotypes by Daphne G. Trasler.[4] From these observations there emerged the idea of a threshold, beyond which delayed shelves could not close and cleft palate would result. They also showed how an embryo's susceptibility to environmental "insults" could be altered by genetic differences in its normal developmental pattern that determined its distance from the threshold. This provided the most extensively defined experimental model for the multifactorial threshold concept as it relates to the common congenital malformations.[5]

Groups around the world are still exploring the many factors involved in palate closure and in susceptibility to cleft palate induced by various teratogens.[6,7] The reason this paper is cited so often is probably because of the morphological-rating concept that, by removing the variation in developmental age between embryos of the same chronological age, revealed otherwise obscured patterns of development.

1. **Fraser F C & Fainstat T D.** Production of congenital defects in the offspring of pregnant mice treated with cortisone. *Pediatrics* 8:527-33, 1951. (Cited 295 times since 1955.)
2. **Fraser F C, Kalter H, Walker B E & Fainstat T D.** The experimental production of cleft palate with cortisone and other hormones. *J. Cell. Comp. Physiol.* 43(Supp.1):237-59, 1954. (Cited 135 times since 1955.)
3. **Walker B E & Fraser F C.** The embryology of cortisone-induced cleft palate. *J. Embryol. Exp. Morphol.* 5:201-9, 1957. (Cited 145 times.)
4. **Trasler D G.** Strain differences in susceptibility to teratogenesis. (Wilson J G & Warkany J, eds.) *Teratology.* Chicago, IL: University of Chicago Press, 1965. p. 38-55.
5. **Fraser F C.** Evolution of a palatable multifactorial threshold model. *Amer. J. Hum. Genet.* 32:796-813, 1980.
6. **Pratt R M & Christiansen R L,** eds. *Current research trends in prenatal craniofacial development.* New York: Elsevier/North Holland, 1980. 456 p.
7. **Vekemans M J J & Biddle F G.** Genetics of palate development. *Curr. Top. Develop. Biol.* 19:165-92, 1984.

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