Rakic P. Prenatal genesis of connections subserving ocular dominance in the rhesus monkey. *Nature* 261:467-71, 1976; and, **Rakic P.** Prenatal development of the visual system in rhesus monkey. *Phil. Trans. Roy. Soc. London B* 278:245-60, 1977.
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These papers contain the first evidence that connections carrying input from the two eyes to the fetal brain overlap before sorting out into separate neuronal territories. This finding suggested that development of some neuronal connections proceeds from a diffuse to a segregated stage, and the role of competitive elimination in the genesis of the binocular system begins before visual experience. [The *SCI*® indicates that these papers have been cited in more than 315 and 240 publications, respectively.]

Competitive Interactions in Genesis of Connections

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Developmental neurobiology in the mid-1970s was dominated by a belief that neuronal connections are immutably specified by matching molecules on the pre- and postsynaptic elements. I wondered whether this level of precision could account entirely for the development of complex neural systems. However, I could not examine this issue until D.H. Hubel, T.N. Wiesel, and D.M.K. Lam[1] showed that intraocular injection of radioactive amino acids can expose termination of the input from the left and right eyes in separate layers of the geniculate nucleus and, transneuronally, in ocular dominance columns of the cortex. I reasoned that similar experiments in embryos could resolve whether axons from each eye recognize their proper synaptic targets in the absence of vision. Although cortical neurons are less committed to either eye in newborns than in adults,[2] anatomical evidence was lacking.

The study required exteriorization of the monkey fetus for intraocular injections and its replacement into the uterus to allow transneuronal transport—a procedure at that time thought to be unrealistic. As beginner's luck would have it, the first experiments were successful. The pattern of radiolabel in fetuses showed that input from each eye spread across the geniculate nucleus without indication of lamination. In the cerebrum, geniculocortical fibers first accumulated below the cortex in the transient subplate zone, which I termed a "waiting compartment." After entering the cortex, fibers subserving the two eyes spread across layer IV without indication of ocular dominance columns. Thus, the areas that receive input from a single eye in adults, received input from both eyes during midgestation. The projections segregated into appropriate territories in older fetuses.

The main contributions of this study were evidence that the inputs to separate territories may be initially intermixed; the discovery that thalamocortical terminals "wait" in the transient subplate zone before entering the cortex; and, the suggestion that competitive interaction of inputs before birth (and before visual stimulation) play a role in the development of connections. Later, we found that the number of optic axons in a fetus is greater than in the adult,[3] and most of this excess is eliminated during the phase of segregation.[4] The discovery that supernumerary projections from one eye can be spared by prenatal enucleation of the contralateral eye[5] suggested the role of competition among axons from two sides.

I submitted these results to *Nature* and a chapter to *Philosophical Transactions*, which was to publish the proceedings of a meeting. Surprisingly, the paper in the world's oldest, but less visible *Philosophical Transactions* was quoted more often, possibly because it appeared next to Hubel, Wiesel, and LeVay's celebrated article on binocular plasticity after birth.[6] However, I fancy that my paper was quoted primarily because it has challenged the dogma that neural connections are precise from the start and has inspired experimentation in mammalian embryos. By now, the concept of two-stage development (from intermixed to segregated) has been confirmed in many species and other parts of the brain.

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2. **Hubel D H & Wiesel T N.** The period of susceptibility to the physiological effects of unilateral eye closure in kittens. *J. Physiol.* 206:419-36, 1970. (Cited 815 times.)
3. **Rakic P & Riley K P.** Overproduction and elimination of retinal axons in the fetal rhesus monkey. *Science* 219:1441-4, 1983. (Cited 115 times.)
4. ---------. Regulation of axon number in primate optic nerve by binocular competition. *Nature* 305:135-7, 1983.
5. **Rakic P.** Development of visual centers in primate brain depends on binocular competition before birth. *Science* 214:928-31, 1981.
6. **Hubel D H, Wiesel T N & LeVay S.** Plasticity of ocular dominance columns in monkey striate cortex. *Phil. Trans. Roy. Soc. London B* 278:377-409, 1977. (Cited 400 times.)

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