system appears to be in maintaining *RAG* expression, which then supports V(D)J rearrangement. We cannot determine whether the *RAG* gene expression in the starting population was a response to IL-7 previously encountered in vivo, which would be possible because the IL-7 and *RAG* genes are all first detected at about the same time (day 12) of embryogenesis.

IL-7 (*11*) serves as a growth factor rather than as an inducer of Ig gene rearrangement in early B cell development (*18*). Large amounts of IL-7 mRNA in the thymus implicate IL-7 in T cell development also (*12*) (Fig. 3). IL-7 is required for thymocyte development (*19*) and can sustain the viability of immature thymocytes in suspension cultures without inducing cell proliferation (*20, 21*). Transgenic mice that overexpress IL-7 display more of all subsets of thymocytes (*22*). We assume that the IL-7 effects in these and our studies are due to direct effects on thymocytes, which display IL-7 receptors (*23*), although indirect effects by means of other cells cannot be excluded.

Our data suggest that IL-7 is an essential cofactor for V_β rearrangement in precursor T cells. In addition to sustaining *RAG* expression, IL-7 could also promote rearrangement by other means. IL-7 could enhance the production or activity of components of a recombinase complex (*24*). Considering that transcription has also been suggested to be necessary for rearrangement (*25*), IL-7 could promote transcription of the V_β genes.

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Chemorepulsion of Axons in the Developing Mammalian Central Nervous System

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During development of the nervous system, distinct populations of nerve cells extend specialized processes, axons and dendrites, over considerable distances to locate their targets. There is strong evidence for two general mechanisms by which these connections are made. The first involves attractive and repulsive interactions, both between cells and between them and their extracellular matrix. The second depends on the release of diffusible chemoattractants by target structures. Evidence is now provided for a mechanism of axon guidance in which diffusible chemorepulsive factors create exclusion zones for developing axons, causing them to turn away from inappropriate territory.

Axons reach their final destinations by locating successive intermediate targets (*1, 2*). Thus, it is important to understand the local control of the axon and its terminal sensory-motor apparatus, the growth cone. Interactions between growth cones and their environment may promote the advance of axons by contact guidance (*2*) or cause their arrest by contact inhibition (*3*). Guidance also occurs as a function of diffusion gradients, in which case both intermediate (*4*) and final targets (*5*) release diffusible factors that attract developing axons.

If guidance mechanisms that operate by cell-cell contact can be either attractive or repulsive, then attractive guidance mechanisms operating by diffusible factors might have counterparts in repulsion. I have examined this possibility in the olfactory system of the embryonic rat. Here, the olfactory bulb is continuous posteriorly with the anterior olfactory nucleus, which connects medially with the septum, laterally with the lateral olfactory cortex, and superiorly with the cerebral cortex. Around embryonic day 15 (E15) of development, mitral and tufted cells of the olfactory bulb are arranged concentrically. They project axons that turn within the bulb away from the midline and emerge laterally on the surface of the brain to form the lateral olfactory tract (LOT) (Fig. 1, a and b) (*6, 7*). At this stage, LOT axons form a discrete bundle immediately beneath the pial surface over the lateral part of the olfactory cortex. Only later, at E17 to E18, do these axons extend collateral branches that innervate the olfactory cortex, and at no stage do they innervate the cerebral cortex (*6*). It is possible that the divergence of these axons away from the midline is caused by the release of diffusible chemorepulsive factors from nearby medial structures.

To test this hypothesis, I cocultured explants of septum and olfactory bulb from E14.5 to E15 embryos 100 to 400 μm apart for 40 to 48 hours in collagen gel matrices, which establish gradients of diffusible factors (Fig. 2a) (*4, 5*). Under these conditions (*8*), axons from olfactory bulb explants consistently grew away from the septum, the outgrowth from which was unaffected ($n = 87$) (Fig. 2b). Explants of E14.5 to E15 lateral olfactory cortex ($n = 8$) or cerebral cortex ($n = 8$) also produced inhibitory effects on the growth of olfactory bulb axons. However, when cocultured with E18 olfactory cortex, E14.5 to E15 olfactory bulb explants grew radially and in equal numbers, so that 28.5 ± 2.13%, 22.5 ± 2.28%, and 49.8 ± 1.88% (mean ±

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SEM, n = 20 explants) of all axons emerged from the mesial, distal, and lateral quadrants, respectively (Fig. 2a). Thus, this loss of inhibitory activity released by the olfactory cortex coincides with the stage at which the cortex is first innervated by LOT collaterals. These observations are consistent with the distribution of the LOT and demonstrate that divergence from the midline does not result from chemoattractants emanating from the lateral aspect of the olfactory cortex. Individual control explants of all these tissues extended axons radially and were not affected when cocultured with explants of their own type.

Sections of cultures stained with an antibody to microtubule-associated protein (MAP 1b) (9) demonstrated that axons turn within olfactory bulb explants when cocultured with septum (Fig. 3A). Another antibody, 1C12, recognizes a cell surface adhesion molecule, TAG-1 (*10*), which is present on olfactory tract axons (*11*). This antibody identified all axons emerging from olfactory bulb explants in culture (n = 20) (Fig. 3B). These results are consistent with those of morphological studies showing that, at this stage of development, almost all neurons in the olfactory bulb are mitral and tufted cells (6). Thus, in vitro, a diffusible factor directs lateral olfactory tract axons away from the same central structure that they grow away from in vivo (5).

The possibility that lateral olfactory tract axons extend toward septal explants or their axons but then diverge through contact inhibition was excluded by the results of careful sequential observations of cocultures. Axon outgrowth was initiated from the distal and lateral aspects of olfactory bulb explants; outgrowth should not have occurred before any contact had been made. Similarly, the outgrowth of axons leaving olfactory bulb explants should, on average, be radial and equally distributed between the quadrants M, D, and L, but this was not the case. Only 1.8 ± 0.88% (n = 7 explants) of these axons emerged from the septal-facing (M) aspect of olfactory bulb explants, and outgrowth was biased away from a radial distribution (Fig. 2, a and b, and Table 1). Finally, contact inhibition causes growth cones to retract and reform close to the original point of encounter (3). This mechanism would cause radially extended axons to be held just off septal explants, whereas those that did not make contact would continue to grow; this behavior was not observed. These results suggest that the outgrowth pattern of lateral olfactory tract axons was set by a diffusible factor originating from septal explants and acting at a distance within olfactory bulb explants. Further lines of evidence support this view. First, the effect persisted when a nitrocellulose filter was placed between the explants (n = 7) (Fig. 2c). Second, immunocytochemical and fluorescent-tracer analyses (Fig. 3, A, C, and D) (*12*) demonstrated that axons turn within olfactory bulb explants to avoid the septum. Third, this effect was lost when explants were separated by a distance >1 mm (n = 12).

Coculture of olfactory bulb explants with septum resulted in a 33.5% reduction in axon outgrowth compared with those cultured alone (Table 2). Only 2% of the axons from the coculture emerged from the septal-facing (M) quadrant, with 42.5 ± 6.12% and 55.6 ± 5.7% of axons emerging from the L and D quadrants, respectively (Fig. 2a). This growth pattern probably did not result from a nonspecific toxic effect emanating from septal explants for several reasons: First, septal explants extended axons toward the near-facing aspects of olfactory bulb explants (Fig. 2b). Moreover, when two septal explants were positioned on either side of an olfactory bulb explant, septal growth again occurred normally, whereas that of the olfactory bulb explant

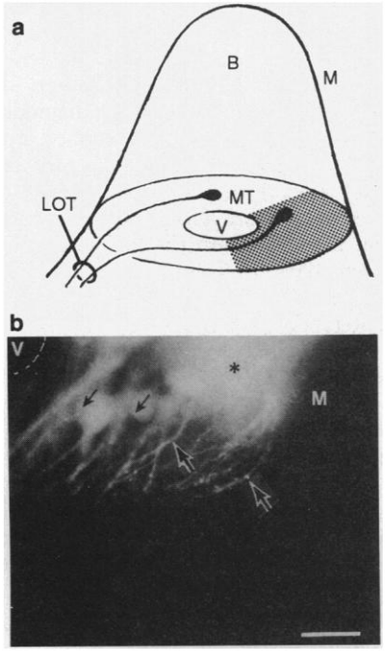

Fig. 1. Axonal trajectory of mitral and tufted cells (MT) within the olfactory bulb (B) at E15; V, ventricle; LOT, lateral olfactory tract; and M, midline. (**a**) Diagram (view from above) of MT axons turning across the bulb from medial to lateral orientations. (**b**) Fluorescent micrograph of a horizontally sectioned olfactory bulb after injection of DiI (*7*). Small arrows, cell bodies; axons (large arrows) are visible turning away from the midline within a region corresponding to the shaded area in (a); the dotted line defines the ventricular border; the injection site is marked with an asterisk. Scale bar, 100 μm.

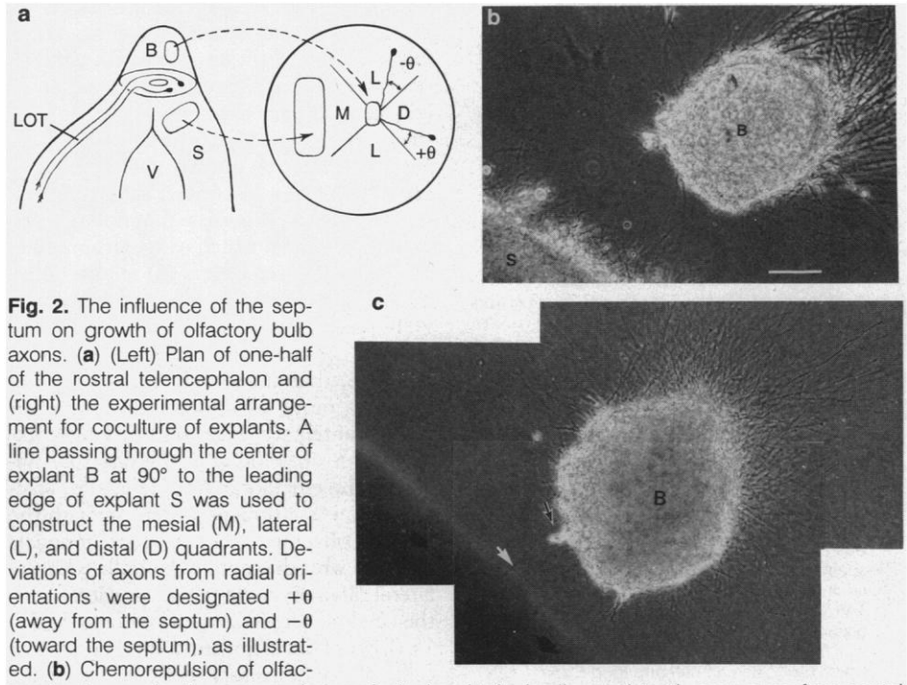

Fig. 2. The influence of the septum on growth of olfactory bulb axons. (**a**) (Left) Plan of one-half of the rostral telencephalon and (right) the experimental arrangement for coculture of explants. A line passing through the center of explant B at 90° to the leading edge of explant S was used to construct the mesial (M), lateral (L), and distal (D) quadrants. Deviations of axons from radial orientations were designated +θ (away from the septum) and −θ (toward the septum), as illustrated. (**b**) Chemorepulsion of olfactory tract axons by the septum. Axons of mitral and tufted cells consistently grew away from septal explants whose axons grew normally. Scale bar, 100 μm; S, septum; B, olfactory bulb. (**c**) Coculture of E14.5 olfactory bulb, B, and septal explants separated by a permeable barrier (pore size, 0.45 μm; Sartorius, Göttingen, Germany). The chemorepulsive effect of the septum clearly persists in the absence of septal axons. Large black arrows indicate the edge of the barrier. This experiment was the only case in which a septal axon approached an olfactory bulb explant; the septal explant is not visible behind the barrier. A single branched septal axon (white arrow) has grown over the barrier, and its growth cone is indicated by the small black arrow. Scale bar, 100 μm.

was almost completely suppressed (n = 10). Second, in cocultures of septum and cortex (n = 15), growth was unaltered on the septal-facing aspect of cortical explants. In further experiments, olfactory bulb explants grew radially when cocultured with septal explants that had been killed by dehydration immediately before culture (n = 6). Finally, retrograde labeling of axons with the fluorescent tracer 1,1′-dioctadecyl-3,3,3′,3′-tetramethylindocarbocyanine perchlorate (DiI) (n = 25 explants) and the results of immunocytochemical observations showed abundant cell bodies and axons within the septal-facing aspects of olfactory bulb explants (Fig. 3, A and C). Taken together, these results indicate that the effect is not due to nonspecific toxic effects, which should not bias the orientation of outgrowth in the manner observed here.

These findings are consistent with the idea that the septum releases a repulsive factor that diffuses into the olfactory bulb, where it contributes to a morphogenetic gradient that directs olfactory tract axons laterally. The identity of the mediator and the mechanisms of this effect are unknown but clearly influence both the orientation and extent of axon outgrowth. Gradients of diffusible factors could induce directional change by acting either directly on the growth cone or haptotactically by way of the substratum. Moreover, gradients of different molecules could interact to generate chemotactic factors, or these factors could arise as metabolites of other secreted molecules.

The creation of exclusion zones by diffusible factors would prevent excursions of axons into inappropriate territory and would enable the selection of distant targets to be made early in axonogenesis. A plausible general hypothesis is that axon guidance operates through a developmentally regulated set of strategies in which attraction and repulsion occur through contact and through diffusion gradients. Thus, different pathways would form on the basis of differential contributions of these mechanisms. It appears that, in conjunction with other mechanisms, chemorepulsion might contribute to the early patterning of the lateral olfactory tract.

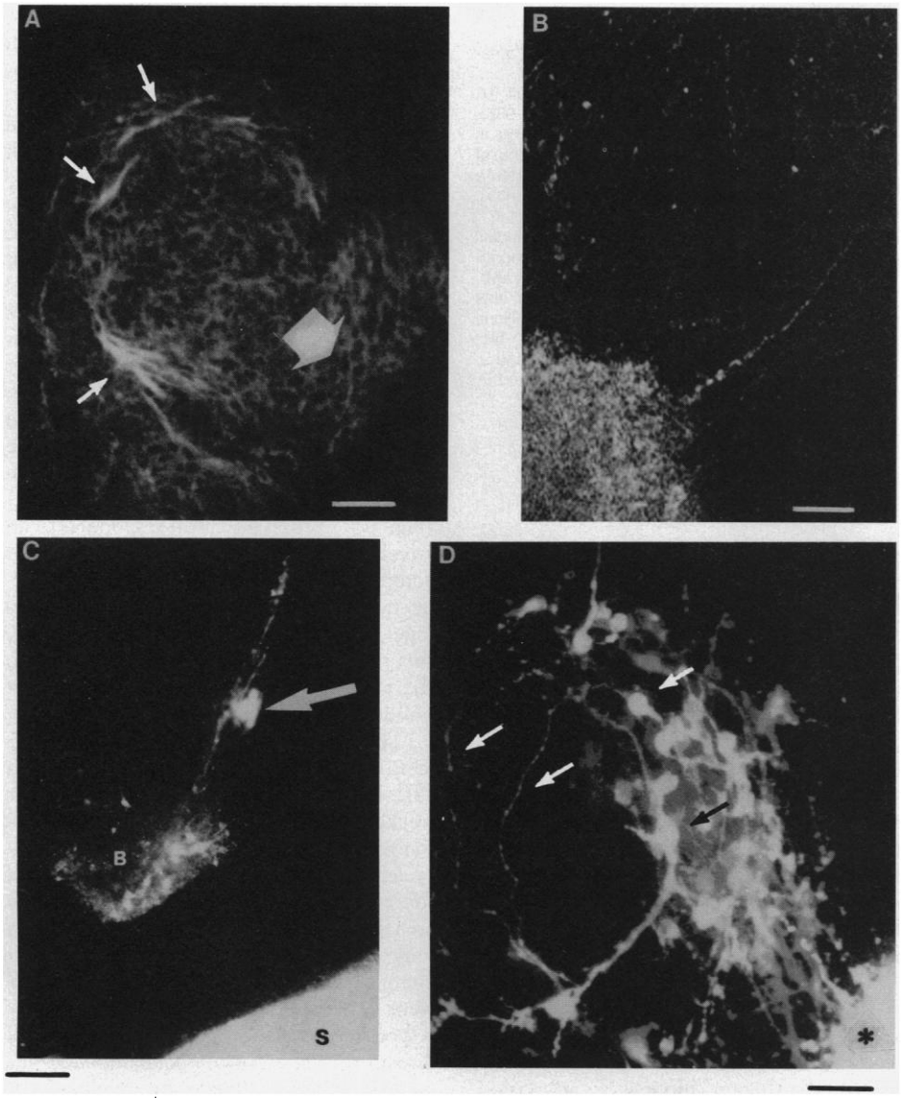

Fig. 3. Axonal trajectories within olfactory bulb explants. (**A**) Immunofluorescent cryostat section (15 μm) prepared according to (*11*). MAP 1b–positive axons (small arrows) turn within an olfactory bulb explant away from a septal explant positioned to the top left, out of the field of view. The large arrow is on a line passing through the center of the explant and produced at 90° to the leading edge of the septal explant. Scale bar, 50 μm. (**B**) Expression of TAG-1 by axons of mitral and tufted cells, shown by immunofluorescence in a whole gel observed by confocal microscopy. Scale bar, 25 μm. (**C**) Retrograde labeling with DiI of olfactory bulb axons in coculture with a septal explant. The lack of outgrowth from the septal-facing aspect of this explant is caused by axons turning within it and not by the absence of mitral and tufted cells. Abbreviations as in Fig. 2b; arrow, injection site. Scale bar, 100 μm. (**D**) Confocal imaging of the trajectories of axons retrograde-labeled with DiI within an olfactory bulb explant cocultured with septum. The axons (arrows) of two cell bodies are shown turning 180° away from a septal explant, which is to the top, out of the field of view. The injection site is indicated by an asterisk. Scale bar, 50 μm.

Table 1. The effects of the septum on the orientation of lateral olfactory-tract axons. Numbers and deviation of axons from radial orientation ($+\theta$ or $-\theta$) were determined as shown in Fig. 2a from photographic records of 19 representative experimental (olfactory bulb and septum) and eight control (olfactory bulb only) cultures (axons emerging radially were excluded). The orientation of lateral olfactory tract axons was significantly biased away from the septum (χ^2 = 62.8, 1 df, $P < 0.0001$).

Deviation	Number of axons	
	Experimental	Control
$+\theta$	425	157
$-\theta$	136	162

Table 2. The effects of the septum on the growth of lateral olfactory tract axons. There was a significant reduction in the number of axons growing from olfactory bulb explants that were cocultured with septum ($P < 0.005$, t test). Values for the number of axons per explant represent the mean ± SEM.

Condition	Axons per explant	Number of explants
Olfactory bulb and septum	28.6 ± 2.42	26
Olfactory bulb only	43.0 ± 4.07	9

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7. For the tracing of axons, forebrains were dissected from E14.5 to E15.5 embryos and, after removal of the meninges, immersion-fixed in 4% paraformaldehyde in phosphate buffer at room temperature for 3 hours. Day E0 is defined by the appearance of the vaginal plug. The fluorescent tracer DiI (1% in dimethylformamide, Molecular Probes) was injected into the medial aspect of the olfactory bulb. Two to 3 days later olfactory bulbs were removed and sectioned horizontally into two pieces, flat-mounted in *p*-phenylenediamine (pH 8 in glycerol), and examined under green filtered ultraviolet light.
8. Explants of olfactory bulb, septum, olfactory cortex, and cerebral cortex were dissected from E14.5 to E15 embryos (and from E18 embryos for the olfactory cortex) in cold Eagle's minimum essential medium (Gibco). Explants that were positioned between 100 μm and ~1 mm apart in collagen-gel matrices were incubated for 40 to 48 hours in Dulbecco's modified Eagle's medium plus glutamine (Gibco) with 10% fetal calf serum for 40 to 48 hours at 37°C in a 5% CO_2 atmosphere and photographed in phase contrast.
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A Processing Stream in Mammalian Visual Cortex Neurons for Non-Fourier Responses

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Mammalian striate and circumstriate cortical neurons have long been understood as coding spatially localized retinal luminance variations, providing a basis for computing motion, stereopsis, and contours from the retinal image. However, such perceptual attributes do not always correspond to the retinal luminance variations in natural vision. Recordings from area 17 and 18 neurons of the cat revealed a specialized nonlinear processing stream that responds to stimulus attributes that have no corresponding luminance variations. This nonlinear stream acts in parallel to the conventional luminance processing of single cortical neurons. The two streams were consistent in their preference for orientation and direction of motion but distinct in processing spatial variations of the stimulus attributes.

The receptive fields of simple cells in the early visual cortex consist of elongated, alternating excitatory and inhibitory regions. Selectivity for stimulus orientation and spatial frequency is conventionally explained in terms of linear spatial summation: only those stimuli whose luminance variations match the layout of antagonistic receptive field regions will produce a response (*1*). The wide range of preferred spatial frequencies of cortical neurons has supported a theoretical view of early vision in terms of local (piecewise) Fourier analysis (*2*). However, this scheme cannot explain visual responses to motion, stereopsis, edges, and spatial position when these attributes do not correspond to the Fourier spatial frequency power of the stimuli (*3*). One stimulus that reveals the existence of "non-Fourier" processing is an envelope stimulus, which consists of a noise pattern or a high spatial frequency luminance grating (carrier) whose contrast is modulated by a low spatial frequency pattern (envelope). Because there is no Fourier component corresponding to the pattern modulation, the detection of envelope patterns suggests the existence of nonlinear processing in the visual system (*4*). The nonlinear analysis may occur after the cortical spatial frequency–selective filtering, or before, as a consequence of early nonlinearity (*5*).

We determined whether area 17 and 18 neurons responded to spatially one-dimensional envelope stimuli (*6*), using single stationary high spatial frequency (f_c) luminance gratings as the carriers and single moving low spatial frequency (f_e) sine waves as the envelopes (Fig. 1A). Such envelope stimuli were perceived as a moving pattern of spatially alternating transparency and occlusion placed on a high spatial frequency luminance grating. The stimuli were generated by the multiplication of two grating patterns (carrier times envelope; Fig. 1B). In the Fourier frequency domain, such envelope stimuli consisted of a linear sum of three components closely centered about the high spatial frequency carrier: a stationary middle component at the carrier spatial frequency (f_c), a low side band ($f_c - f_e$), and a high side band ($f_c + f_e$) (Fig. 1C). The two side bands moved oppositely at the same temporal frequency as the envelope (f_t). However, no Fourier energy was at the envelope spatiotemporal frequency (f_e,f_t) (Fig. 1C). When a neuron responded to an envelope stimulus in which all the Fourier components were clearly outside its frequency-selective range and only the envelope spatiotemporal frequency was inside, this neuron must have been responding to the envelope of the stimulus as a result of nonlinear processing (*7*).

Thirty-nine of 94 cells responded significantly to the non-Fourier envelope pattern (*8*), although the envelope response was weaker than the same cell's luminance grating response at its optimal spatial frequency. Half of the simple (n = 22) and most of the complex (70%, n = 30) type cells in area 18 were envelope-responsive, whereas only 1 out of 12 simple and a minority of complex (20%, n = 30) cells in area 17 were envelope-responsive (*9*). Envelope-responsive cells showed the same preferred direction, degree of temporal modulation, and preferred orientation to envelope patterns as they showed to luminance grating stimuli (*10*).

The simplest explanation of such responses would be an early nonlinear transform (Fig. 2A) in which any stimulus goes through a pointwise nonlinearity (*11*) before spatial frequency–selective filtering. In this model, the nonlinearity produces a Fourier component (distortion product) at the envelope spatiotemporal frequency, and the subsequent frequency filtering picks out the distortion product and removes the

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