Virtually no modulation was observed in the level of N-*myc* mRNA during the time course analyzed. N-*myc* is frequently amplified and expressed at high levels in neuroblastoma cells (*19*). Thus, treatment of PC12 cells by NGF and 7-3351 results in a very dramatic and specific stimulation of the c-*fos* oncogene.

The actions of NGF on PC12 cells may be divided into two categories. The first category consists of effects that occur relatively soon after addition of NGF and that do not require transcription, such as the altered phosphorylation of endogenous substrates (*20*). The second category contains the more long-term actions that are transcription-dependent. Alterations requiring transcription include the elevation of ODC activity (*21*), the increase in microtubule-associated proteins (*22*), and the generation of neurites (*23*). Of the transcription-dependent changes caused by NGF, the induction of c-*fos* is the most rapid described thus far (Fig. 3). If proto-oncogenes are involved in the normal control of cell development, c-*fos* could fulfill a critical early function in coupling NGF to other long-term transcription-dependent events. This is supported by the finding that c-*fos* is superinduced when certain peripheral-type BZD's are present in the culture with NGF (Fig. 2). This finding is significant for two reasons. First, the concentrations of BZD's used are sufficient to modify both the neurite and ODC responses of PC12 cells to NGF (*10*). That is, a modification in c-*fos* expression correlates with an alteration in biological response. Furthermore, both of these responses occur subsequent to the induction of c-*fos* (Fig. 1) (*24*). Second, the structure-activity relation for the superinduction of c-*fos* is indistinguishable from that for the modification of NGF-induced neurite outgrowth (Fig. 2B) (*10*). Thus, it would appear that the mechanism of action of the BZD's is the same in both instances. That such a mechanism is relevant to other cell types is emphasized by the fact that the structure-activity relation for BZD's reported here (as well as previously for PC12 cells) is the same as that for the direct BZD induction of hemoglobin synthesis in FEL cells (*17*). The same mechanism appears to modify differentiation in cells of two quite distinct phenotypes. It is possible that c-*fos* fulfills a similar function in the other cell types in which it is expressed. However, the differentiated or physiological state of the stimulated cell may determine the nature of the long-term events to which c-*fos* action is coupled.

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Migration and Differentiation of Cerebral Cortical Neurons After Transplantation into the Brains of Ferrets

Abstract. *Cells from the cerebral proliferative zones of newborn ferrets were labeled with tritiated thymidine and a fluorescent dye and were transplanted as a single-cell suspension into the occipital region of newborn ferrets. The transplanted cells became thoroughly integrated into the host environment: many cells migrated through the intermediate zone and into the cortical plate, where they developed as pyramidal neurons. Other transplanted cells came to resemble glial cells. After 1 to 2 months most transplanted neurons had taken up residence in layer 2 + 3, the normal destination of neurons generated on postnatal days 1 and 2. Thus the sequence of morphological differentiation and the eventual laminar position of the isochronically transplanted neurons closely paralleled that of their normal host counterparts.*

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The laminar arrangement of neurons in the mammalian cerebral cortex is one of the most striking features of cortical organization. Not only do most neurons in a given layer tend to share certain morphological features, but they also have similar patterns of connectivity and physiological properties (*1*). Tritiated thymidine "birth-dating" studies have revealed that neurons in a layer undergo their terminal mitotic divisions at about the same time and that the layers are generated in an inside-out manner, with cells of the deepest layers being born first and those of the most superficial layers last (*2, 3*). That cortical neurons in a lamina share common birth dates and

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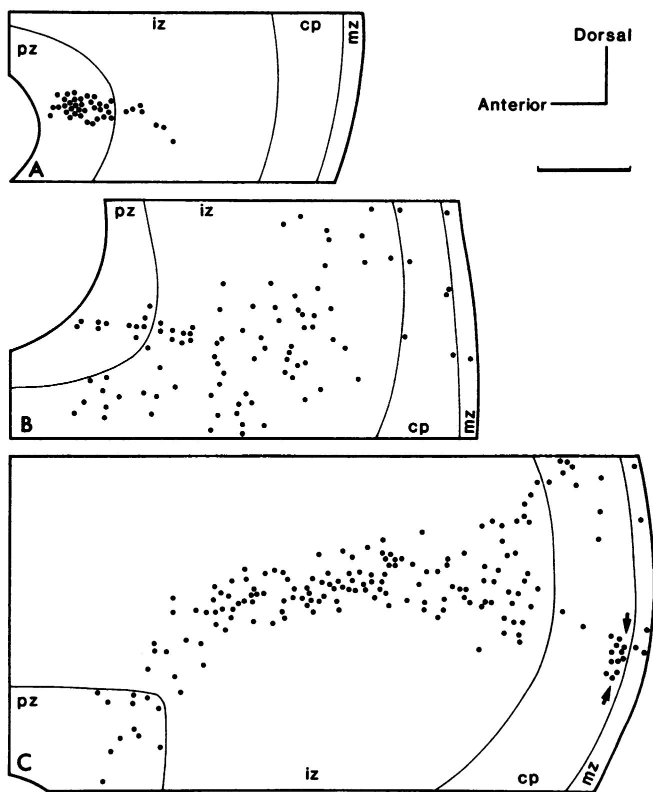
projections raises the possibility that the ultimate fate of these cells may be determined early in development, perhaps before migration. Several studies have lent at least partial support to this view (*4*).

Recently, transplants of brain tissue were used to explore the rules that guide the normal development of neurons in terms of their morphogenesis and formation of specific connections (*5*). In these studies, however, transplants tended to develop as distinct microenvironments in the host brain. In studying the development of lamina-typical morphology and connectivity it would be more desirable for transplanted neurons to migrate and differentiate side by side with host neurons, in the hope that any cues in the host environment that direct or permit normal development will act on the transplanted cells as well. In the experiments described here, cells normally destined for the visual cortex were transplanted as a suspension into the proliferative zone (*6*) of the occipital cerebral mantle of host animals of the same age (isochronic transplants). The donors and hosts were ferrets *(Mustela furo)*, a species in which there is a prolonged period of postnatal neurogenesis (*7*).

Transplants were performed successfully in 33 host ferrets from 12 litters. Most donor animals were given six successive injections of [^{3}H]thymidine (50 to 80 Ci/mmol; 10 μCi per gram of body weight, intraperitoneally) at 6- to 12-hour intervals on postnatal days 1 and 2. Four to 18 hours after the final injection, the donors were decapitated and the occipital portions of their cerebral hemispheres were placed in Hanks balanced salt solution (HBSS) buffered with Hepes to *p*H 7.4. Tissue from the proliferative zones lining the lateral ventricles was dissected out, incubated for 15 minutes in one of two fluorescent dyes [diamidino phenylindole (DAPI, 1 μ*M*) or Fast Blue (0.002 percent)], washed, and mechanically dissociated in HBSS. From samples of the resulting cell suspension it was determined that about 80 percent of healthy cells were dye-labeled, and of these roughly 30 percent had incorporated [^{3}H]thymidine.

Host ferrets of the same age as the donors were anesthetized with ether, and 0.2 to 0.3 μl of the cell suspension was pressure-injected from a glass micropipette into or near the occipital proliferative zone. The pipette was lowered into the brain vertically, an angle roughly perpendicular to the radial glia of the presumptive visual cortex, to afford the injected cells the opportunity to migrate out into areas of host cortical plate undamaged by the injection. After 2 hours to 2 months of survival the host ferrets were perfused with buffered formalin. The brains were removed, embedded in glycol methacrylate or gelatin-albumin, and sectioned (5 to 20 μm) in the parasagittal plane. Sections were mounted onto slides and examined with epifluorescence optics or processed for autoradiography.



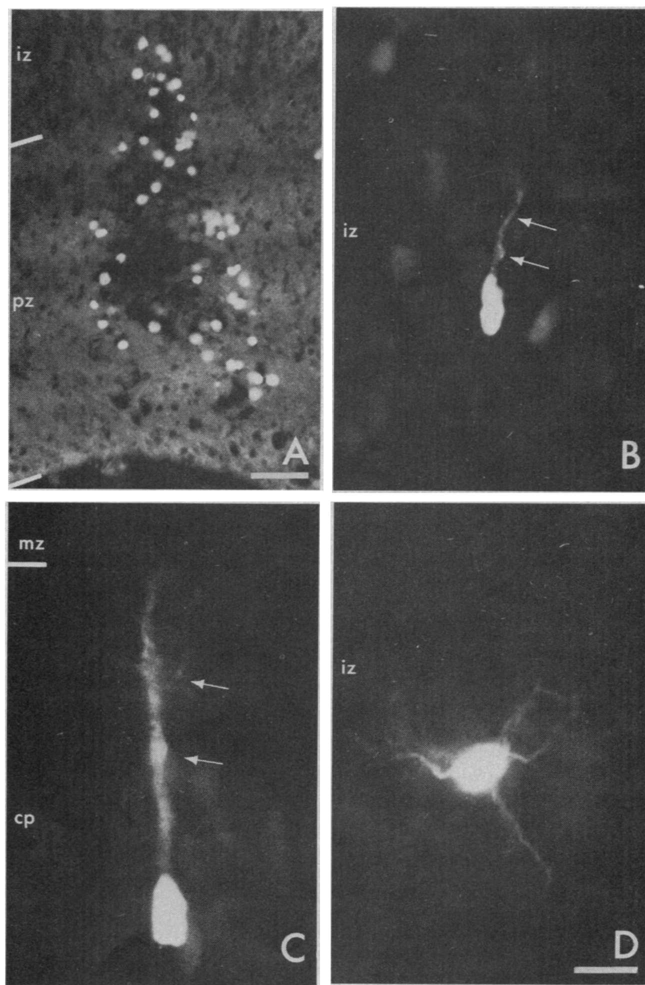


Fig. 1 (left). Reconstruction of positions of fluorescently labeled transplanted cells (dots) after survival times of (A) 2 hours, (B) 4 days, and (C) 12 days. Arrows in (C) dilineate the region where fluorescent cells showing pyramidal neuronal morphology were found (pz, proliferative zone; iz, intermediate zone; cp, cortical plate; and mz, marginal zone). Scale bar is 300 μm for (A) and (B) and 500 μm for (C). Fig. 2 (right). (A) DAPI-labeled cells in a host brain 2 hours after transplantation. (B) Migrating neuron (labeled with Fast Blue) in the intermediate zone of a host 4 days after transplantation. Arrows point to the leading process. (C) Pyramidal neuron in the cortical plate, labeled with Fast Blue after a 12-day survival. Arrows show the cell's apical dendrite extending toward the marginal zone. (D) Fast Blue–labeled cell showing glial morphology, seen in the host intermediate zone 12 days after transplantation. Such cells were observed in all regions of the cerebral mantle. Scale bars are 50 μm (A) and 10 μm (B to D). In each panel the posterior side (pial surface) is up.

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DAPI and Fast Blue were used to identify transplanted cells in tissue from ferrets killed after short survival periods; these dyes were retained by cells for about 1 week and 3 weeks after transplantation, respectively. Figure 1A shows a reconstruction of an injection site in a host ferret 2 hours after transplantation. The transplanted cells were found in a cluster in the proliferative zone and at the base of the intermediate zone. The fluorescent cells were small and round (Fig. 2A) and resembled freshly dissociated cells in vitro.

Both the position and morphology of many labeled cells were different in ferrets killed 2 days after the injection. No longer tightly clustered, the fluorescent cells were typically found in a stream that extended radially from the proliferative zone well into the intermediate zone. After 4 days the stream of labeled cells reached through the entire thickness of the cerebral mantle (Fig. 1B). The transplanted cells were well integrated with surrounding, unlabeled host cells. Although a variety of morphologies were observed, many labeled cells in the intermediate zone were spindle-shaped and bore a leading process that extended radially toward the cortical plate (Fig. 2B); these cells thus resembled young migrating cortical neurons (*8*). After 4 to 6 days of survival many fluorescent cells were found in the most superficial region of the cortical plate. These cells were no longer spindle-shaped: they were larger, had oval nuclei (often with multiple nucleoli), and were similar in appearance to surrounding host neurons.

The overall distribution of fluorescent cells 12 days after transplantation is reconstructed in Fig. 1C. Two classes of dye-labeled cells were distinguished. In the first group were many cells in the cortical plate (arrows in Fig. 1C) which appeared to have undergone further differentiation characteristic of young neurons: these cells were clearly pyramidal in shape and extended apical dendrites radially toward the marginal zone (Fig. 2C). A second class of labeled cell was seen in all regions of the host cerebral mantle, but was observed most commonly in the intermediate zone. These had round cell bodies with fine processes that radiated irregularly outward (Fig. 2D). They may have been glial in nature; however, this was not examined by staining for glia-specific markers.

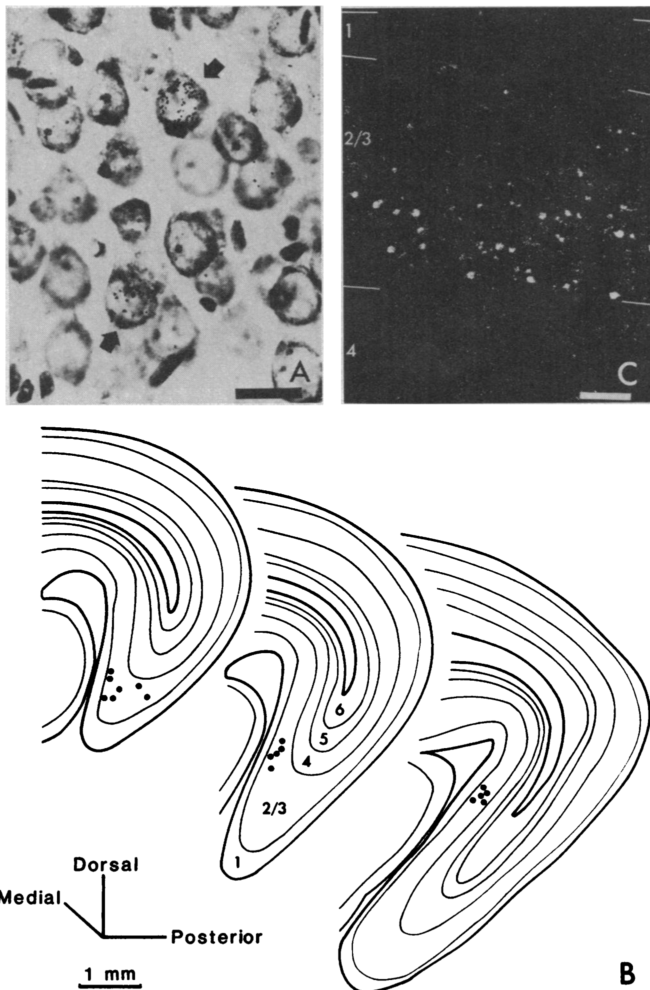

Fig. 3. (A) Autoradiograph of a section of a host brain, showing [^{3}H]thymidine-labeled, transplanted neurons (arrows) 6 weeks after injection. Scale bar, 20 μm. (B) Reconstruction showing the positions of labeled transplanted neurons (dots) in three sections from the same host brain. All labeled cells in this case were found in layer 2 + 3, in the peripheral visual field representation of area 17. (C) Dark-field autoradiograph of area 17 from a normal adult ferret injected with [^{3}H]thymidine on postnatal day 1. Heavily labeled cells (bright spots) were found in layer 2 + 3. Scale bar, 100 μm.

Tritiated thymidine autoradiography was used to identify transplanted cells in host animals after survival times of 1 to 2 months, at which times all the cortical layers were clearly differentiated. Figure 3A shows two typical labeled cells: both were neuronal in morphology, having pyramidal shapes and readily apparent apical dendrites. These and other labeled cells were morphologically indistinguishable from surrounding unlabeled host neurons. Figure 3B shows the laminar distribution of [^{3}H]thymidine-labeled neurons in three sections through area 17 of one host ferret: all the transplanted cells were found in layer 2 + 3. Inspection of every fifth section from each brain revealed a total of 127 labeled cells in six host ferrets from four experimental litters. Of these cells, 114 were located in layer 2 + 3, 1 was in layer 6, and 12 (all from a single animal) were found in the remnant of the embryonic proliferative zone (*9*). From rough estimates of the numbers of cells injected, it appears that a large fraction of the injected cells survived (*10*).

To compare the laminar positions of the transplanted neurons to those of normal cortical neurons generated at similar times, five normal ferrets were given a single injection of [^{3}H]thymidine (10 μCi per gram, intraperitoneally) on postnatal day 1 or 4 and were perfused 3 months later and processed for autoradiography. A dark-field autoradiograph of a section from area 17 of one such ferret is shown in Fig. 3C: labeled neurons were primarily found in layer 2 + 3. Thus both the final laminar positions of the transplanted cells and the morphological changes that injected cells underwent during migration and differentiation were strikingly similar to those of normal cortical neurons with similar birth dates (*3, 8, 11*). Isochronically transplanted neurons therefore appeared to respond normally to the signals that guide or allow the migration and morphological differentiation of young neurons. Whether the transplanted cells also form connections typical of upper layer neurons is not known.

It appears that transplantation per se does not alter the fate of cortical neurons in terms of their adult morphology and laminar position. The experiments described thus suggest a means by which the separate contributions of birthday and local environment to the eventual fate of a cortical neuron may be determined.

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10. Labeled cells were counted from a one-in-five series of autoradiographs for each host brain—thus, allowing for the remaining sections and estimating that only cells in the upper third of each 20-μm section were detected autoradiographically, it was calculated that on average 300 labeled neurons (range, 25 to 795 cells) were present in each host. Typically, 2000 to 3000 cells were injected (calculated from the volumes used and density of the suspensions and from counts of cells in host animals killed shortly after transplantation); of these roughly 600 to 900 would be labeled with [^{3}H]thymidine. The estimated survival rates ranged from 6 to 80 percent and represent a minimum survival, since some labeled cells may have reentered the mitotic cycle and diluted out their label after transplantation.
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Differential Control of U1 Small Nuclear RNA Expression During Mouse Development

Abstract. *During normal mouse development the relative amounts of two types of U1 small nuclear RNA's (U1 RNA) change significantly. Fetal tissues have comparable levels of the two major types of mouse U1 RNA's, mU1a and mU1b, whereas most differentiated adult tissues contain only mU1a RNA's. Those adult tissues that also accumulate detectable amounts of embryonic (mU1b) RNA's (for example, testis, spleen, and thymus) contain a significant proportion of stem cells capable of further differentiation. Several strains of mice express minor sequence variants of U1 RNA's that are subject to the same developmental controls as the major types of adult and embryonic U1 RNA. The differential accumulation of embryonic U1 RNA's may influence the pattern of gene expression during early development and differentiation.*

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U1 small nuclear RNA (U1 RNA) (*1*) is essential in the processing of messenger RNA precursors (pre-mRNA's) (*2*). The U1 ribonucleoprotein particle (U1 snRNP), which contains U1 RNA plus a set of seven to nine proteins (*3*), appears to function in the recognition of 5′ splice sites of pre-mRNA (*4*).

Since pre-mRNA splicing occurs in all eukaryotic cells (*5*) it has generally been assumed that the genes for U1 RNA and snRNP-associated proteins are expressed constitutively as "housekeeping" genes (*6*). We demonstrated, however, that a class of the *Xenopus laevis* U1 RNA genes (which we called embryonic U1 RNA genes) was subject to control of expression during development (*7*). On the basis of that observation, we proposed that differential expression of certain genes for U1 RNA's or U1 snRNP proteins might result in changes in pre-mRNA splicing patterns. We now report that the expression of mouse U1 RNA genes is also developmentally controlled and that two types of mouse U1 RNA's exist; one is found in all cells, whereas the other is present primarily in embryonic tissues.

The U1 RNA's in brain, liver, and testis isolated from mouse embryos or adult mice were analyzed by Northern blot hybridization (*8*) (Fig. 1, A and B). At all stages of fetal development, these tissues contained mU1a and mU1b, the two major types of mouse U1 RNA that had previously been identified in mouse tumor cells (*3*) (see also below). In contrast to fetal tissues or the testis, the brain and liver of newborn or adult mice contained primarily mU1a RNA and little or no mU1b RNA. The relative amounts of the U1 RNA's in brain and liver were unaffected by the sex of the mice from which these tissues had been isolated.

The changes in the relative amounts of mU1a and mU1b RNA's, as a function of time after fertilization, were examined by analyses of RNA's isolated from brain, liver, or testis (Fig. 1B). In both liver and brain the level of mU1b RNA's decreased continuously from day 13 after fertilization (day 0 is day of plug) until it was undetectable at about 1 or 2 weeks after birth. The same pattern was observed for kidney. The apparent half-life of the mU1b RNA's was about 4 or 5 days, which is similar to the previously reported half-life of U1 RNA in HeLa cells (*1*). This decrease in mU1b RNA levels may be due to a higher rate of turnover of mU1b RNA's or to a reduction in the number of cells containing mU1b RNA in these tissues.

In testis, a different pattern of differential accumulation was observed (Fig. 1B). Shortly after birth of the mice, the mU1b RNA's began to increase rapidly so that in testes of 4- to 6-week-old mice, mU1b RNA's accounted for about 50 percent of the total U1 RNA. Since the number of germ cells in testes show similar changes during late fetal and postnatal development (*9*), the differential accumulation of embryonic U1 RNA's in the developing testis is consistent with the notion that mU1b RNA's are expressed in the pre-spermatid cells but not in other types of cells in the testis.

We showed that the presence of mU1b RNA in the embryos resulted from the state of differentiation of the tissues rather than from the rapid rate of cell division in embryonic tissues. Three secondary cultures of skin fibroblasts, all growing with a generation time of about 24 hours, were analyzed for their ability to synthesize mU1b RNA. Fibroblasts from day 13 embryos produced both mU1a and mU1b RNA's, whereas fibroblasts from late embryos (days 16 to 18) or neonates synthesized only mU1a RNA.

A minor variant of mU1b RNA (middle band in Fig. 1, A and B) is also evident in fetal tissues from inbred strain ICR/Au mice (*10*). This variant (called mU1b-3 RNA) and additional variants of mU1b and mU1a RNA's found in tissues from other strains of mice (Fig. 2) were tentatively classified as mU1a (adult) or mU1b (embryonic) RNA's according to their patterns of differential accumulation; variants present in both adult and fetal tissues were called mU1a RNA's, whereas those species found only in fetal

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