aggregation by a trawler directed from an acoustic vessel confirmed that scouts were the largest fish (median, 50 cm for scouts, 46 cm for middle; 44 cm for rearguard). This result occurred despite a low range of sizes in 1992 (interquartile ranges 45–57 cm in 1990, 41–53 cm in 1991 and 42–48 cm in 1992). Rearguard fish apparently followed the scouts. On several occasions scouts veered sharply off-course in pursuit of prey (Fig. 3). In each case the whole aggregation veered: it is unlikely that the rearguard could have seen the prey initially and were probably following the fish ahead.

Several questions emerge from these observations. How do cod achieve a high degree of spatial precision in their migrations? What signposts do they use? Do cod pilot[11] relative to persistent hydrographic and bathymetric features (the highway was predicted on the basis of such a thermal assumption). Indeed, the constancy of the temperatures chosen by cod (when they could go elsewhere) suggests that routes develop and persist, at least in part, because of suitable and stable temperatures. Still, the mechanisms by which cod migrate await further inquiry. The lack of use of the northerly highways is attributed to the southerly cod distributions of recent years[12].

What is the function of the spawning columns? In laboratory experiments, cod spawn in pairs in midwater after more demersal courtship[13]. Acoustic records suggest the columns may comprise pairs of spawning fish, having paired near bottom then swum up to spawn.

Why do migrating cod form large aggregations[4,14]? Could the answer relate to feeding and learning by juveniles? These fish migrate long distances in search of food. Perhaps younger follow older cod to take advantage of feeding opportunities, and by doing so learn migration routes[15–17]? Juvenile Arcto–Norwegian cod have been reported to make a dummy run accompanying adults to the spawning grounds[18,19]. If routes are partially learned then loss of older fish might lead to changed routes. Interestingly, a major reduction of older fish in 1991 and 1992 paralleled lower rates of passage shoreward than in 1990 (but equivalent daily displacements). Perhaps older fish sustain migratory routes and behaviours. The migration patterns of Norwegian spring spawning herring (*Clupea harengus*) changed after adult stocks were depleted in the late 1960s (ref. 20). The original patterns have yet to be re-established. For Newfoundland cod, migration patterns may also be expected to change, possibly irrevocably, in response to population declines in the early 1990s. □

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A *C. elegans* mutant that lives twice as long as wild type

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We have found that mutations in the gene *daf-2* can cause fertile, active, adult *Caenorhabditis elegans* hermaphrodites to live more than twice as long as wild type. This lifespan extension, the largest yet reported in any organism[1], requires the activity of a second gene, *daf-16*. Both genes also regulate formation of the dauer larva, a developmentally arrested larval form that is induced by crowding and starvation and is very long-lived[2–4]. Our findings raise the possibility that the longevity of the dauer is not simply a consequence of its arrested growth, but instead results from a regulated lifespan extension mechanism that can be uncoupled from other aspects of dauer formation. *daf-2* and *daf-16* provide entry points into understanding how lifespan can be extended.

Temperature-sensitive mutations in several genes lead to formation of long-lived dauer larvae in the absence of inducing signals. To learn whether these mutations might also increase lifespans of non-dauers, we examined the lifespans of dauer-constitutive *daf-2*, *daf-11*, *daf-7* and *daf-14* mutants (refs 4, 5 and E. Malone and J. Thomas, personal communication). The decision to enter the dauer stage, an alternative third larval stage (L3) must be made during the first larval stage (L1). Therefore, we shifted the mutant larvae to the non-permissive temperature at later stages, allowed them to grow to adulthood, and measured their lifespans[6]. Because many temperature-sensitive mutations lead to reduced gene activity even at the permissive temperature, we also measured the lifespans of these mutants at lower temperatures. The lifespans of *daf-11*, *daf-7* and *daf-14* adults were not noticeably different from wild type (Fig. 1 legend). In contrast, each of three *daf-2* mutations, *e1370*, *sa189* and *sa193* greatly extended lifespans of adults when shifted to the non-permissive temperature during L4 (Fig. 1*a*, *b* legend). *daf-2(e1370)* and *daf-2(sa193)* were also examined at the permissive temperature; the lifespans of both were extended (Fig. 1*c*, and data not shown).

The magnitude of the lifespan extension was striking. For example, when shifted from 15 °C to 20 °C at the L4 stage, the mean lifespan of wild type was 18 days, whereas that of *daf-2(sa189)* was 42 days (Fig. 1*a*), 2.3-fold greater than wild type. The difference between ageing rates of *daf-2* and wild-type animals was also readily apparent. When all the wild-type animals had died or become immobile, 90% of the *daf-2(e1370)* animals still moved actively on their plates (Fig. 2*c*). The long-lived *daf-2* adults resembled wild-type adults much more closely than the dauer. The dauer is developmentally arrested as a small, thin, and sexually immature larval form[4]. In contrast, the *daf-2* non-dauer animals became full-size adults, and appeared to feed and defaecate normally (Fig. 2, and data not shown). Furthermore, at 20 °C, where its lifespan was twice that of wild type, *daf-2(e1370)* animals had nearly normal brood sizes (212 ± 36 for *daf-2(e1370)* ($n = 29$); as compared to 278 ± 35 for wild-type animals grown in parallel ($n = 19$)).

Because one theory of ageing postulates that reproduction decreases lifespan[1], we wondered whether the slight decrease in the brood size of *daf-2* animals could possibly be responsible for their longevity. *spe-26* hermaphrodites, which are defective in spermatogenesis, live longer than the wild type[7]. This is consistent with the model that sperm production decreases the lifespans of *C. elegans* hermaphrodites[7]. To investigate directly whether reproduction shortens lifespan, we ablated the precursors of the germ cells and somatic gonad (the cells Z1, Z2, Z3 and Z4) in wild-type hermaphrodites using a laser microbeam[8,9]. The

lifespans of these animals were normal (Fig. 3*a*), as were the lifespans of *fem-3(e1996)* mutants[10], which do not produce sperm or self-progeny (Fig. 3*b*). We conclude that production of germ cells and progeny in itself does not shorten the lifespan of the *C. elegans* hermaphrodite. As expected, *daf-2(e1370)* animals still exhibited the longevity phenotype after ablation of the gonad and germ cells (data not shown). It seems likely that factors other than decreased germ cell or progeny production are responsible for the longevity of *C. elegans* lifespan mutants, including *spe-26*.

Why did dauer-constitutive mutations in the genes *daf-7*, *daf-11* and *daf-14* not affect lifespan? These genes function upstream of *daf-2* in regulating dauer formation[5]. They appear to act within partially redundant parallel pathways to keep *daf-2* activity levels high in the absence of dauer-inducing signals[11]. *daf-11* lies in one pathway, and *daf-7* and *daf-14* lie in the other pathway. Our data imply that mutations in these genes do not reduce the activity of *daf-2* in such a way that the lifespans of adults can be lengthened. It may be that because these gene functions are partially redundant, none of these mutations alone has a strong enough effect on *daf-2* levels to affect lifespan. Another possibility is that *daf-11*, *7* and *14* are capable of regulating *daf-2* levels only during L1, when dauer formation can be initiated. If so, shifting these mutants to the non-permissive temperature at later times would have no effect on *daf-2* levels.

How do *daf-2* mutations extend lifespan? The gene *daf-16* functions downstream of *daf-2* to promote dauer formation (refs 5, 12 and D. L. Riddle, personal communication). We found that the *daf-16* mutation *m26* completely suppressed the lifespan extension of *daf-2(e1370)* adults (Fig. 4). This suggests that *daf-2* mutations extend lifespan by allowing inappropriate activation of *daf-16* function. But how *daf-16* activity extends lifespan is unclear. The simplest model is that *daf-16* activity extends the lifespans of *daf-2* adults by triggering expression of a regulated lifespan extension mechanism that is normally coupled to dauer formation. This would imply that the long lifespan of the dauer is not simply a consequence of the fact that it is developmentally arrested, as has been widely assumed[4,13]. Alternatively, the mechanism by which *daf-16* extends the lifespans of *daf-2* adults could be different from the mechanism that allows dauers to live longer.

Could a similar type of lifespan extension operate in other organisms? Lifespans of mammals, and, to a limited extent, *C. elegans*, can be increased by food limitation[14]. It is possible that

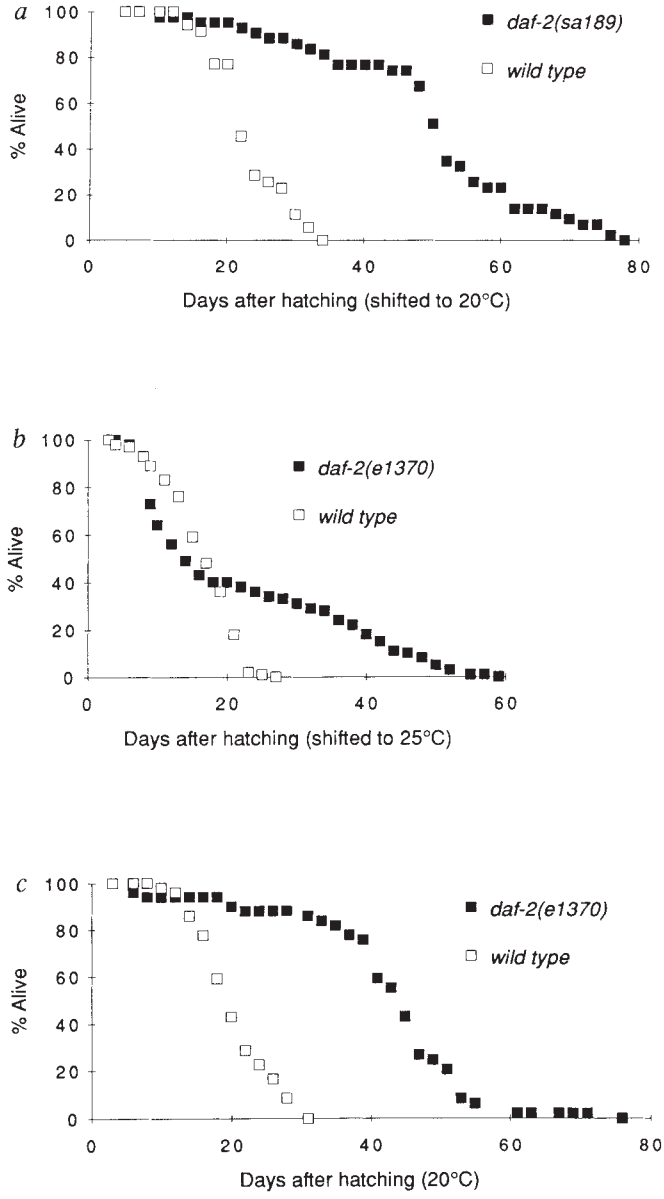


FIG. 1 *daf-2* adults have extended lifespans. *a*, *daf-2(sa189)* and wild type (N2) shifted from 15 °C to 20 °C, the non-permissive temperature, at the L4 stage. Mean lifespans were 42 days for *sa189* ($n=43$) and 18 days for N2 ($n=35$). Comparisons of these means with each other using the log-rank test[17] yielded a χ^2 value of 62.9 (P, the probability of these lifespan differences occurring by chance, $\ll 0.00001$). *b*, Lifespans of *daf-2(e1370)* and N2 (wild-type) animals shifted from 20 °C to 25 °C, the non-permissive temperature, as L4 larvae. Mean lifespans were 22.5 days for *e1370* ($n=120$) and 17 days for N2 ($n=119$). $\chi^2=10.0$ ($P<0.0016$). This is one of two experiments; both gave similar results. When shifted to 25 °C, about half the *daf-2(e1370)* animals died as young adults containing newly hatched progeny. *c*, Lifespan extension of *daf-2(e1370)* cultured continuously at 20 °C. Mean lifespans were 42 days for *daf-2(e1370)* ($n=42$) and 20 days for N2 ($n=49$); $\chi^2=67.1$ ($P\ll 0.00001$). At this temperature, *daf-2(e1370)* mutants did not die prematurely as 'bags of worms', which probably contributed to the greater mean lifespan of the population. The third allele, *daf-2(sa193)*, also exhibited an extended lifespan when shifted from 20 °C to 25 °C (non-permissive temperature). Mean lifespan for *sa193* was 25 days ($n=21$) and for N2 controls, 15 days ($n=44$). The efficiency of dauer formation in this strain was lower than *daf-2(sa189)* and *daf-2(e1370)* (not shown), as was its maximum lifespan (39 days). When cultured continuously at 20 °C, the mean lifespan of this strain was also extended slightly (not shown). *sa189* and *sa193* were isolated recently; the N2 control used in those lifespan experiments was the direct parent of these mutants. *sa189* and *sa193* were isolated recently by E. A. Malone and J. Thomas (personal communication). The lifespans of *daf-7(e1372)*, and *daf-14(m77)* were examined when grown continuously at 15 °C, or when shifted from 15 to 20 °C and from 15 to 25 °C as L4 animals. The lifespan of *daf-11(m84)* was determined after shifting L4 animals from 15 to 25 °C during L4. Under some conditions, a fraction of the mutants died prematurely as bags of worms[11]. The lifespans of the remaining animals were not significantly different from wild type (data not shown). In all experiments, five L4 animals were placed on NGM plates seeded with *Escherichia coli* OP50 (ref. 18). Animals were transferred to fresh seeded plates every two days when producing progeny, and about once a week thereafter. Animals were scored as dead when they no longer moved or twitched when prodded or pushed several times. All experimental strains were grown in parallel with wild type.

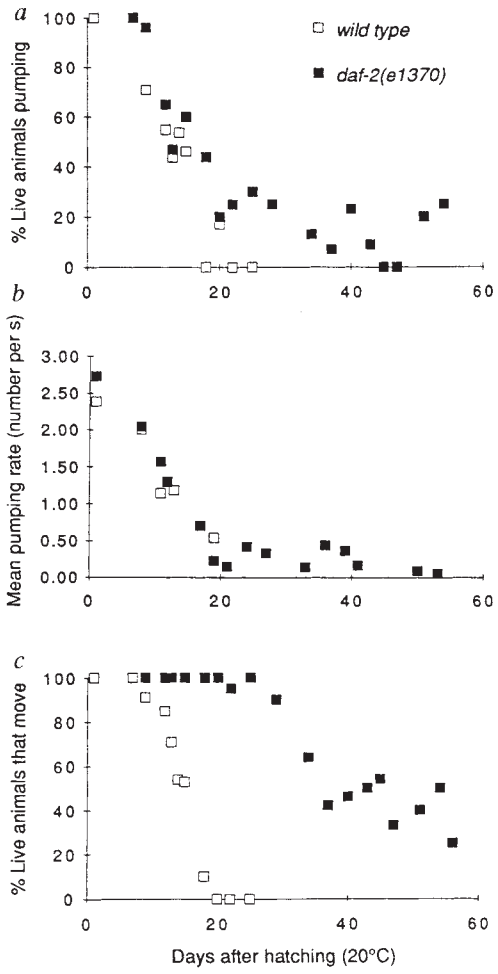
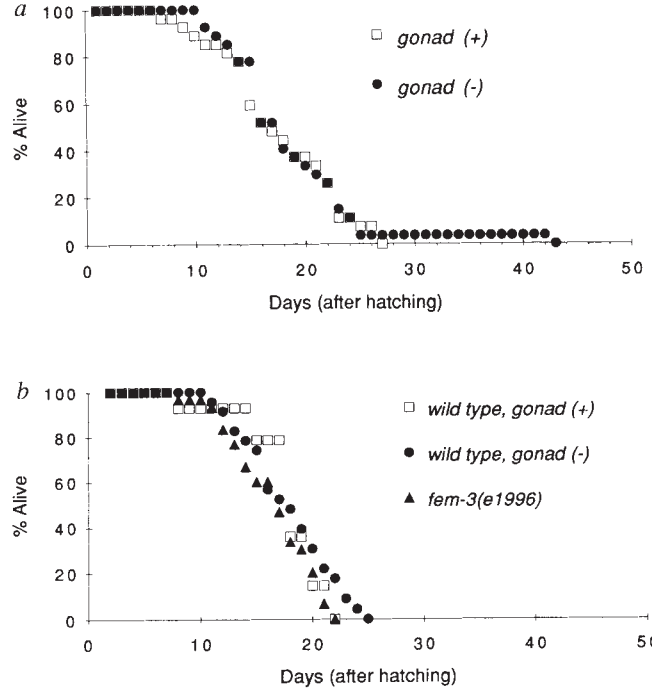


FIG. 2 Behaviours of *daf-2(e1370)* and wild-type adults. Animals were cultured individually on separate plates at 20 °C, and their feeding behaviour and movement were observed ($n = 19$ for N2 and $n = 20$ for *daf-2(e1370)*). *C. elegans* ingests food by periodic contraction of its pharynx, called 'pumping'[19]. To determine the per cent of live animals pumping (*a*), each animal was examined twice within a 1 h period for at least 30 s each time. Average pumping rate (*b*) was determined by measuring the pumping rates of at least five randomly selected animals that were pumping (dead and non-pumping animals were not included). As both wildtype and *daf-2* mutants aged, their pumping became sporadic. Often the animals lay still when first observed, but when stimulated, began to move across the plates, and often to pump. Individuals not pumping on one day would sometimes be pumping a few days later. Thus it seems likely that whereas young adults pump continuously, older animals (including mutant and wild type) pump intermittently until close to death. It is possible that the decrease in pumping rate, which occurs with similar kinetics in wild-type and *daf-2* animals, is not due to senescence, but instead reflects a decreased requirement for food when production of progeny ceases. To assay movement (*c*), we investigated what fraction of animals were moving actively on their plates, or began to move across the plates when touched with an eyelash[20]. Animals that moved their heads or bodies when stimulated but stayed in place were scored as negative. As *C. elegans* senesces[2,3,21], it becomes lethargic and eventually moves only its nose when touched. The inability to move appears to be a good indicator of impending death for both wild type and *daf-2*. (Compare the survival curves of these same animals, shown in Fig. 4, with the per cent capable of moving.) *daf-2* mutants did appear different from wild-type adults in at least two respects. First, they grew to adulthood more slowly than wild type, taking 3 days rather than 2 at 20 °C. In addition, like the dauer, their intestines appeared dark when viewed with a dissecting microscope. Neither of these phenotypes is sufficient to account for the extended lifespans of *daf-2* animals, as *daf-7* and *daf-14* mutants exhibit these phenotypes[11] but did not have extended lifespans.

FIG. 3 The lifespan of the *C. elegans* hermaphrodite is not affected by the production of germ cells or progeny. *a*, Lifespans of hermaphrodites lacking the reproductive system. The germ-cell precursors, Z2 and Z3, as well as the precursors of the somatic gonad, Z1 and Z4, were ablated in 27 newly hatched N2 hermaphrodites using standard procedures[8,9,22]. Mean lifespans were 18 days (s.d. = 6) for ablated animals ($n = 27$) and 17 days (s.d. = 5) for N2 controls ($n = 27$). These survival curves were not significantly different from one another ($\chi^2 = 0.015$; $0.89 < P < 0.92$). Control animals were anaesthetized with 10 mM sodium azide and placed on agar pads in parallel with experimental animals. To ensure that the ablation procedure was satisfactory, a sample of 5 operated animals was examined using Nomarski optics several hours after the microsurgery, and found to lack Z1–Z4. In addition, all the experimental animals were sterile and appeared to lack the gonad when viewed with a dissecting microscope. The act of ablation itself was unlikely to affect lifespan, because *daf-2* mutants still expressed the full longevity phenotype following ablation (data not shown). *b*, Lifespans of *fem-3(e1996)* mutants, which develop as females[10]. Germ-line precursors that normally differentiate into sperm differentiate into oocytes instead. In parallel with these animals, we examined a second set of animals in which Z1–Z4 had been ablated. This experiment demonstrates the reproducibility of the gonad ablation experiment. Mean lifespans were 16 days for *fem-3(e1996)* ($n = 30$); 17 days for gonad-ablated animals ($n = 23$); and 17 days for N2 controls ($n = 14$). These survival curves were not significantly different from one another: $\chi^2 = 0.01$ and $0.89 < P < 0.93$ for gonad (+) versus (−), and $\chi^2 = 0.94$ and $0.32 < P < 0.34$ for gonad (+) versus *fem-3*.



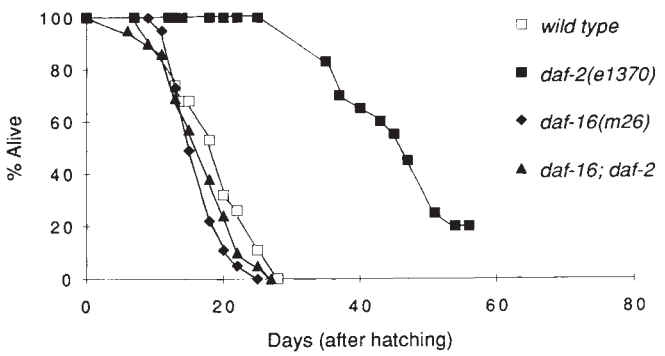


FIG. 4 The longevity of *daf-2* mutants is blocked by *daf-16(m26)*, a dauer-defective mutation in a gene that acts downstream of *daf-2* in dauer formation. Lifespans were determined in parallel for N2, *daf-2(e1370)* and *daf-16(m26)* single mutants as well as *daf-16(m26); daf-2(e1370)* double mutants. Mean lifespans were 17 days for *m26* ($n=37$); 17 days for *m26; e1370* ($n=42$); and 19 days for N2 ($n=19$). For *daf-2(e1370)*, $n=20$. The lifespan differences between N2, *daf-16* and *daf-16; daf-2* were not significantly different from one another (for example, for N2 versus *daf-16*, $\chi^2=1.68$; $0.19<P<0.21$), whereas differences between these three strains and *daf-2* were statistically significant (for example, for *daf-2* versus *daf-16*; *daf-2*, $\chi^2=50.6$; $P\ll0.00001$).

daf-2 mutations elicit an internal signal also generated by food limitation, which can extend lifespan without substantially affecting fertility or general activity. It would be interesting to learn whether lifespan extension caused by food limitation in *C. elegans* requires *daf-16* activity. Strains of *Drosophila* with mean lifespans roughly 30% longer than normal have been obtained by selective breeding[1,15]. Like *daf-2* mutants, these flies appear robust and healthy. Intriguingly, they are also resistant to starvation and desiccation[16], as is the *C. elegans* dauer. Perhaps a common underlying mechanism operates to extend the lifespans of these different types of organisms. If so, then identification of *C. elegans* genes that act downstream of *daf-16* could lead to a general understanding of how lifespan can be extended. □

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Modulation of the cell cycle contributes to the parcellation of the primate visual cortex

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AN as-yet unresolved issue in developmental neurobiology is whether the discrete areas that form the mammalian cortex emerge from a uniform cortical plate or whether they are already specified in the germinal zone[1,2]. A feature of the primate striate cortex is that the number of neurons per unit area is twice that of anywhere else in the cerebral cortex[3]. Here we take advantage of this unique structural feature to investigate whether the extra striate cortical cells are due to increased neuron production during neurogenesis. We labelled precursors undergoing terminal cell division with ^{3}H-thymidine and allowed them to migrate to the cortical plate. Cell counts revealed that their rate of production in the germinal zone of striate cortex is higher than in that giving rise to extrastriate cortex. Also, we used ^{3}H-thymidine pulse injections to investigate cell cycle dynamics and found that this phase of increased production of striate cortical cells is associated with changes in the parameters of the cell cycle. These results show that cortical area identity is at least partially determined at the level of the ventricular zone.

A total of eight ^{3}H-thymidine pulse injections have been carried out on fetal monkeys. Fetuses received an intraperitoneal injection of ^{3}H-thymidine at known gestational ages and were returned to the uterus for a survival period before being processed for autoradiographic histological observation. The position and density of labelled cells were determined in either the cortical plate or the underlying germinal zone (Fig. 1*a*). Using frequent sampling, we were able to employ a statistical test (ANOVA) to show that differences between striate and extrastriate cortex were not a result of spurious variations in labelling density in each area; we found significant differences in labelling for all ages except in the E64 case (see Table 1). Experimental cases fell into two groups (I and II in Table 1) according to the length of the survival period.

In the first group (5 cases), a long survival period of 14–84 days allowed neurons to migrate out to the cortical plate as well as a variable degree of cortical differentiation. In this group the numbers of labelled cells per unit area of cortical plate were estimated in striate and extrastriate cortex. In all cases, regardless of the age of the fetus at the moment of injection, striate cortex was found to have significantly more labelled cells per unit area than adjacent extrastriate cortex. Quantitative analysis of the results showed that there were developmental changes in the percentage increase of labelled cells in striate cortex compared with extrastriate cortex (Table 1).

Differences in labelling of striate and extrastriate cortex are illustrated in Fig. 1*b*, which shows cortical labelling in a neonate that had received a ^{3}H-thymidine pulse injection on embryonic day 81 (E81). Different intensities of labelling broadly correspond to successive generations of cells, because there is roughly a halving of labelling intensity at each mitosis[4]. The radial location of successive generations of cells can be determined from the positions of cells with maximum, 50% of maximum and 25% of maximum labelling. Besides the increased rate of cell production in striate cortex (as indicated by the higher densities of labelled neurons in this area), Fig. 1*b* illustrates two common

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