when the latter are elevated during DFMO treatment. Exogenous spermine, however, may gain access to the enzyme, perhaps through the lysosomal system. Alternatively, high intracellular levels of spermine achieved during treatment with DFMO and spermine could inhibit spermine synthase and thereby lead to an accumulation of spermidine.

Of the putrescine homologs, only DA_5 and DA_6 afforded some growth in the presence of DFMO, but this may be attributable to their conversion by the cell to $_3TA_5$ and $_3TA_6$, respectively. Apparently, the substrate specificity of spermidine synthase is broader than the structural specificity for biological function since the enzyme converted DA_7 to $_3DA_7$ (Table 2), but the latter did not support growth (Table 3). In no instance was there indication of further biological conversion of spermidine homologs to spermine homologs at a detection limit $\sim$ 5 pmole per 10^6 cells. The putrescine homolog DA_8 was not converted to a spermidine homolog. Despite having a chain length similar to that of spermidine, DA_8 did not support growth, suggesting that the central nitrogen is essential in spermidine function.

Similar data for prokaryotes has been obtained by measuring the growth of *Haemophilus parainfluenzae* (*13*) or polyamine auxotrophs of *Escherichia coli* (*14*) in media supplemented with spermidine homologs. As we have found with eukaryotes, the structural stringencies of prokaryotes for spermidine are not absolute, and limited variation in the tetramethylene moiety still permits biological function as indicated by growth. One striking difference between eukaryotes and prokaryotes is that norspermidine ($_3TA_3$) was not toxic to bacteria and substituted for spermidine in supporting growth (*14*).

Although polyamines influence various cellular reactions, particularly in vitro, many of these are nonspecific ionic interactions that probably would not impose structural constraints on the spermidine molecule. The interaction of spermidine with DNA, however, is potentially structure dependent. The spacing of the positively charged nitrogen atoms in the polyamines is particularly well suited to stabilize double-stranded regions of nucleic acids. Molecular models based on x-ray diffraction studies (*6*) indicate that the tetramethylene portion of spermidine can bridge the narrow groove of the helix, thus binding together phosphate groups on opposite double helical DNA strands, whereas the trimethylene moiety can bridge adjacent phosphate groups on the same strand. If this represents a critical biological function of polyamines, our study demonstrates that DNA exhibits unexpected tolerance for variation in the structure of spermidine. However, rotations of the cationic groups around the carbon–carbon and carbon–nitrogen bonds impart considerable conformational flexibility on these polycations, and this could account for the apparent allowances in the structural variability of spermidine.

Other intracellular functions of spermidine may also be essential for cell proliferation. Cellular protein synthesis, for example, is affected by polyamines at the transcriptional and translational levels (*14*), as are the structure and activity of transfer RNA (*15*). It may now be possible to obtain an indication of which of these or other spermidine functions are essential for cell proliferation by mapping the structural specificity of each and comparing it with that described in this report.

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9. Cells were treated for 24 hours with 1 μM MGBG in the presence and absence of 10 μM spermidine or spermidine homolog. Spermidine and spermidine homologs that competed effectively with [^{3}H]spermidine for uptake prevented MGBG-induced cytotoxicity. The putrescine homologs were not tested.
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Discrete Visual Defects in Pearl Mutant Mice

Abstract. *The mutant mouse pearl, characterized by its hypopigmentation, has a specific functional defect in a sensory system—the retina. The intact pearl mouse has reduced sensitivity in the dark-adapted condition. Normal sensitivity is restored by isolation and superfusion of the retina with bicarbonate-buffered Ringer solution, suggesting that the retinal expression of the pearl mutation depends on a diffusible substance. The pearl phenotype is described as a possible model for human congenital stationary night blindness.*

Successful analysis of neurological mutants of the mouse (*1*) depends on the ability to recognize defective phenotypes. Mutants with gross malformations or abnormalities of locomotion are easily detected; however, mutants with sensory defects are often indistinguishable from normal mice. Consequently, mutants such as reeler (*2*), dystonia musculorum (*3*), and retinal degeneration (*4*), as well as the coat-color mutants (*5, 6*), have been extensively examined, but mutants with sensory defects (*7*) have received little attention. We report here a mouse mutant that has no gross malformations or abnormalities of locomotion

or motor systems but has a functional defect within a sensory system (*8*).

The hypopigmentation mutant pearl (*5, 6, 9*) has a specific defect in retinal function—that is, decreased dark-adapted sensitivity, but has no photoreceptor degeneration. Normal sensitivity is restored in pearl by isolation and superfusion of the retina, suggesting that the retinal expression of the pearl mutation depends on a diffusable substance. Pearl is an autosomal recessive mutation in the mouse that has been mapped to chromosome 13 (*5, 6*). Sarvella (*9*) reported the spontaneous occurrence of this mutation and described it as resulting in a dilution of hair and eye pigmentation. More recently, the pearl locus has been implicated as one of several unique chromosomal sites related to coat-color mutations that also regulate kidney lysosomal function in a novel manner (*10*).

Although we identified pearl as a visual system mutant by measuring optokinetic nystagmus (OKN) (*11, 12*), the present report concerns a different disorder that we identified with subsequent investigation. The retinas of pearl mice were examined in 1-μm-thick plastic sections stained with toluidine blue and were found to have normal retinal histology (*13*); however, the density of melanosomes in the pigment epithelium was reduced in pearl (*14*). In addition, pearl's ipsilateral projections to the lateral geniculate nucleus, superior colliculus, and olivary pretectal nucleus were reduced (*11, 14, 15*). Aberrant retinal projections of this same nature have been described for a number of other murine pigmentation mutants and seem to be correlated with the reduction of pigment in the pigment epithelium (*6, 16*).

We recorded from central visual structures in intact, anesthesized pearl animals. The light sensitivities for single units recorded in the visual cortex, superior colliculus, and in the optic nerve from retinal ganglion cell axons were comparable to those of wild-type mice when measured in the light-adapted state [levels that were used during the OKN testing (*11*)]. However, the sensitivity was, on the average, 1.8 log units subnormal with dim backgrounds (see Fig. 1A). We also measured visual sensitivity for unanesthetized, unrestrained animals using a black versus white discrimination task (*17*). Pearl mice performed the task as well as wild-type animals in the light-adapted state ($> 10^{-3}$ cd/m^2). However, in the dark-adapted state, wild-type mice performed consistently better than pearl mice. Thus, behavioral experiments confirmed the subnormal sensitivity that was found in electrophysiological experiments in intact, anesthetized pearl mice.

To identify the retinal target of the pearl mutant gene we measured the electroretinograms (ERG's) in intact, anesthetized mice and measured the concentration of visual pigment in the photoreceptors and the sensitivity of the retinal ganglion cell reponses in isolated, superfused retinas. The ERG's were recorded from dark-adapted animals. The maximum amplitudes of the a- and b-waves recorded from pearl mice were, on the average, smaller than those from normal mice (*11*). However, when these values were normalized relative to the maximum voltage and plotted against stimulus luminance there was no significant difference between the half-maximum amplitudes of the a- and b-waves from pearl compared to those from wild-type mice (*11*). In isolated, superfused retinas, the concentration of rhodopsin was computed from absorbance difference spectra and was approximately equal for pearl and wild-type retinas (*18*). In addition, in the isolated retina, pearl's retinal ganglion cell sensitivity in both the light- and dark-adapted states was indistinguishable from that of wild-type animals (from either intact or isolated retinas) (see Fig. 1, A and B). This restoration of the mutant phenotype to wild-type implies that either some substance necessary for the restoration of normal function is added to the pearl retina or something deleterious is removed when the optic nerve is cut and the retina is separated from the pigment epithelium and superfused with normal mouse Ringer solution.

The work of Novak and Swank and their co-workers (*10*) suggests that pearl has a defect in the regulation of kidney lysosomal enzymes. Although the ex-

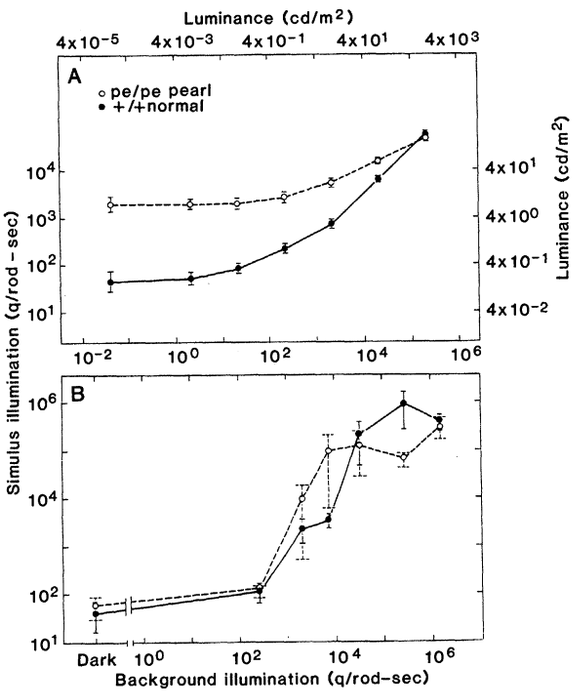

Fig. 1. (A) Increment sensitivity curves obtained from recordings of single axons in the optic tract of intact, anesthetized mice. Symbols: ○, pearl mutants; ●, wild-type mice. Sensitivity was below normal for pearl mutants when measured against dim backgrounds. Mice in this study were of the C57BL/6J inbred strain and of the congenic pearl strain, C57BL/6J *pe/pe*. Surgical preparation and recording procedures were as described (*11, 21*). For both mutant and wild-type mice most of the 120 receptive fields had concentric, center-surround organization. Sensitivity was measured as a function of background luminance for 33 cells. The inverse of the luminance that was required to evoke a criterion response was defined as the sensitivity (*22*) (ordinate); sensitivity was determined for each of many background luminances (abscissa). (Bars indicate standard error.) Two scales (illuminance = cd/m^2 and illuminance = quanta/rod-sec) are presented to illustrate the relation between these two photometric units. (B) Increment sensitivity curves obtained from retinal ganglion cell recordings in the isolated, superfused retina. Symbols: ○, pearl retinas; ●, wild-type retinas. The ordinate and abscissa are the same as described for (A). In contrast to the result from intact, anesthetized mice, the sensitivity in the isolated, superfused pearl retinas is not reduced in the dark-adapted condition. For both mutant and wild-type mice the 58 cells had concentric, center-surround organization and the response waveforms were similar to those recorded from anesthetized, intact mice. For these experiments, mice that had been dark-adapted for at least 24 hours were decapitated; the eyes were removed and placed in a dish of bicarbonate-buffered Ringer solution (NaCl, 120 m*M*; KCl, 4.8 m*M*; $MgCl_2$, 0.5 m*M*; $CaCl_2$, 1.9 m*M*; $NaHCO_3$, 25 m*M*; 2.8 m*M* Hepes; glucose, 5 m*M*; PCO_2, 40 mmHg, *p*H 7.4, PO_2, 570 mmHg, 35°C). The lens was removed and the retina was separated from the pigment epithelium and pinned vitreal side up in a 1-ml perfusion chamber with a transparent bottom. The dish was placed on the stage of a compound microscope. The retina was superfused with the Ringer solution at a rate of 1.5 ml/min. Infrared illumination was used to view the retina and position the electrode. The stimulus was focused on the retina by the microscope condenser. Action potentials were recorded with glass-insulated tungsten electrodes (*23*). Retinal illumination was measured with a calibrated photodiode placed on the microscope stage. The effective retinal illumination was calculated (*24*) with the following assumptions: (i) the rhodopsin quantum efficiency is 0.62; (ii) rhodopsin specific absorbance is 0.014/μm; and (iii) the length of mouse rod outer segments is 25 μm and the cross-sectional area is 2.27 μm^2.

pression of this defect may share some features with the expression of the retinal sensitivity defect, our results cannot establish the site of gene action for the sensitivity defect. The fact that the ERG responses are relatively normal while ganglion cell sensitivity is reduced implies that the retinal location where sensitivity is affected lies between the photoreceptors and the ganglion cells. However, this affected location may not be the site of gene action because restoration of sensitivity is possible in the isolated retina. Finally, our findings in pearl (reduced sensitivity in the dark-adapted condition, normal a-wave response, normal concentration of visual pigment, and absence of photoreceptor degeneration) suggest that this single gene mutation (*19*) may provide a mutant model for some forms of human stationary night blindness (*20*).

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18. Difference spectra were measured for isolated retinas bathed in $NaHCO_3$-buffered Ringer containing 5 m*M* NH_2OH HCl. Wild-type (N = 3): mean change in absorption (± standard error), 0.12 ± 0.3, λ_{max}, 509; pearl (N = 4): mean change in absorption, 0.16 ± 0.3, λ_{max}, 503.
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Temporal Selectivity in the Central Auditory System of the Leopard Frog

Abstract. *Amplitude modulation is a predominant temporal feature in many vocal signals. The leopard frog,* Rana pipiens, *has a class of neurons in the central auditory system that respond selectively to particular rates of amplitude modulation; these neurons can be characterized by a temporal tuning curve. Such selectivity is absent in the peripheral auditory system. This type of transformation may be fundamental in processing temporal information in the vertebrate sensory nervous system.*

The temporal structure (*1*) of species-specific vocal signals plays an important role in animal communication (*2*). The question of how the vertebrate auditory nervous system processes this information is therefore of interest. Although a great deal is now known about neural processing in the frequency domain, relatively little is known of the neural mechanisms responsible for processing information in the time domain (*3*).

A common feature in many bioacoustic signals is a periodic change in amplitude—amplitude modulation (AM)—, which is encoded in the periodicity of group discharge of single auditory nerve fibers (*4*). This raises the question, Is the neural basis of temporal processing simply the relay of this peripheral code along the central auditory pathways? We have electrophysiologically studied the peripheral and central auditory systems of leopard frogs (*Rana pipiens*). We selected anurans since temporal features, particularly AM, play a significant role in their recognition of species-specific vocal signals (*5*). We found that a novel transformation of the peripheral temporal code occurs in the leopard frog's central auditory system. This transformation gives rise to specialized neurons in the midbrain, which respond selectively to characteristic rates of AM (*6*). Each neuron's selectivity can be represented by a temporal tuning curve with a distinct "best rate" of AM.

To analyze the temporal selectivity of single neurons in the auditory nerve and in the central auditory system, we utilized sinusoidally amplitude-modulated white noise as a stimulus. The rate of AM could be varied while the spectral content of the stimulus remained constant (*7*). The eighth nerve and the optic