The increased phosphorylation of pp60$^{v\text{-}src}$ in TPA-treated cells parallels that observed for the EGF receptor, with the exception that we have consistently observed a low degree of phosphorylation of peptide C in untreated cells. Our results suggest that an interaction (direct or indirect) may take place between pp60$^{v\text{-}src}$ and the phorboid receptor kinase. The use of purified components in an in vitro reaction will determine whether protein kinase C can phosphorylate pp60$^{v\text{-}src}$.

Phosphorylation and dephosphorylation regulate the activity of numerous enzymes (*12*). Phosphorylation of tyrosine residues in the amino-terminal half of pp60$^{v\text{-}src}$ increases the protein kinase activity of pp60$^{v\text{-}src}$ (*8, 13*). Removal of the major phosphorylated tyrosine residue of pp60$^{v\text{-}src}$ does not affect the protein kinase activity or the transformation ability of the molecule in vitro (*14*). However, cells transformed by the mutated gene were able to form tumors only in immunodeficient mice (*15*). Our results suggest that phosphorylation of pp60$^{v\text{-}src}$ at serine residues can occur in a cyclic AMP–independent (in addition to a cyclic AMP–dependent) fashion. Phosphorylation of pp60$^{v\text{-}src}$ at this additional serine site could affect the enzyme in a number of ways, including alteration of enzymatic activity, substrate specificity, or subcellular localization. Preliminary immune-complex tyrosine kinase assays in which casein or angiotensin are used as substrates have revealed no overall difference in the kinase activity of pp60$^{v\text{-}src}$ immunoisolated from control cells and from TPA-treated cells. However, these assays do not rule out small differences in enzyme specificity or kinetic parameters. The effects of phosphorylation on the enzymatic activity of pp60$^{v\text{-}src}$ are not yet clear.

Note added in proof: TPA treatment of normal uninfected cells resulted in the hyperphosphorylation of pp60$^{c\text{-}src}$ at a novel serine residue (*18*).

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Abnormal Visual Pathways in Normally Pigmented Cats That Are Heterozygous for Albinism

Abstract. *The various forms of albinism affect about one in 10,000 births in the United States. An additional 1 to 2 percent of the population has normal pigmentation but is heterozygous and carries a recessive allele for albinism. The retinogeniculocortical pathways were studied in normally pigmented cats that carry a recessive allele for albinism. The cats exhibited abnormalities in their visual pathways similar to those present in homozygous albinos. These results imply that visual anomalies like those found in albinos may be present in 1 to 2 percent of the human population.*

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Over the past 20 years the abnormal retinogeniculocortical pathways in albino mammals have been described in detail (*1–7*). In mammals homozygous for the albino gene, an abnormally large proportion of the axons of retinal ganglion cells originating in the temporal retina cross to the contralateral side of the brain. As a result, in albinos both the visual thalamus [the dorsal lateral geniculate nucleus (LGNd)] and the visual cortex (areas 17 and 18) contain an abnormally large representation of the contralateral temporal retina and, therefore, the ipsilateral visual field (*2–4, 7, 8*).

We report here evidence that normally pigmented heterozygous cats with one homozygous tyrosinase-negative albino parent and one normally pigmented parent (obligate heterozygotes) have visual system abnormalities similar to those in homozygous albinos. The widely held belief that visual system abnormalities are restricted to mammals that are obviously hypopigmented and homozygous for albinism must therefore be reevaluated.

The cats used in this study were bred in our colony originating from albino cats with no measurable tyrosinase activity. These albino cats are presumed to be homozygous for a *c*-locus tyrosinase-

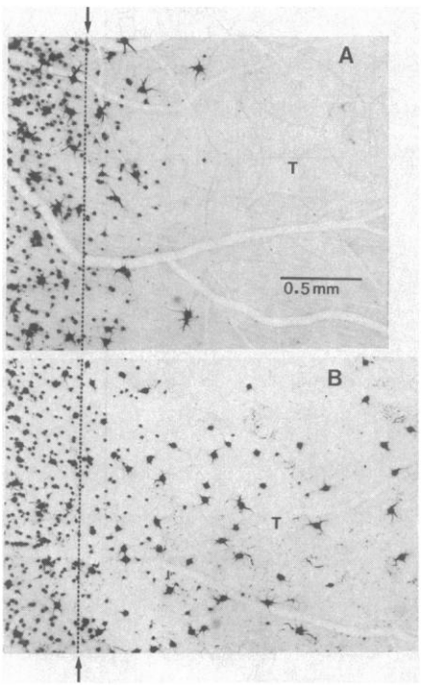

Fig. 1. Photomicrographs showing the contralateral retina of a homozygous, normally pigmented cat (A) and that of a heterozygote for albinism (B). Both animals received injections of HRP unilaterally into the LGNd. The position of the vertical meridian is indicated (arrows). The presence of many labeled cells in the contralateral temporal retina (T) of the heterozygote indicates that an abnormally large proportion of retinal ganglion axons cross at the optic chiasm and project to the opposite side of the brain.

negative allele and are not related to "deaf white cats" *(W)*. The obligate heterozygous cats appear normally pigmented but carry the recessive albino allele *(Cc)*, and, as is the case for most forms of human albinism, are qualitatively indistinguishable from homozygous normal individuals in the general population. Identification of the tyrosinase-negative heterozygote is possible only by tyrosinase enzyme assay *(9)*.

We determined the retinal distribution of ipsilaterally and contralaterally projecting ganglion cells in five cats having one normally pigmented and one albino parent. None of the heterozygotes studied were strabismic. In these animals the receptive field properties and visual field representation of cells in the LGNd and cortical areas 17 and 18 were studied. Control data were obtained on 26 homozygous normally pigmented cats from an established breeding colony that produced only normally pigmented cats.

To visualize ipsilaterally and contralaterally projecting retinal ganglion cells, we anesthetized and paralyzed the animals and injected horseradish peroxidase (HRP) through microcapillary electrodes into the LGNd or optic tract. Injections of HRP into the LGNd reveal the retinal location of ganglion cells having axons that terminate near the injection site. Electrophysiological recording from the LGNd before the injections provided an alternative means of inferring the termination zones of misprojecting fibers. The receptive field properties of neurons in the LGNd and visual cortex were studied with standard single-cell recording and visual stimulation techniques *(8)*.

After an appropriate survival time, the animals were perfused and their retinas were reacted by a procedure based on the *p*-phenylenediamine pyrocatechol reagent and cobalt intensification *(10)*. This permitted visualization of HRP reaction product in the axons, dendrites, and cell bodies of the retrogradely labeled retinal ganglion cells (Fig. 1).

Figure 1 shows the contralateral retina from a normally pigmented homozygous cat and a normally pigmented heterozygous cat. Both animals received multiple injections of HRP unilaterally into the LGNd. An abnormally large number of cells, especially the large alpha cells, were labeled in the contralateral temporal retina of the heterozygote. Labeled alpha cells extended throughout the contralateral temporal retina in this heterozygote; over half the alpha cells in the region 3 mm temporal to the area centralis projected contralaterally. Labeled medium-sized cells (beta cells) extended up to 3 mm temporal to the area centralis; about half the beta cells in the region 1 mm temporal to the area centralis projected contralaterally.

Neurons with receptive fields extending as far as 15° into the ipsilateral hemifield were recorded from injection sites in the medial part of lamina A1 of the LGNd in the heterozygotes but not in the normal cats. The receptive field positions of neurons recorded from along electrode penetrations into areas 17 and 18 are shown in Fig. 2. There is an abnormal representation of 15° of the ipsilateral visual hemifield in area 18 in the heterozygous animals. The visual field map in area 17 appeared closer to normal; only 5° of the ipsilateral hemifield was represented. In areas 17 and 18, receptive fields of cells subserving the ipsilateral hemifield were substantially larger than those subserving the contralateral hemifield (Fig. 2). This is especially striking since cells subserving the ipsilateral hemifield were recorded from the upper layers in both penetrations illustrated. Cells in the upper layers of cat visual cortex tend to have smaller receptive fields than those in the deeper layers. Also, in both areas 17 and 18, an abnormally low proportion of cells (59 percent) within 15° of the vertical meridian were activated binocularly; only 11 percent of the cells studied were activated equally well by the two eyes (Fig. 3).

We found previously in homozygous albino cats that the misprojection of axons of alpha cells is more extreme than that of beta cells *(8)*. Consistent with this, the present findings indicate that a higher proportion of alpha cells than of beta cells misproject in the heterozygote. Also, in both homozygous *(8)* and heterozygous individuals the extent of the abnormal visual field representation is greater in area 18, which receives inputs via the LGNd mainly from alpha cells, than it is in area 17, which receives considerable input via the LGNd from retinal beta cells *(11)*.

Our results demonstrate that the projections of retinal ganglion cells, as well

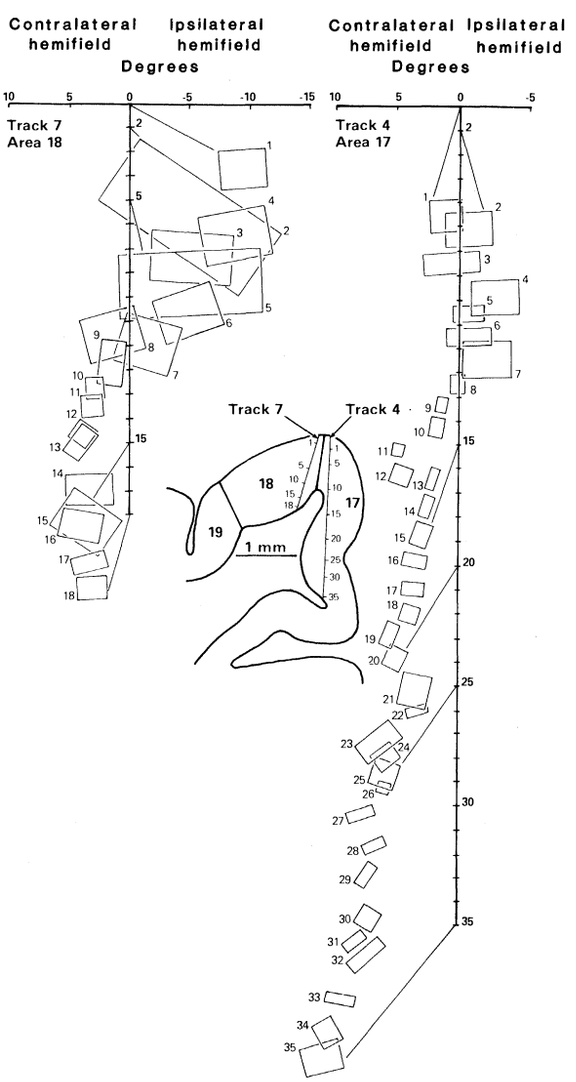

Fig. 2. Receptive field positions of neurons recorded from electrode penetrations into areas 17 and 18 of heterozygous cat visual cortex. The position and size of the receptive field of each cell studied is shown relative to the projection of the area centralis. A cell's receptive field was defined as the area in visual space within which light stimulation projected on a tangent screen evoked a response. The techniques used to determine the projection of the area centralis on a tangent screen are accurate to within about 1°. The vertical meridian is defined as the line passing through the projection of the area centralis, which is orthogonal to the line connecting the projections of the optic disks. The projections of the area centralis for successively studied fields are represented separately along the ordinate and are numbered. The positions of the electrode penetrations in areas 17 and 18 are also shown. The positions of the cells studied along the two penetrations are indicated by the numbers along the penetration. Note that 15° of the ipsilateral hemifield (cells 1 to 8 in track 7) was represented in area 18. In area 17, 5° of the ipsilateral hemifield was represented (units 2 to 7 in track 4). In homozygous normally pigmented cats no more than 1° or 2° of the ipsilateral hemifield is represented in area 17 or 18.

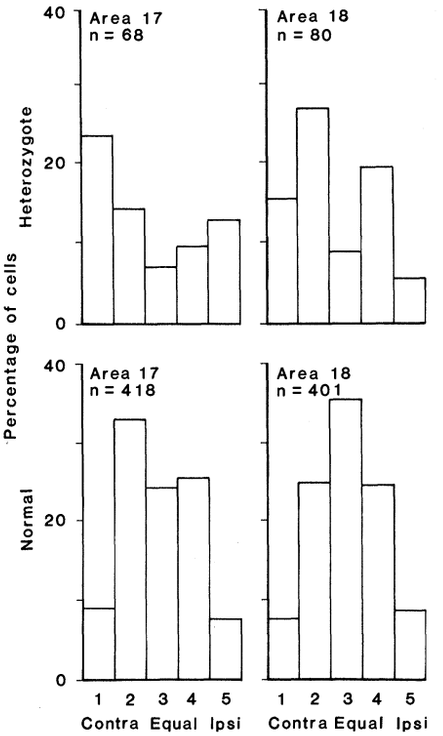

Fig. 3. Ocular dominance distributions of cells recorded within 15° of the representation of the vertical meridian in areas 17 and 18 of homozygous cats and of heterozygotes for albinism. Relatively few cells in areas 17 and 18 of heterozygotes are activated binocularly.

as the representation of the visual field in the LGNd and visual cortex, are abnormal in normally pigmented cats that are heterozygous for a recessive allele for tyrosinase-negative albinism. The retinal abnormalities we observed are similar to but less extreme than those reported for homozygous tyrosinase-negative albino and Siamese cats (*5, 6, 8, 10*). The abnormal representation of the visual field in areas 17 and 18 was close to the border between them. This is reminiscent of the pattern observed in the "Boston variety" of Siamese cats (*2–4*).

Our findings can be interpreted as evidence that the cause of the misdirected retinal projections in hypopigmented individuals is not related to reduced pigment in the retina but rather to some other unknown effect of a gene for albinism. However, the exact amount of retinal pigment in heterozygotes has not been quantified; it is possible that heterozygotes have a reduction in retinal pigment not revealed by qualitative inspection. Also, it may be that the time course of pigment production during development or some other effect of melanin pigment, not the amount of pigment produced, is critical for misrouting of retinal axons at the optic chiasm. Additional research is needed to clarify the mechanisms responsible for the visual system defects associated with albinism.

There are six well-characterized types of human oculocutaneous albinism, and evidence for several other types (*12*). Most common are types IA (tyrosinase-negative) and II (tyrosinase-positive). The frequency of type IA albinism in the United States is approximately 1:39,000 in the white population and 1:28,000 in the black population. The heterozygote frequency for this type of albinism is approximately 1 percent in the total population. The frequency of type II albinism is a little higher. Normally pigmented heterozygous individuals for these two types of albinism constitute approximately 2 percent of the population. If anomalies are also found in heterozygotes for type II albinism, then the frequency of individuals with abnormal optic projections would exceed 2 percent of the population (*13*). Thus our results suggest that visual anomalies similar to those in albinos may be present in the 1 to 2 percent of the human population carrying a recessive allele for albinism (*12*). While the functional significance of these abnormalities remains to be determined, the abnormal visual field representation and relatively low proportion of binocular cells in striate and extrastriate cortex of the heterozygote suggest an adverse effect on binocular depth perception (*14*). The presence of marked abnormalities in the heterozygote indicate that congenital nervous system defects associated with albinism (*15*), and possibly other genetically determined abnormalities, are far more widespread than previously believed.

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Glucocorticoids Potentiate Ischemic Injury to Neurons: Therapeutic Implications

Abstract. *Sustained exposure to glucocorticoids, the adrenocortical stress hormones, is toxic to neurons, and such toxicity appears to play a role in neuron loss during aging. Previous work has shown that glucocorticoids compromise the capacity of neurons to survive a variety of metabolic insults. This report extends those observations by showing that ischemic injury to neurons in rat brain is also potentiated by exposure to high physiological titers of glucocorticoids and is attenuated by adrenalectomy. The synergy between ischemic and glucocorticoid brain injury was seen even when glucocorticoid levels were manipulated after the ischemic insult. Pharmacological interventions that diminish the adrenocortical stress response may improve neurological outcome from stroke or cardiac arrest.*

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Glucocorticoids (GS's) are secreted by the adrenal cortex in response to stress; in adults they increase circulating energy substrates, stimulate cardiovascular tone, alter cognition, and inhibit costly anabolism such as growth, reproduction, and the immune and inflammatory responses (*1*). Although such actions are central to successful adaptation to acute physical stress, prolonged stress or hypersecretion of GC's has deleterious consequences, including myopathy, steroid diabetes, hypertension, infertility,

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