Normally, when one thinks of retinal projections to the brain, the great primary optic terminals of the diencephalon and of the midbrain—the dorsal lateral geniculate nucleus and the superior colliculus—come to mind. At the same time, one thinks of vision in terms of the kaleidoscope of images which are continually passing before the eyes—the train of objects and motions of differing sizes, hues, and velocities which make up the daily visual life of the sighted person.

Recently, there has been a dramatic increase in our knowledge of other retinal projections, projections which have at the moment no apparent relationship to conscious perception. Some of these retinal projections have not been consistently or clearly documented in the past and are generally obscure.

One case in point concerns the hypothalamus. Within this structure there are few nuclei as little recognized (even by neuroanatomists) as the paired suprachiasmatic nuclei of the anterior hypothalamus (Fig. 1). Yet these small nuclei, situated just above the posterior chiasm and to either side of the anterior projection of the third ventricle, have suddenly been pushed front-and-center in vision research. The immediate reason the spotlight has lit upon these tiny neural structures has been the remarkable demonstration by two independent sets of investigators—Moore and Lenn at the University of Chicago and Hendrickson, Wagoner, and Cowan in Seattle and in St. Louis (ironically, in schools that each have Washington in their name)—that the suprachiasmatic nuclei receive axonal projections that originate in the retina.

The essence of both reports is that these retinal projections are (1) exclusive—no other hypothalamic nucleus has been found to receive any direct retinal projection—and (2) universal—every mammalian species investigated from rat to monkey has this primary hypothalamic optic terminal.

These splendid new results have come about because of distinct technical advances—the development of ways to trace neural pathways autoradiographically and the establishment of criteria by which degenerating neuronal terminals can be recognized at the electron microscopic level. Each of these advances adds new dimensions to neuroanatomy. And of special importance to the problem at hand, each also excels in showing nerve fibers of fine diameter, just the nerve fibers which are most difficult to see with silver degeneration methods. When it is also realized that the two techniques are independent of each other, a quite convincing case for the validity of the reported findings can be made.

In a day in which there is more and more call for predictable results from the application of known principles, it is well to note that the powerful radioautographic techniques used to trace neural pathways in these studies came to us as a happy accident. It developed out of the work done by Droz and Leblond and by Taylor and Weiss who wanted to prove or disprove the theory of Weiss and Hiscoe that within axons there was a flow of protoplasm away from the cell body. It was only several years later that Goldberg and Kotani and Lasek and co-workers reversed the coin and used this method not to measure the rate or direction of intraxonal protein flow, but rather to mark a neural trail.

How tantalizingly close and yet how incomplete were the results with some of the older neuroanatomic methods, such as Marchi, can be appre-
Fig. 1. Phantom of rat hypothalamus from W. Krieg "The hypothalamus of the albino rat", J. Comp. Neurol. 55: 19, 1932, clearly shows nucleus suprachiasmaticus (Sch) just above the chiasm (O.C.)

Related by reading a sample of the older literature in this field. For instance, Polyak wrote of the search in monkey for retinohypothalamic nerve fibers:

"An intermediate hypothalamic optic bundle in the center, between the chiasma and the deepest point of the third ventricle, cannot be identified with certainty. A small number of slender, tangentially cut bundles, made up of very fine myelinated fibers, spreading in the lower most zone of the hypothalamus next to the chiasma, may possibly be interpreted in this way."

As Moore and Lenn point out, the identification of retinal projections to nucleus suprachiasmaticus on the basis of silver degeneration techniques is very difficult, even when the advanced Fink-Heimer technique is used and even when one has been guided to the right place by radioautographs. Apparently, silver degeneration methods work to greater effect in cold-blooded animals as there are several recent reports of retinohypothalamic projections in poikilotherms (for recent review see Ebbesson). In addition, there is one clear report of a retinohypothalamic projection in a mammal, that of Campbell for the hedgehog. In an historic vein, credit is also due Pate who, 35 years ago, clearly described transneuronal atrophy in nucleus suprachiasmaticus in the cat following unilateral enucleation.

Once it is appreciated that a direct projection of retina to hypothalamus exists in a wide array of mammalian species, questions such as "what does this nucleus do?" or, in turn, "what are the effects of light on its function?" come immediately to mind.

Several pertinent reports, some of which antedate knowledge of the visual connections of this nucleus, are already at hand to answer, at least in part, these questions. Thus Dey and co-workers showed thirty years ago that focal lesions placed between the infundibular stalk and the chiasm disturbed reproductive function in the guinea pig. In an unusually perceptive review on "the role of light in the neuroendocrine system," Critchlow wrote a decade ago of a significant advance in the understanding of function of nucleus suprachiasmaticus in the female rat. With De Groot, Critchlow prepared three series of experimental animals; animals with (1) bilateral optic tract lesions, (2) bilateral enucleation, or (3) lesions of the suprachiasmatic nuclei. Normally, female rats respond to continuous illumination with persistent cornification of the vaginal epithelium. Critchlow and De Groot reported that control animals or those that were apparently blinded by bilateral optic tract lesions responded in this manner. But animals blinded by enucleation, or sighted animals with suprachiasmatic nucleus lesions did not respond with persistent vaginal cornification to continuous illumination. Instead, either enucleation or destruction of nucleus suprachiasmaticus blocked the normal response to light. On the basis of these results, Critchlow and De Groot postulated that nucleus suprachiasmaticus was essential to the photoneuroendocrine control of vaginal cornification in the female rat.

More recently, nucleus suprachiasmaticus has
been implicated in the control of several circadian rhythms. Thus Stephan and Zucker noted loss of a circadian pattern to drinking and to locomotor activity in rats which had focal suprachiasmatic lesions. In the same vein Moore and Eichler reported loss of the circadian adrenal corticosterone rhythm in rats with similar lesions. Interestingly, when Moore and Eichler spared the nucleus suprachiasmaticus, but blinded the animals by enucleation, the daily rhythm continued, but its timing went awry. This would imply that the basic rhythm is generated in and of itself within the nucleus but that its daily synchronization is dependent upon visual input.

Lastly, important new evidence is accumulating that the daily rise and fall in enzyme levels in the pineal gland is controlled in some manner by nucleus suprachiasmaticus. Work in two laboratories has shown that in the rat the circadian variation in level of the rate-limiting enzyme in melatonin biosynthesis—the enzyme serotonin N-acetyltransferase—is abolished by electrolytic destruction of nucleus suprachiasmaticus.

In summary, it now seems clear that a direct axonal projection from retina to hypothalamus is a constant feature of mammalian neuroanatomy. All evidence to date indicates a role in the regulation of endocrine function for this pathway—a role important enough to guarantee that we shall hear much more of nucleus suprachiasmaticus in the future.

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REFERENCES