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MICROCIRCUITRY OF THE CAT RETINA

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INTRODUCTION

As a device for extracting information from a visual image, the vertebrate retina is unparalleled in its range, reliability, and compactness. Signaling in the retina is slower by six orders of magnitude than in an integrated digital circuit. The advantage of the biological structure must therefore derive from the variety of its fundamental elements and from the subtlety of their connections. Each of the five major classes of retinal neuron, whose synaptic contacts were first described systematically by Dowling & Boycott (1966), is now known to have multiple types, totaling in the cat about 60. Specific local circuits involving about one-third of these neurons have been recognized in the electron microscope. Physiological responses have also been documented for about one-third of the types, and evidence regarding the neural transmitter, or at least the sign of the synapse, has accumulated also for about one-third.

These discoveries have abundantly supported certain concepts of retinal function developed in the 1960s by Lettvin & Maturana. The function of the retina, they proposed, "is not to transmit information about the point-to-point distribution of light and dark in the image, but to analyze this image at every point in terms of . . . arbitrary contexts . . ." (Maturana et al 1960). Each of these "contexts," they suggested, corresponds to some operation on the local image performed by a ganglion cell of particular size and shape (Lettvin et al 1961). This idea, based on studies of the frog, seemed for a time inapplicable to the cat, which was thought to have a "simple" retina with only center-surround type ganglion cells. Subsequent studies to be reviewed here have firmly established for the cat the validity of this idea.

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Lettvin & Maturana also paid special attention to the stratification of processes in the frog's inner plexiform layer, believing that the operation performed by a ganglion cell is determined by specific bipolar inputs delivered to the strata of its dendritic arbor. This idea, too, was thought to be inapplicable to the cat, whose inner plexiform layer is less obviously stratified than the frog's. Studies to be reviewed here now strongly support this concept for the cat.

Nothing of the actual circuits between particular neuron types was known to Lettvin & Maturana, but fragments of such knowledge accumulated for the cat during the 1970s. Some of the first observations were extremely puzzling. It turned out, for example, that rods and cones have separate bipolars and thus apparently separate pathways to ganglion cells. But rod signals are also transmitted directly to cones, so why the separate bipolars? Further, the rod bipolar does not contact most ganglion cells, as one might have anticipated, but contacts an amacrine, which in turn contacts, not ganglion cells, but cone bipolar axons! What could be the meaning of this second convergence of rod and cone pathways, and why send the rod signal through such a tortuous route?

The functions of such apparently bizarre paths have been difficult to comprehend for the same reasons that fragments of an integrated circuit cannot be grasped except in the context of its larger diagram. Now, however, with links established between about one-third of the neuron types, broad pathways can be identified and specific hypotheses can be suggested regarding their function. The outline of a detailed mechanistic account of retinal function emerges, and many of the necessary strategies and techniques for achieving it seem at hand. In reviewing this subject now, when many puzzling findings of the last 15 years begin to fit, one is deeply impressed with the intelligence and care of the many individual studies from laboratories that literally girdle the globe.

In this article the first section reviews our knowledge of particular cell types comprising each major class of retinal neuron. Information is presented, where available, for each type regarding morphology, circuitry, distribution, transmitter, and physiology. Such details constitute the primary evidence that the retina is composed of many discrete cell types arranged in a regular mosaic. This section also serves in effect as a "parts list" for the second section, which describes a complex circuit involving thirteen types of neuron and suggests how the circuit might function.[1]

[1]Many features of the cat retina reviewed here were described first in other species. Were careful reference made in each case to this prior work, the bibliography would mushroom and the special focus on cat retina would be lost. Therefore, I have omitted reference to other species except where data is unavailable for the cat. Access to the larger literature may be found, of course, in the original papers I have cited.

CELL TYPES

In describing a cell type I refer, where the data permit, to its "coverage factor." The *physiological* coverage factor is the number of neurons of a particular type whose receptive fields overlap a particular point on the retina. It is calculated for a given point as the receptive field area (mm^2) X the cell density (cells/mm^2) (Cleland et al 1975). The *anatomical* coverage factor is similar: the number of cells of a given type whose dendritic fields overlap a particular point. It is calculated similarly, as the dendritic field area (mm^2) X the cell density (cells/mm^2) (Wässle & Riemann 1978). The coverage factor for a given eccentricity appears to be characteristic for each cell type. Another useful analytic expression introduced by Wässle & Riemann (1978) as a measure of regularity in a pattern is the ratio, mean/standard deviation. The higher this ratio, the greater the regularity. This value, too, is apparently characteristic for a given feature of a specific cell type.

Receptors

RODS   Only two types of photoreceptor have been identified in the cat retina, rods, and cones. The rod has an extremely fine outer segment, which increases in diameter (1.0 μm to 1.6 μm) and length (25 μm to 50 μm) from the periphery to the central area (A. Laties, cited by Barlow et al 1971; Steinberg et al 1973). The rod soma is small (4.5 by 6 μm) and the inner segment is narrow (2 μm). The axon is extremely fine (0.25 μm), ending in a "spherule" (3 μm diameter) in the outer half of the outer plexiform layer. The spherule, which contains mitochondria and 1–2 synaptic ribbons, is invaginated by 2–3 laterally placed processes from horizontal cells and two centrally placed processes from rod bipolars (Figure 1; Boycott & Kolb 1973, Kolb 1974, Kolb 1977). The rod spherule receives 4–6 punctate gap junction contacts from the basal processes of neighboring cone pedicles (Kolb 1977).

The response of the cat rod to light must be inferred from the responses of rods in other species and from responses of neurons postsynaptic to rods in cat. In darkness, according to Penn & Hagins (1972), a steady depolarizing electric current flows in the interstitial space and enters the rod outer segment (rat). This "dark current" is suppressed transiently by a flash, the hyperpolarizing change being termed the "photocurrent." The amplitude of the rod photocurrent increases with light intensity until the dark current is just balanced. Beyond this point, which corresponds psychophysically to rod saturation, increases in light intensity increase the photocurrent's rate of rise and greatly prolong its duration (to more than 50 min; Penn &

example, chromatic differences between cones are associated with morphological differences (Scholes 1975, Stell & Lightfoot 1975). Such correlates have not been observed in the cat, nor has the mosaic distribution of the chromatic types been determined as in goldfish (Marc & Sperling 1976) and monkey (Marc & Sperling 1977, DeMonasterio et al 1981). The antagonistic surround demonstrated for cones in the turtle (Baylor et al 1971) has not been found in cat, possibly for technical reasons (Nelson 1977).

Among the more astonishing of recent findings is the discovery that cones have input from rods (Nelson 1977). The main lines of evidence, illustrated in Figure 2, are as follows: The threshold of the 556 nm cone to a rod stimulus (blue, 441 nm) is the same as the rod's threshold and about 3 log units below the cone's threshold to a cone stimulus (red, 647 nm). The cone's response function to blue light of increasing intensity shows a break at rod-saturation, whereas its response function to red light is smooth. Finally, the rod after-effect is recorded in cones. This rod input is presumably mediated by the rod-cone gap junctions. Evidence of the reverse pathway, passage of the cone signal to rods, has not been obtained from rod bipolars, where it might have been anticipated (Nelson et al 1976). Whether this reflects rectification at the gap junction or simply dilution of the cone signal among the rods, which are at least ten times more numerous, is unknown. It seems clear, however, that rod and cone signals mix in the cone pedicle before transmission to the horizontal cells.

MOSAIC DISTRIBUTION OF RODS AND CONES   The rods are arranged in well-defined rows; each rod is surrounded by six others (Figure 3). Their density reaches a maximum of 460,000/mm^2 at an eccentricity of 10–15° and is high (275,000/mm^2) even in the central area (Steinberg et al 1973). The cone density reaches a maximum of about 26,000/mm^2 in the central area, where the rod/cone ratio is 10.6, and falls to 3100/mm^2 in the periphery where the rod/cone ratio is 90 (Steinberg et al 1973; see also Höllander & Stone 1972, Wässle & Riemann 1978).

The distribution of cones appears upon simple inspection to form a regular pattern (Figure 3). The reason for this impression, expressed by Wässle & Riemann (1978), is that the distances of each cone to its nearest neighbors are regular. The distribution of these distances is Gaussian and the ratio, mean standard/deviation, for this distribution is relatively high. A standard of comparison is the distribution of nearest neighbor distances for a random dot pattern of the same density. This distribution is skewed and the ratio, mean/standard deviation, is relatively low. Wässle & Riemann made their measurements on what is almost certainly a heterogeneous population. When these measurements can be repeated on distributions for individual cone types, the degree of regularity may be even greater. This
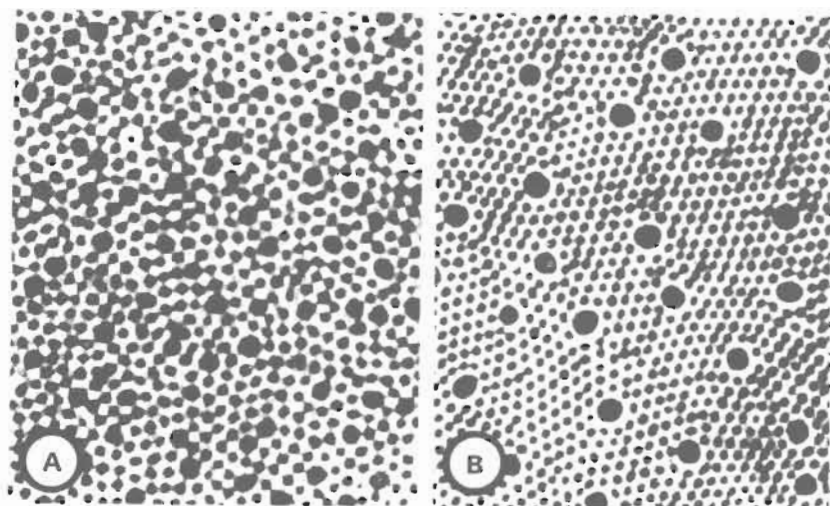
Figure 3   Rod and cone mosaic at level of inner segments. A. Central area. Density for cones, 32 X 10^3/mm^2; for rods, 338 X 10^3/mm^2. B. About 1 mm from central area. Density for cones, 11 X 10^3/mm^2; for rods, 537 X 10^3/mm^2. Reprinted from Steinberg et al (1973).

has been found to be strikingly so for blue cones in the monkey (DeMonasterio et al 1981).

Horizontal Cells

TYPES A AND B   There are two types of horizontal cell in the cat retina (Dowling et al 1966, Fisher & Boycott 1974, Kolb 1977, Boycott et al 1978). Type A has a large soma (12 by 15 μm), an indented nucleus, and 4–6 thick, filament-packed dendrites radiating to form a circular or oval field about 80 μm in diameter.[2] Type B has a smaller soma, an unindented nucleus, and densely branched, relatively slender dendrites radiating to form a circular field about 60 μm in diameter. Clusters of terminals from the finer dendritic branches of both cell types lie in register with the overlying cone pedicles to form the lateral elements of the triad. In each triad one lateral element is from type A and the other from type B (Kolb 1974, Boycott et al 1978). Neither type of horizontal cell makes or receives typical chemical synaptic contacts. The type A cells, however, commonly form gap junctions with each other and, less commonly, "basal junction"-type contacts with cone bipolars (Kolb 1977), at least one of which is the type CBb$_2$ of McGuire et al (1983b). The type B horizontal cell emits a fine (0.5 μm) axon

[2]Cell sizes and dendritic diameters, unless otherwise noted, are given for the central area.

that meanders for 300–500 μm before producing an elaborate arborization whose terminals penetrate the rod spherule to form the lateral elements of the triad. Each triad receives from two different axons (Kolb 1974, Nelson et al 1975, Boycott et al 1978).

MOSAIC DISTRIBUTION   The mosaic distribution of each horizontal cell type is regular and independent of the other. The densities of both types peak centrally and decline peripherally, though their ratio (2.7 B/A) remains constant. This decline is offset, however, by a corresponding increase in dendritic field diameter so that the coverage factor (See above) for each type remains constant at about 4 (Figure 5), except in the central area where the coverage by type B increases to 7 (Wässle et al 1978b). In a tour de force of quantitative light microscopy, Wässle et al (1978a) estimated that each type A cell contacts 120–170 cones and each type B cell contacts 60–90. (Every cone is connected with several horizontal cells of each type.) They argued that since each horizontal cell contacts at least 80% of the cones in its field, at least 60% of the cones must be common to both types and there can be no strict selectivity of cone type. The axon of type B contacts 2000–3000 rods (Wässle et al 1978a).
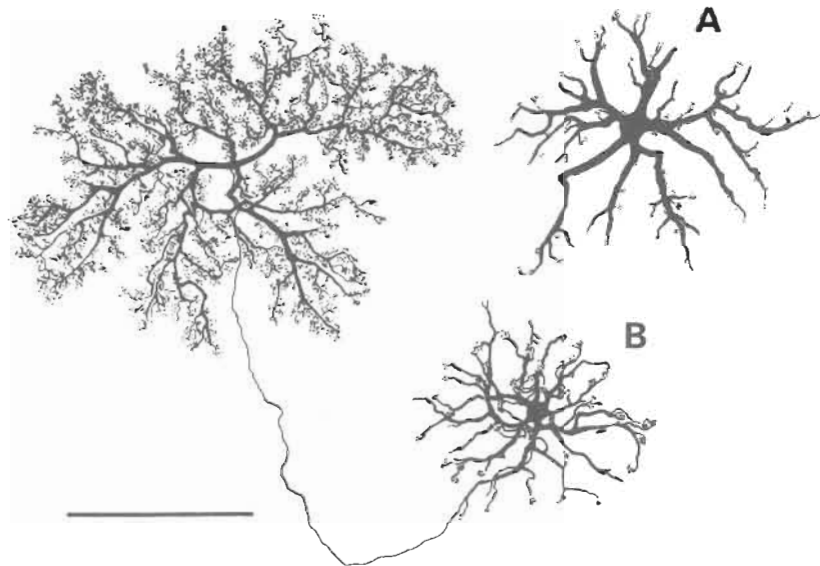

Figure 4   Type A and B horizontal cells drawn from Golgi preparations. Dendrites from the A and B somas contact only cones; axon terminal of type B (upper left) contacts only rods. Reprinted from Nelson et al (1976).
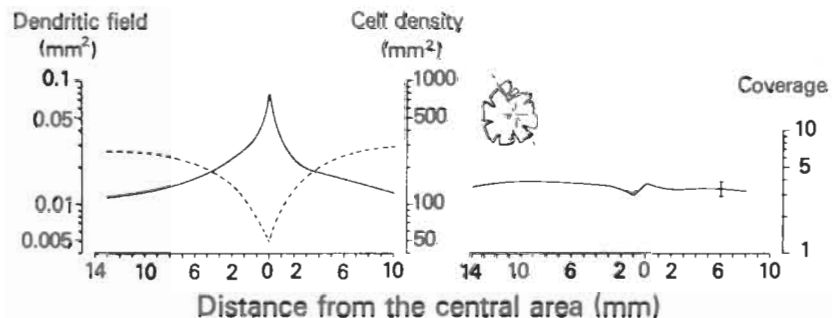
Figure 5   Coverage of retina by A-horizontal cells. A. *Left solid curve*, cell density; *dotted curve*, dendritic field area. Reciprocity of these curves holds coverage (*right*) constant across retina. Schematic retinal map indicates sampled strip. Reprinted from Wässle et al (1978b).

PHYSIOLOGY   Intracellular recordings followed by dye injection (Nelson et al 1975, Nelson 1977) show that the A and B somas and also the B axon respond to a flash of light with a sharp, sustained hyperpolarization, called the "S-potential" (Steinberg 1969a–c, 1971, Steinberg & Schmidt 1970, Niemyer & Gouras 1973). To a dim flash the response is rod-generated with a spectral sensitivity peaking at 500 nm, coincident with the absorption peak of rhodopsin (Steinberg 1969a). The amplitude of the S-potential increases with intensity to about 2.5 log units above threshold. At higher intensities (3 log units or more above threshold) the peak amplitude is saturated but the S-potential's return to baseline is greatly prolonged, and this is the rod after-effect whose basis is described above.

Rod input to the type B axon terminal probably comes directly from the rod spherule in which it is housed. This, however, is probably not the source of rod input to the type B soma because the connecting axon does not spike and seems too thin to conduct much of the rod signal passively (Nelson et al 1975). Further, were the B axon to convey rod signals, the soma's rod receptive field would be offset from its cone receptive field, but in fact they are almost exactly superimposed (Nelson 1977). The rod signal to the A and B somas is believed to be conveyed from rod spherule to cone pedicle and thence to the dendrites of these horizontal cells.

To a bright flash, three log units or more above rod threshold, the S-potential in the type A and B somas is cone-driven (Figure 6). Experiments with chromatic adaptation indicate the input to be overwhelmingly from the 556 nm cone with no evidence of contributions from the 450 or 500 nm types (Nelson 1977). The axon terminal of type B shows relatively little response to cone stimuli (Nelson et al 1975).

The horizontal cell receptive fields show spatial summation over 1.0–1.7 mm for rod stimuli and over 0.8–1.0 mm for cone stimuli (Steinberg 1969a)
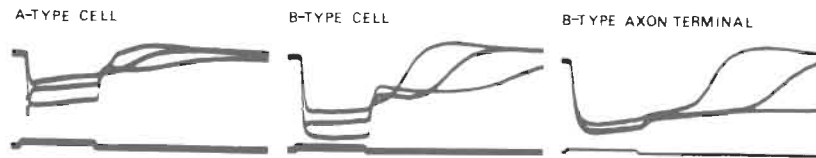
A-TYPE CELL   B-TYPE CELL   B-TYPE AXON TERMINAL

Figure 6 Horizontal cell responses to rod-saturating blue (400 nm) stimuli of increasing intensity (roughly half log unit steps). Note for A and B, somas increase in peak amplitude of hyperpolarization (cone response); this is absent for B axon. For all three elements, prolonged hyperpolarization following the stimulus (rod after-effect) increases with intensity. Reprinted from Nelson et al (1976).

with space constants ranging from 210–410 μm (Nelson 1977). The larger space constants probably belong to the type A cells with their larger dendritic fields and gap-junction interconnections (Nelson 1977). Intracellular recordings in vivo provide evidence for three classes of response based on the critical flicker frequency, but their assignment to the three anatomical types of horizontal cell process is not yet established (Foerster et al 1977a,b).

In species other than cat the horizontal cell hyperpolarization induced by a broad field stimulus feeds back to the cone as a depolarization, thereby providing the cone with an antagonistic surround (Baylor et al 1971). Cone bipolars, which share the cone triad with horizontal cell dendrites, also have antagonistic surrounds (Werblin & Dowling 1969, Kaneko 1970, Schwartz 1974). Whether the cone bipolar surrounds arise directly from horizontal cell input or indirectly via the cone's surround is unknown (reviewed by Kaneko 1979).

To assign distinct functions to the A and B horizontal cells in the cat is at this point purely speculative. One might suggest that the type A horizontal cell, activated by either rod or cone input, provides the antagonistic surrounds of the cones and/or cone bipolars. The axonal terminals of the type B horizontal cell might conceivably perform a corresponding function for rods and/or rod bipolars, but there is no evidence from any species that rods or rod bipolars have surrounds. On the contrary, rods show broad spatial summation (See above), apparently maximizing sensitivity at the expense of contrast-enhancing mechanisms. The dendritic terminals of type B might act in similar fashion to those of type A, but this would not explain why the two types should inhabit the same cone, nor would it offer a role for the axonal pathway connecting the axonal and dendritic terminals of type B.

One function for the type B horizontal cell might be to regulate the direct rod → cone pathway. This pathway might be open under mesopic illumination, giving rods access to high-acuity, cone bipolar pathways, and closed

at the end of dark adaptation when rod bipolars are thought to take over and acuity is sacrificed for the last degree of sensitivity (See Microcircuitry of the Beta Ganglion Cell Receptive Field, below; Sterling & Megill 1983). The rod after-effect recorded in the type B axon terminal, when the rods are saturated, might represent the state of adaptation. This prolonged hyperpolarization might be transduced to a chemical signal that might be conveyed by axoplasmic transport to the type B dendritic terminals in the cone pedicle. There, the hypothetical substance would hold the rod → cone pathway open. This signal would decay during dark adaptation, consequent to the decay of the rod after-effect, allowing the rod-cone pathway to close after about an hour in the dark. Such chemical signaling would require an axoplasmic transport rate of about 12 mm/day which is well within the known rates. This speculation is unsupported by evidence but links several physiological and anatomical observations for which at present there is no other interpretation.

Bipolar Cells

Cajal (1892) observed that certain bipolars in mammals are associated exclusively with rods (rod bipolars) and others exclusively with cones (cone bipolars). Boycott & Kolb (1973), examining Golgi-impregnated bipolars by electron microscopy, showed that in the cat rod bipolar dendrites do indeed form the central elements of the triad in rod spherules (Figure 1A). Rod bipolar axon terminals end in sublamina *b* of the inner plexiform layer where they receive input from reciprocal and nonreciprocal amacrines and send output to reciprocal and AII amacrines (Kolb & Famiglietti 1974, Kolb 1979, McGuire et al 1983b).

Cone bipolar dendrites were shown by Boycott & Kolb (1973) to be associated only with cones (Figure 1B). They found the dendrites of certain cone bipolars, called "invaginating," to form the central element of the cone pedicle triad and the dendrites of other cone bipolars, called "flat," to form superficial contacts with the cone pedicle at some distance from the synaptic ribbon. This distinction proved fundamental when evidence from other species showed that invaginating cone bipolars depolarize to illumination of their receptive field centers, whereas flat cone bipolars hyperpolarize (reviewed by Kaneko 1979). Surprisingly, the rod bipolar, despite its invaginating, ribbon-related dendrite, is hyperpolarizing (Figure 7A; Nelson et al 1976).

It was believed at first that axons of flat (hyperpolarizing) bipolars terminate exclusively in the outer third of the inner plexiform layer (sublamina *a*) and those of invaginating (depolarizing) bipolars exclusively in its inner two-thirds (sublamina *b*) (Famiglietti & Kolb 1976). This fit the observation that ganglion cells branching exclusively in sublamina *a* or *b* are, respec-
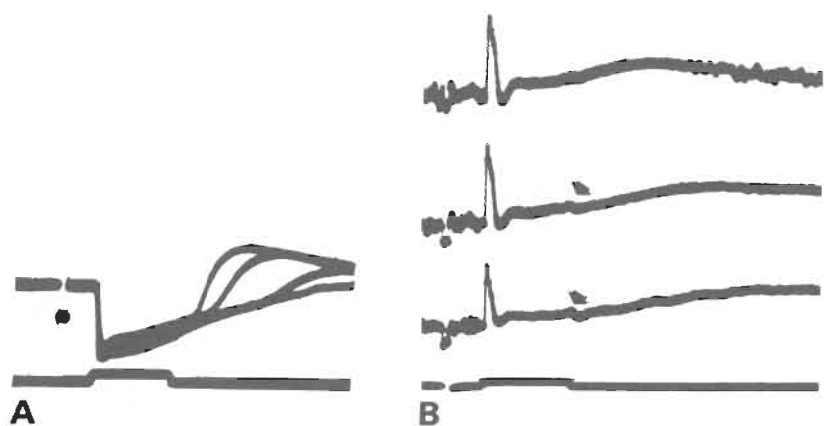
Figure 7 A. Hyperpolarizing responses of rod bipolar to rod-saturating, blue (441 nm) stimuli of increasing intensity (roughly half log unit steps). Note similarity to cone response (Figure 2A). B. Responses of AII amacrine to similar stimuli (intensity increasing from top to bottom). Note all-or-none spike followed by prolonged depolarization. Arrows mark "cone notch" seen at stimulus "off." Calibrating pulse, 2 mv; flash length 520 msec. Reprinted from Nelson et al (1976).

tively, off- or on-center (Famiglietti & Kolb 1976). In turn this implied that both flat and invaginating bipolars are excitatory, and this fit the fragmentary (though hard won) evidence from other species (see Kaneko 1979).

The situation, however, proved more complicated. Nelson (1980) found an hyperpolarizing bipolar ending in sublamina *b,* and McGuire et al (1983b) described an invaginating cone bipolar (CBa$_2$) with an axon terminal in sublamina *a.* There is reason to believe, furthermore, that at least one cone bipolar type in each sublamina is inhibitory (McGuire et al 1983b, Sterling et al 1983).

Renewed study of cone bipolars with the Golgi method now suggests at least eight types based on the morphology of the axon and its stratification and tangential spread in the inner plexiform layer (Kolb et al 1981, Famiglietti 1981). Strong support for such a robust number of types is provided by detailed reconstructions, (Stevens et al 1980a,b) performed on rod and cone bipolars from electron micrographs of serial sections (McGuire et al 1983b). These reconstructions, all taken from a small region near the central area of a single retina, provide morphological detail comparable to that of the Golgi method and simultaneously provide information on cytology and patterns of synaptic connection. This approach has so far revealed at least seven types of cone bipolar, four terminating in sublamina *a* and three terminating in *b.* Their detailed description and comparisons with the Golgi types are presented in McGuire et al (1983b). The description is restricted

here to four types (Figure 8): two from each sublamina, whose connections with other types of retinal neuron suggests their specific functions (p. 31).

In sublamina *a,* type CBa$_1$ is pale with flat cone contacts, while type CBa$_2$ is dark with invaginating contacts (Table 1). Both types get input from reciprocal and nonreciprocal amacrines, though in different proportions, but only CBa$_1$ has extensive input from the AII amacrine. Both types have output to reciprocal and nonreciprocal amacrines, again in different proportions, but only CBa$_1$ has a strong output to the AII. Both types are presynaptic to dark (off-beta) and pale (some, probably off-alpha) ganglion cell dendrites. CBa$_2$ appears to accumulate exogenous ^{3}H-glycine.

In sublamina *b,* type CBb$_1$ is pale and is believed to be invaginating, while type CBb$_2$ is darker and believed to be flat (Table 1). Both receive inputs from reciprocal and nonreciprocal amacrines in different proportions, but only CBb$_1$ makes multiple, extensive gap junctions with the AII amacrine.
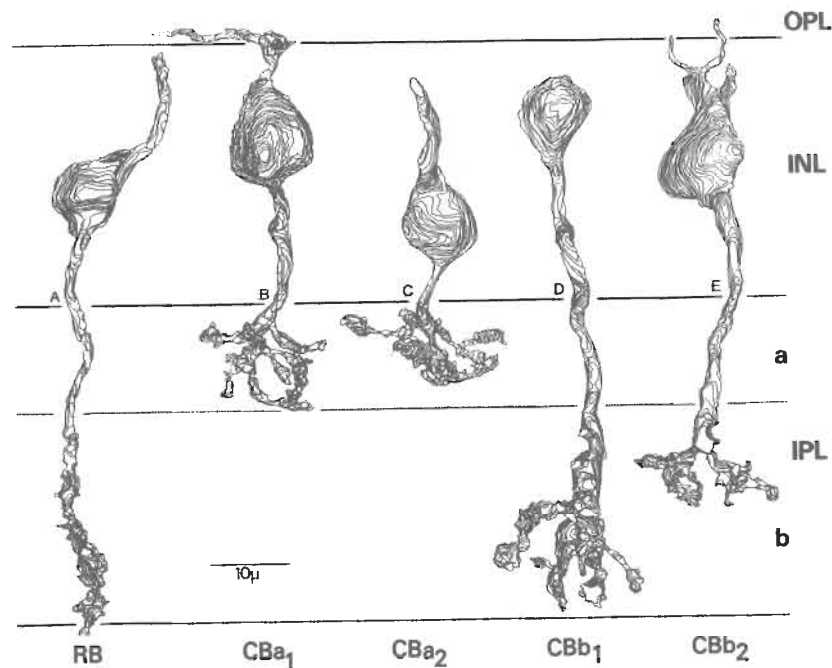

Figure 8 Five types of bipolar partially reconstructed from electron micrographs of 189 serial sections by the method of Stevens et al (1980a). RB, rod bipolar; CBa$_1$, flat cone bipolar ending in sublamina *a;* CBa$_2$, invaginating cone bipolar also ending in *a;* CBb$_1$, cone bipolar believed invaginating, ending in sublamina *b;* CBb$_2$, cone bipolar believed flat, ending in *b.* Note morphological differences in their axonal arborizations. See Table 1 for differences in input and output. IPL, inner plexiform layer; OPL, outer plexiform layer; *a, b,* sublaminae of IPL. Reprinted from McGuire et al (1983b).

Table 1   Characteristics of four types of cone bipolar[a]

Bipolar type	Cone contact	Cyto-plasm	IPL stratum	Inputs AII	NR%	R%	Outputs AII%	NR%	R%	DG%	PG%	Transmitter
CBa₁	F	pale	1, 2	36% (chem)	57	7	24	12	2	28	18	E (?)
CBa₂	I	dark	1, 2	3% (chem)	70	28	4	21	15	23	11	glycine uptake −In (?)
CBb₁	I(?)	pale	3, 5	4.5 gj	73	27	0	21	10	26	22	E (?)
CBb₂	F(?)	dark	3, 4	1 gj	44	56	0	17	20	34	4	glycine uptake −In (?)

[a]Calculated from Tables 1–3, McGuire et al (1983b). Percentages, based on small sample (1–4) of each type, indicate differences between types. AII, AII amacrine; DG, PG, dark and pale ganglion cell dendrite; chem., chemical synapse; gj, gap junction; E, excitatory; F, flat; I, invaginating; In, inhibitory; NR, nonreciprocal; R, reciprocal.

Both types have outputs, in different proportions, to reciprocal and nonreciprocal amacrines and to dark (on-beta) and pale (some, probably on-alpha) ganglion cell dendrites. CBb₂ may accumulate exogenous ^{3}H-glycine (McGuire et al 1983b, Sterling et al 1983).

Amacrine Cells

Golgi-impregnated amacrine neurons in the cat retina have been sorted into at least 22 types based on differences in soma size and in the length, stratification, and morphology of their processes in the inner plexiform layer (Kolb et al 1981). The expectation by now is strong that each morphological type will also have a specific wiring pattern and physiology. Anatomical support for this belief comes from partial EM reconstructions of amacrine processes that show consistent correlations between fine morphology and synaptic patterns (Kolb 1979, Sterling & Megill 1983). Simultaneous physiological and anatomical support for the view comes from intracellular recordings in three amacrine types followed by electron microscopy of their HRP-injected processes (Kolb & Nelson 1981).

Amacrine types have also been identified by their association with a particular neural transmitter (Table 2). Such data can not yet be perfectly integrated with the Golgi and physiological studies but we shall see (see section below on Microcircuitry of the Beta ganglion Receptive Field) that where integration is possible, rather specific hypotheses emerge regarding function.

BIOGENIC AMINES, NEUROPEPTIDES, AND ACETYLCHOLINE   One type of amacrine in the cat retina fluoresces for catecholamines (Ehinger 1966, Boycott et al 1975) and is apparently dopaminergic (Kramer 1971, Kramer et al 1971). Törk & Stone (1979) described this type as a large cell distributed at a density of 40–50/mm², whose intertwining dendrites form

rings of catecholamine fluorescence at the base of another amacrine type. Kolb et al (1981) argue convincingly that this dopamine amacrine corresponds to their wide-field (about 500 μm) amacrine, A₁₈. The coverage factor at a density of 40/mm² and a field diameter of 500 μm is 7.9. Pourcho (1981) has shown that the cell encircled by the dopaminergic rings and postsynaptic to them is the AII amacrine. An indoleamine amacrine was described along with its synaptic contacts by Holmgren et al (1981), and amacrines immunoreactive for substance P, vasoactive intestinal polypeptide, and possibly cholecystokinin have been observed by H. Karten and N. Brecha (unpublished observations). Choline acetyltransferase activity in the cat retina is less than a tenth that in the rabbit (Ross & McDougal 1976), where Masland & Mills (1979) have identified cholinergic amacrines. The enzyme in the cat retina peaks, however, in the amacrine and inner plexiform layers, thus suggesting that at least one amacrine type is cholinergic.

Table 2   Amacrine transmitters

Transmitter	Cell density	Field diam.	Coverage	Percentage of total amt. layer
Dopamine[a, b, c]	40/mm²[c]	500 μm[d]	7.9	1
GABA-accumulating:				
interplexiform[e]	90/mm²[e]	250[f]	4.4	2[e]
GABA I[g]				12[g]
GABA II[g]				5[g]
GABA III[g]				6[g]
GABA IV[g]				1[g]
Glycine-accumulating:				
AII[h, i]	5000/mm²[j]	35 μm[j, k]	4.8	25[j]
unidentified[h, i]				15[h]
				67
Indoleamine[l]				
Substance P[m]				
Vasoactive intestinal polypeptide[m]				
Cholecystokinin[m]				
Acetylcholine[n] (no morphological identification)				

[a] Ehinger (1966).
[b] Kramer et al (1971).
[c] Tork & Stone (1979).
[d] Kolb et al (1981).
[e] Nakamura et al (1980).
[f] Boycott et al (1975).
[g] Freed et al (1983).
[h] Nakamura et al (1978).
[i] Pourcho (1980).
[j] Sterling & Megill (1983).
[k] Famiglietti & Kolb (1975).
[l] Holmgren et al (1981).
[m] H. Karten and N. Brecha (unpublished).
[n] Ross & McDougal (1976).

AMINO ACIDS Gamma aminobutyric acid (GABA) and glycine are widely considered to be transmitters in the mammalian retina because of their high endogenous levels, the presence of the GABA synthetic enzyme glutamic acid decarboxylase (Graham 1972, Wood et al 1976, Brandon et al 1979), the light-evoked, calcium-dependent release of glycine (Ehinger & Lindberg-Bauer 1976), and the potent physiological effects of their antagonists (Kirby & Enroth-Cugell 1976, Kirby 1979, Saito 1981, Caldwell & Daw 1978). Many neurons in the cat amacrine layer accumulate ^{3}H-GABA or ^{3}H-glycine following intravitreal injections (Bruun & Ehinger 1974, Marshall & Voaden 1975), and the problem since this discovery has been to determine which specific amacrine types are involved and the nature of their circuitry.

Five cell types accumulating GABA have been described by partial reconstructions from serial, electron microscope autoradiograms (Freed et al 1983), and one of these has been identified more specifically as the interplexiform cell (Nakamura et al 1980). This type is known from Golgi studies (Gallego 1971, Boycott et al 1975) to ramify in the outer and inner plexiform layers. The dendritic field diameter of the best Golgi-impregnated interplexiform cell is about 250 μm (Figure 8; Boycott et al 1975), and the type is distributed near the central area at a density of about 90/mm^2. The coverage factor calculated from these figures is about 4.4. The cat interplexiform cell receives amacrine input and has output to amacrines. The cell also provides output in both the outer and inner plexiform layers to rod bipolars and cone bipolars of both the flat and invaginating types (Kolb & West 1977, Nakamura et al 1980, McGuire et al 1983b). One might well wonder what the function of such a cell could be that innervates, and perhaps affects simultaneously, all bipolars, including those with opposite responses to light. One possibility is that the interplexiform cell might function in dim light as part of a gain-control system for bipolars.

AII AMACRINE The best characterized amacrine in the cat retina is the AII, first described from Golgi and electron microscope studies (Kolb & Famiglietti 1974, Famiglietti & Kolb 1975) and later from detailed reconstructions (Sterling & Megill 1983). The AII cell, with a medium soma (about 9 μm) and narrow dendritic field (about 35 μm near the central area), sends a distinctly different set of processes to each sublamina. To sublamina b it sends radially a single stout process that branches to at least the eighth order and contains large mitochondria. To sublamina a it sends laterally fine processes that swell into large varicosities ("lobular appendages") and contain large mitochondria and synaptic vesicles.

The base of the AII soma bears roughly a dozen synaptic contacts (Sterling & Megill 1983) that are apparently from the dopamine amacrine (Pour-
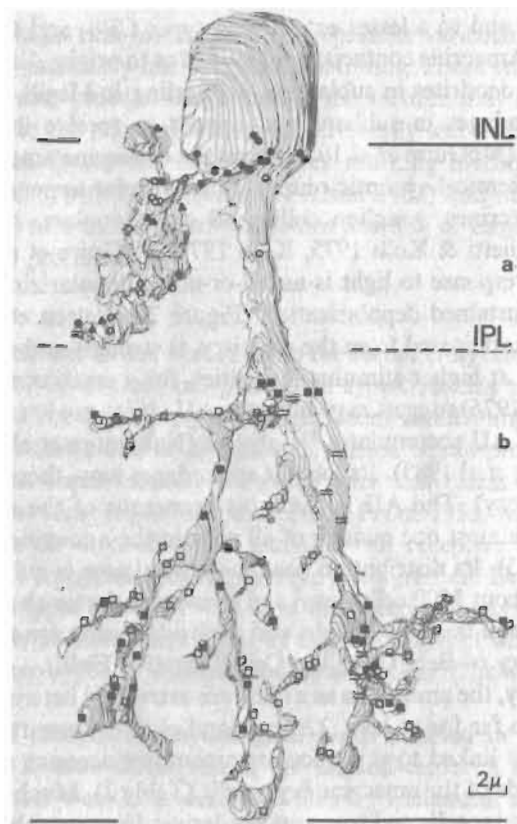
Figure 9 AII amacrine and its synaptic connections partially reconstructed from electron micrographs of 189 serial sections. Radial process branches in sublamina b; receives input from rod bipolars (□) and unidentified amacrine (■) and has gap junctions (=) with cone bipolars (primarily type CBb$_1$). Lobular appendage in sublamina a and soma receive amacrine (probably dopamine) input (•); lobular appendage receives input also from cone bipolar CBa$_1$ (o) and has outputs to cone bipolars CBa$_1$ and ganglion cell dendrites (Δ). Reprinted from Sterling & Megill (1983).

cho 1981). The AII arborization in sublamina b collects numerous synaptic contacts from rod bipolars (Famiglietti & Kolb 1975). One rod bipolar axon can contribute at least nine contacts to a single AII, and the amacrine as a whole may collect from as many as 30 rod bipolars, representing the convergence of an estimated 420 rods (Sterling & Megill 1983). The AII cells near their rod bipolar inputs make small gap junction contacts with each other (Kolb 1979). Large gap junctions are established between the AII processes and certain cone bipolar axons (Famiglietti & Kolb 1975, Kolb 1979). Detailed reconstructions show these to be principally with cone

bipolar CBb_1 and to a lesser extent with types CBb_2 and CBb_3 (McGuire et al 1983b). Amacrine contacts, unidentified as to origin, distribute sparsely over the AII dendrites in sublamina b (Sterling & Megill 1983). The AII lobular appendages in sublamina a appear to receive input from cone bipolar CBa_1 (McGuire et al 1983b) and the dopamine amacrine (Pourcho 1981). The chemical synaptic output of the lobular appendage is directed to other amacrines, ganglion cells, and cone bipolars, specifically type CBa_1 (Famiglietti & Kolb 1975, Kolb 1979, McGuire et al 1983b).

The AIIs response to light is an all-or-none, depolarizing transient followed by a sustained depolarization (Figure 7b; Nelson et al 1976). This response, as anticipated from the circuitry, is strongly rod-driven. There is also evidence at higher stimulus intensities, for a small cone signal, which Nelson et al (1976) suggest may enter the AII via its gap junctions with cone bipolars. The AII accumulates ^{3}H-glycine (Nakamura et al 1978, Pourcho 1980, Sterling et al 1983). Its lobular appendages may, therefore, be glycinergic (inhibitory). The AII is the most numerous of the amacrine types, representing almost one quarter of all cells in the amacrine layer (Sterling & Megill 1983). Its distribution near the central area is quite regular, with a density of about 5000 cells/mm^2 and a coverage factor about 4.8. Possible roles for this cell in states of light and dark adaptation are suggested below (Microcircuitry of Beta Ganglion Cell Receptive Field).

In summary, the amacrines as a class are extremely heterogeneous. There is evidence so far for at least 22 types and eight transmitters. Such types as are already linked to a particular transmitter account numerically for over two-thirds of the amacrine layer cells (Table 2). Much of the evidence linking particular cells and transmitters derives from morphological studies following in vivo transmitter accumulation. That a correspondence exists between a cell's morphology and its accumulation of a particular transmitter has been firmly established. It remains to be determined whether such accumulation invariably reflects a cell's *use* of that transmitter. Evidence on this point is badly needed and can be gathered by localizing antibodies to transmitter-synthesizing enzymes.

The distribution in the retinal mosaic has been determined for three cell types in the amacrine layer (Table 2). In each case the distribution is quite regular, but the density can vary between types by a factor of more than 100. The dendritic field area varies inversely with density so that every point on the retina falls within the field of at least one member of each type. The range of coverage factors (4.4–7.9) is, so far, surprisingly narrow. For only one type, the AII, is there detailed knowledge of circuitry. One reason is that electron microscopy of Golgi-impregnated amacrines has been hampered by the difficulty of obtaining good ultrastructural preservation. Serial reconstruction has also proved difficult because the large amacrine profiles,

so obvious in a single thin section, mostly represent varicosities that are interconnected by extremely fine cytoplasmic strands. These strands, being in thickness the same order of magnitude as the section, may be followed when orthogonal to the plane of section but are easily lost when they turn tangentially (Ellias & Stevens 1980). Newer marking methods such as intracellular staining with HRP (Kolb & Nelson 1981) and immunocytochemical staining with monoclonal antibodies Sterling & Lampson 1983) hold considerable promise.

Ganglion Cells

Ganglion cells in the cat retina, according to the recent Golgi study of Kolb et al (1981), are of 23 distinct morphological types. At this point in the present review such a figure may no longer seem astonishing. But it is sobering to realize that a decade ago this conclusion would probably have been judged to be unpublishable. To grasp why this claim now seems reasonable requires some historical perspective. From 1953, when Kuffler first described the on- and off-center ganglion cell receptive fields, until 1966, only these two physiological types were distinguished. Evidence suggesting additional types (Wiesel 1960) went unappreciated. As to morphological types, many had been illustrated by Cajal (1892), but whether these represented discrete types or a continuum was unclear (Brown & Major 1966).

The number of recognized physiological types doubled in 1966 when Enroth-Cugell & Robson distinguished on- and off-center X and Y type ganglion cells. These were later described also by Cleland et al (1971) as "brisk-sustained" and "brisk-transient." By 1974 fully a dozen physiological types had been described (reviewed by Rodieck 1979, Rowe & Stone 1977, Stone et al 1979), and in that year as well the problem of morphological typing was dramatically clarified.

The crucial step in defining discrete morphological types of ganglion cell was to compare neurons at equivalent retinal positions (Boycott & Wässle 1974). With this approach, two fundamental types, termed alpha and beta, suddenly became obvious (Table 3). The alpha has a large soma and axon and a wide-field (180–1000 μm diameter), sparsely branched, dendritic tree. The beta has a medium soma and axon, and a narrow-field (20–300 μm diameter), densely branched, dendritic tree (Figure 10). Each type is represented at *all* eccentricities and increases in size from center to periphery. Evidence that alpha cells are physiologically brisk-transient (Y) while beta cells are brisk-sustained (X) was obtained from comparisons at a given eccentricity between soma and dendritic field size on the one hand, and axonal conduction velocity and receptive field center size on the other (Cleland & Levick 1974).

Table 3 Characteristics of alpha and beta ganglion cells in central area

Cell type	Soma size	Sub-lamina of dend. strat.	Dend. field diam.	R.F. center diam.	Density	Physiol. coverage
on-alpha	17 μm[a]	b	180 μm[b]	175 μm[d]	77/mm²[c]	1.35[a]
off-alpha	17 μm[a]	a	180 μm[b]	175 μm[d]	94/mm²[c]	1.7[a]
on-beta	13 μm[e]	b	20 μm[b]	66 μm[d]	3250/mm²[d]	11[d]
off-beta	13 μm[e]	a	20 μm[b]	66 μm[d]	3250/mm²[d]	11[d]

Cell type	Inputs[k] from:				Output[j] to:
	CBa_{1-4}[f,g]	CBb_{1-3}[f,g]	AII lob. append.[h,i]	AII via CBb_1[h,i]	
on-alpha	−	+	−	+	Lgn, Sc
off-alpha	+	−	+	−	Lgn, Sc
on-beta	−	+	−	+	Lgn
off-beta	+	−	+	−	Lgn

[a] Wassle et al 1981a.
[b] Boycott & Wassle 1974.
[c] Calculated from Wassle et al 1981a.
[d] Peichl & Wassle 1979.
[e] Wassle et al 1981b.
[f] McGuire et al 1983b.

[g] McGuire et al 1983c.
[h] Sterling & Megill 1983.
[i] Kolb 1979.
[j] Reviewed by Rodieck 1979.
[k] Known only for region 1–2° from central area.

Cleland et al (1975) mapped the position of every brisk-transient cell in a small patch of retina. Subsequently they identified all the alpha cells in the same patch and showed the correspondence to be essentially complete. They showed further that over a wide range of eccentricities every retinal locus is covered by the receptive fields of 3–7 alpha cells. Although the distribution density of alpha cells declines from the central area outward, at each locus they are a constant fraction (about 4%) of the total ganglion cell population (Wässle et al 1975). Their increase in dendritic field diameter with eccentricity offsets their decline in numbers; this is the reason the coverage factor is constant.

When Boycott & Wässle (1974) pointed out the resemblance between a central alpha cell and a peripheral beta cell, the root of much doubt and confusion was exposed. Since then, anatomical observations have been reported in the context of their eccentricity; hence the conclusion of Kolb et al (1981) that there are several dozen types of ganglion cell is convincing. Boycott & Wässle (1974) also described several types of smaller ganglion cells with rather wide dendritic trees, termed gamma and delta, and to this Leventhal et al (1980) have added the epsilon cell. Kolb et al (1981) have
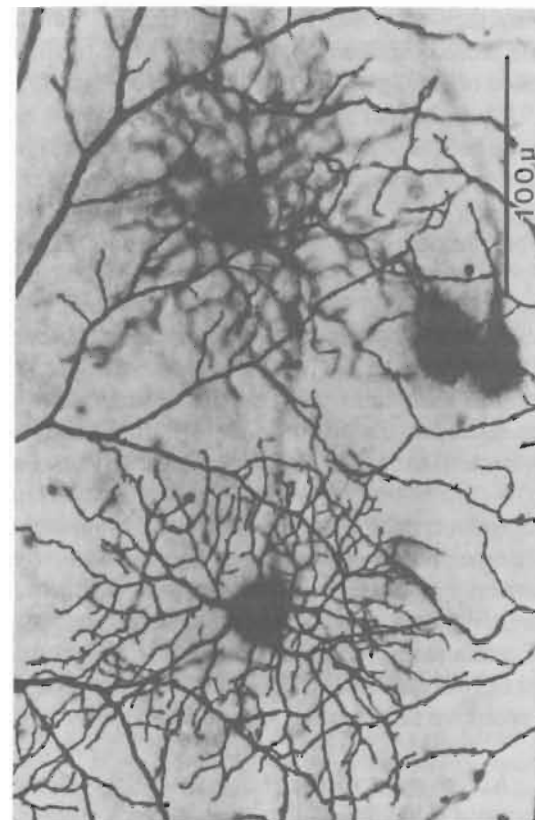
Figure 10 Micrograph from retinal flat-mount stained with Golgi-Cox. Focal plane through sublamina *b* of inner plexiform layer. Narrow-field cell with bushy dendrites on left is an on-beta ganglion cell. Matching cell on right with dendrites out of focus in sublamina *a* is off-beta. Sparsely-branched dendrites, belonging to two on-alpha cells, overlap the whole field. Reprinted from Wässle et al (1981b).

also recognized the gamma and delta types, terming them, respectively, G_3 and G_{19}. These types probably have physiological counterparts among the heterogeneous W category (see Rodieck 1979). Because so little is known of their circuitry, these types are omitted here from further discussion.

The next crucial observation in developing a typology for ganglion cells was made by Famiglietti & Kolb (1976). They noticed that the dendrites of both alpha and beta cells stratify either in the outer third of the inner plexiform layer (sublamina *a*) or in the inner two-thirds (sublamina *b*) (Figure 10). Believing that invaginating (depolarizing) cone bipolars end exclusively in sublamina *b* and flat (hyperpolarizing) cone bipolars end

exclusively in *a*, they proposed that ganglion cells branching in *b* are on-center, while those branching in *a* are off-center. Intracellular recordings from ganglion cells followed by dye-injection confirmed this conjecture (Nelson et al 1978). Only later was it learned that flat and invaginating cone bipolars innervate *both* sublaminae (see Section above on Bipolar Cells). In summary, dendrites of off- and on-center ganglion cells stratify, respectively, in sublaminae *a* and *b* (see also Peichl & Wässle 1981, Wässle et al 1981b), and appear in each sublamina to receive input from both depolarizing and hyperpolarizing bipolars (McGuire et al 1983b,c,).

ALPHA CELLS   Knowledge of the on- and off- alpha cells' dendritic stratification permitted Wässle et al (1981a) to work out, using neurofibrillar stains selective for alpha cells, their detailed distributions in the retinal mosaic. The on-alpha was found to be slightly smaller and less numerous than the off-alpha, and the coverage factor for each type, respectively, was 1.4 and 1.7. The distribution of somas formed a regular lattice independently for each alpha type. For such a lattice the ratio, mean/s.d., for the distribution of nearest neighbor distances is about 4.5 whereas this ratio for a random distribution of the same density is 2.4. By this measure (mean/s.d.) the distribution of on-alpha dendritic field diameters for a small patch of retina is also extremely regular, the numerical value being 10.9 (Wässle et al 1981a). Peichl & Wässle (1979) found similar regularity in the size of receptive field centers within a small patch of retina.

BETA CELLS   Across most of the retina the beta cells constitute about 55% of the ganglion cells, the on-betas being slightly less numerous than the off-betas (Peichl & Wässle 1979, Wässle et al 1981b). Their density is highest in the central area (about 3250 cells/mm² for each type; Peichl & Wässle 1979) and their dendritic fields the smallest (about 20 μm diameter; Boycott & Wässle 1974). Each beta type forms a regular lattice (Figure 11) that is independent of the other, and provides an anatomical coverage factor in the central area of about one. The minimum diameter of the physiological receptive field center is about 66 μm, providing a *physiological coverage* for each type of about 11 (Peichl & Wässle 1979). This spacing and field size matches closely, according to Hughes (1981), the optimum predicted from sampling theory for a system that can resolve about 6 cycles/deg. using elements with the cut-off frequencies of the beta cells (Cleland et al 1979). Thus the evidence grows that the maximum spatial resolution demonstrated behaviorally in cat (6 cycles/deg; reviewed by Hughes 1981) depends on the simultaneous reports from these two types of beta ganglion cells. This is consistent with the observation of Berkeley & Sprague (1979) that the major effect of removing area 17 (to which beta cells project via the lateral geniculate nucleus) is a loss of spatial resolution.
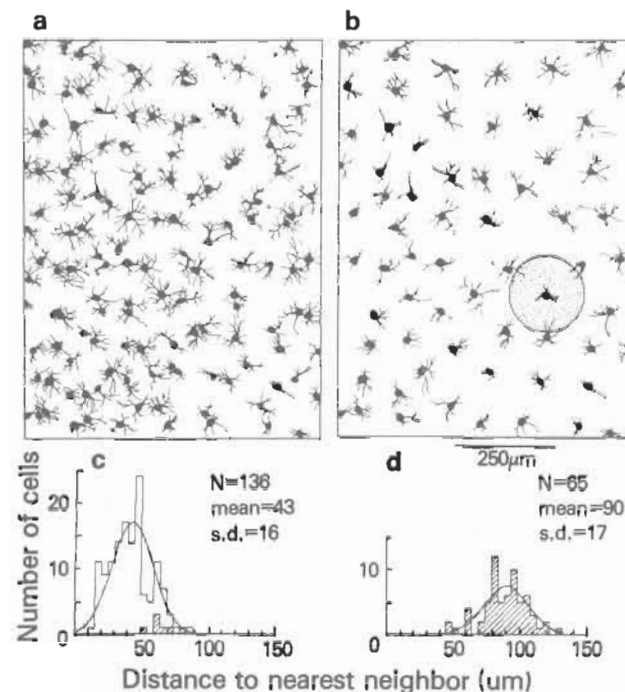
Figure 11   (*a*) Retrograde filling by HRP of all beta cells in a small field. (*b*) Same field with only on-betas drawn. Note regularity of mosaic. Stippling indicates dendritic field of a beta cell from Golgi material at same eccentricity. Below, distributions of distances to nearest neighbor for drawings above (*c*) Mean/sd for all betas is 2.7. (*d*) Mean/sd for on-betas only is 5.3. Reprinted from Wässle et al (1981b).

CIRCUITRY OF ALPHA AND BETA GANGLION CELLS   Once the alpha and beta types of ganglion cell were defined by light microscopy, they could be recognized in serial sections at the electron microscope level and a start could be made in defining their circuitry. The first observations showed that the inputs to each type are not on the soma but are concentrated on the dendrites in the sublamina of the cell's major arborization (Kolb 1979, Stevens et al 1980b). Beta cells receive about 70% of their input from cone bipolars, whereas the alpha cells get relatively more of their input from amacrines (Kolb 1979). McGuire et al (1938b) found that all four cone bipolar types in sublamina *a* (CBa$_1$–CBa$_4$) and all three types in sublamina *b* (CBb$_1$–CBb$_3$) contact dark ganglion cell dendrites (presumed beta) and pale ganglion cell dendrites (some probably alpha). Thus, whatever information is conveyed to the inner plexiform layer by this heterogeneous group of bipolar neurons, it all appears to reach both the alpha and the beta ganglion cells.

The convergence onto on- and off-beta cells from two pairs of cone bipolars was reconstructed in more detail (McGuire et al 1983c). The partially reconstructed beta cells had adjacent somas near the central area and overlapping dendritic fields estimated to be 30–40 μm diameter. The on-beta reconstructed to its sixth order branches received a total of 69 synaptic contacts from three CBb_1 cells and 34 contacts from a single CBb_2 (Figure 12). The contacts from CBb_1 were concentrated on the proximal dendrites in strata 4–5, while those from CBb_2 were concentrated more distally in strata 3–4. The off-beta, reconstructed to its seventh order branches, received 23 contacts from a single CBa_1 and 14 from a CBa_2. The actual proportions of input from the different bipolar types cannot be read from these data because the reconstructions were incomplete. It was estimated, for example, that the on-beta might actually collect as many as 400 contacts from up to six cone bipolars. Clearly, however, each type of beta cell receives substantial input from at least two types of cone bipolar. the possible functions of these arrangements are discussed below (See Microcircuitry of the Beta Ganglion Cell Receptive Field).
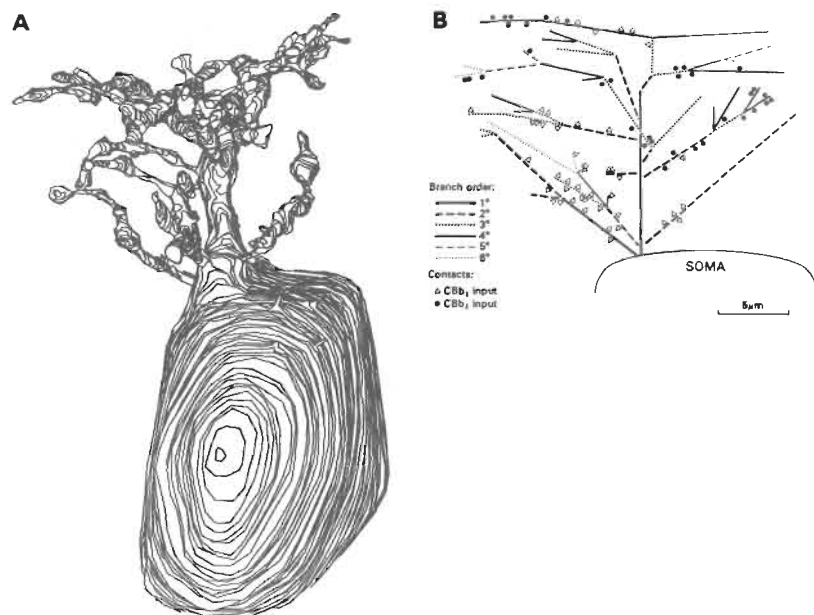

Figure 12 A. On-beta ganglion cell partially reconstructed from electron micrographs of 189 serial sections. B. Branch schematic of same cell, showing branches to the sixth order and distribution of inputs from cone bipolars CBb_1 ($\triangle$) more proximally and CBb_2 ($\bullet$) more distally. Reprinted from McGuire et al (1983c).

The diameter of the receptive field center of an alpha cell corresponds almost exactly to the diameter of its dendritic field. In contrast, the receptive field center of the beta cell is about three times larger than its dendritic field (Peichl & Wässle 1979). According to Hochstein & Shapley (1976), the alpha's receptive field center contains nonlinear subunits corresponding roughly in size to the beta's receptive field center. These authors suggested that both the subunit of the alpha cell and the full receptive field center of the beta cell might correspond to the receptive field of a single bipolar.

Although it is now clear that each beta cell receives from several bipolars, this basic idea may still have merit. The relation between a single cone bipolar and its target beta cell is strong, the narrow-field bipolar richly enveloping the beta's dendritic tree and investing it with multiple contacts (Kolb 1979, McGuire et al 1983c). These contacts distribute widely over the beta's dendritic tree, which might contribute to the linear summation of their postsynaptic effects (Rall 1967). The relation of the same cone bipolar and its target alpha cell is both weaker and more punctate, the bipolar contributing a smaller number of contacts to a relatively short segment of the alpha dendrite. The postsynaptic effects of these contacts, which are locally concentrated, might tend to sum nonlinearly (Rall 1967). Obviously, more detail must be gathered on the alpha cells' circuitry before this argument can be pursued.

Summary of Retinal Cell Types

The crucial insight emerging from the work reviewed here is that the neurons in the cat retina belong to discrete types. A "type" has come to be defined by the regular association of particular morphological, cytological, connectional, chemical, and physiological features. Thus, among ganglion cells, neither soma size nor dendritic branching pattern alone defines a fundamental type. The strict association, however, of medium size and "bushy" dendritic branching restricted to sublamina *b*, and the physiological properties, "X-ness," brisk-sustained, and on-center, define what is almost certainly a fundamental type, the on-center beta/X cell. Similarly, the accumulation of a particular neural transmitter does not define a type because neurons of several different morphologies accumulate the same transmitter. But a strict association between accumulation of a particular transmitter, such as glycine, and a distinctive morphology, connectivity, and physiology does define a fundamental type, the glycine-accumulating, depolarizing, AII amacrine. Each type, so defined, turns out to have a characteristic stoichiometry and distribution in the retinal mosaic; thus further supporting the idea that the type is fundamental.

In certain respects, the definition of a type is not absolute but relational. Thus, the on-alpha cell cannot be defined by its absolute dendritic field

diameter because this increases about five-fold from center to periphery. Nor can the on-alpha be defined by its absolute distribution density, because this falls from center to periphery by about sixteen-fold. The relation *between* these two features is strong, however, so that coverage factor at every retinal locus is the same and this becomes a defining feature of the type. Furthermore, although the on-alpha's absolute density changes, its fractional relationship to the other ganglion cells remains constant across the retina at about 4%, and this, too, is a defining feature. The same is true physiologically. Absolute receptive field size rises from center to periphery, but the fundamental properties, Y-ness, brisk-transient, and on-center, can be recognized at every eccentricity. This is probably because the synaptic relations are constant between the on-alpha and the various cell types that provide its input. Direct evidence on this point is badly needed.

For a particular cell type at a given retinal locus there is evidence, though still fragmentary, for a surprising degree of regularity of feature. Thus, the distances between neighboring cells of a particular type form a relatively narrow, Gaussian distribution, the ratio, mean/sd, (see Cell Types, above) ranging from 3.5–6.5 (Table 4). The soma diameters for a particular type at a particular locus are similarly regular, the ratio, mean/sd, for each of five types ranging from 5.4 to 7.7 (Table 4). Similar regularity has been observed for the dendritic field diameters of on- and off-alpha ganglion cells; the mean/sd for their distributions is about seven (Table 4). The synaptic relationships between particular cell types may be even more highly regular (Table 4; McGuire et al 1983b). Thus, inputs to adjacent rod bipolars from reciprocal and nonreciprocal amacrines form rather constant fractions of the total input, and rod bipolar outputs to each of these amacrines form rather constant fractions of the total output (mean/sd, 10.3–46.4). Inputs and outputs of the cone bipolar CBb_1 are similarly regular (mean/sd, 6.0–16.3).

Considered simply as nervous tissue, a small patch of cat retina resembles in some ways an invertebrate ganglion. Both tissues are composed of many discrete cell types, each highly regular in size, distribution, synaptic connections, and neural transmitter. Just as the developmental rules for forming an invertebrate ganglion are repeated for each segment with appropriate modification, so the rules for forming a patch of the mosaic seem to be repeated with appropriate modification across the retina. Possibly, mammalian neurons are wired with a precision similar to that for which the invertebrates are famous (Sterling 1982). If so, perhaps there exist wide similarities across phyla in the principles, if not the detailed instructions, by which nervous tissue is formed. Such speculation aside, an appreciation of retinal tissue as composed of many definite types has sharpened the confidence of microscopists that even subtle differences between cells can have meaning and has led to a renewed and truly inspired microscopy.

Table 4 Quantitative evidence for regularity of feature in certain cell types

	Coverage factor[a]	Distance nearest neighbor	Soma size	Axon diam.	Dend. field diam.	Total input from (%): Recip. Am	Non Recip.	All	Total output to (%): Recip. Am	Non Recip.	Dark Gang.	Pale Gang.
cone		6.5[g]										
A-horizontal	4[c]	6.7[h]										
B-horizontal	7[c]	6.0[h]										
rod bipolar			7.7[k]	11.5[k]		46.4[k]	16.9[k]	10.3[k]	17.9[k]			
cone bipolar CBb₁						6.0[k]	16.3[k]		7.4[k]	12[k]	13[k]	9.9[k]
interplexiform	4.4[d]	3.5[i]										
on-alpha	1.4[c]	4.5[e]	5.9[e]		7.5[e]							
off-alpha	1.7[e]	4.7[e]	6.6[e]		6.7[e]							
on-beta	11[f]	5.3[j]	5.4[j]									
off-beta	11[f]	5.3[j]	5.4[j]									

Mean/SD[b]

[a] Horizontal and ganglion cell values are for central area.
[b] Ratio introduced by Wassle & Riemann (1978) as a measure of regularity in a pattern.
[c] Anatomical coverage, Wassle et al 1978b.
[d] Anatomical coverage, calculated from Nakamura et al 1980 and Boycott et al 1975.
[e] Wassle et al 1981a.
[f] Physiological coverage, Peichl & Wassle 1979.
[g] Wassle & Riemann 1978.
[h] Wassle et al 1978b.
[i] Calculated by M. Freed from data in Nakamura et al 1980.
[j] Wassle et al 1981b.
[k] McGuire et al 1983b.

COVERAGE FACTOR   The coverage factor (see Cell Types, above) has been determined for nine cell types (Tables 2–4). In every case coverage is complete. It has been determined for six types that the coverage is largely constant across the retina from center to periphery. Because cell density falls continuously across the retina while dendritic field diameter rises, a constant coverage factor implies a close matching of these two parameters at every eccentricity. This appears to be a large scale regularity that should perhaps be distinguished in our thinking from local regularities such as dendritic field diameter, cell spacing, and synaptic connections.

Certain cell types, the wide-field, sparsely distributed, alpha ganglion cells, for example, have small coverage factors (1.4–1.7), close to the minimum required for completeness. Other types, such as the narrow field, densely distributed, beta ganglion cells, have much larger coverage factors (as large as 11, in the central area). It is believed that the beta cell's large coverage is not redundant. Rather, the particular combination of receptive field size and density that produces such a coverage appears matched to the optimum predicted by sampling theory for a system resolving about 6 cycles/deg (Wässle et al 1981b, Hughes 1981). The distribution density of the narrow-field, AII amacrine resembles that of the beta ganglion cells, and this is probably because the AII forms the beta cell's dark-adapted receptive field (see below). On the other hand, the dopamine amacrine, a cell that

provides input to the AII, is wide-field and sparse, suggesting that the information it conveys to the AII is poor in spatial detail. Such observations as a whole suggest that the coverage factor for each cell type reflects the specific role of that type and that coverage beyond the minimum has little to do with abstract notions of "redundancy" (Sterling 1982).

MICROCIRCUITRY OF THE BETA GANGLION CELL RECEPTIVE FIELD

The preceding sections described individual elements and anatomical circuits linking photoreceptors to ganglion cells. An obvious next step is to infer which of these circuits form the actual physiological pathways that generate the ganglion cell receptive fields. With this aim I consider for the beta cell a circuit involving 13 neuron types. Connections between eight of these types, reconstructed directly from a series of 189 thin sections, are shown in Figure 13. Two ganglion cell somas, an on- and an off-beta, abut each other in the series, and their dendritic fields overlap, but in Figure 13 they are teased apart for clarity.

Major input to each beta cell is from a pair of cone bipolars, each of which is presumed to have a center and an antagonistic surround. The bipolars seem to be arranged in "push-pull" fashion; that is, excitation delivered from one bipolar to the beta cell is accompanied by withdrawal of inhibition delivered by the other, and vice-versa (Figure 14). For the on-beta cell, one
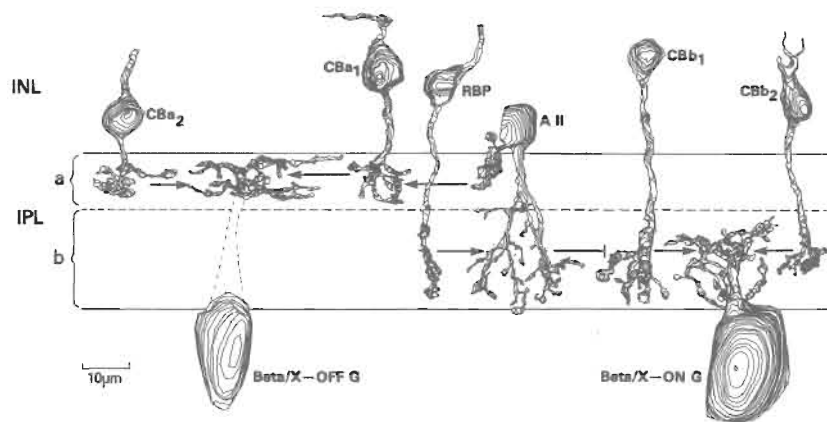

Figure 13 Eight neurons with synaptic interconnections partially reconstructed from electron micrographs of 189 serial sections. Chemical synapse (→); gap junctions (⊣). Dendritic fields of all these neurons overlap extensively and are separated here only for clarity. [Reprinted from Sterling & Megill (1983).] INL, inner nuclear layer; CB, cone bipolar; RBP, rod bipolar; G, ganglion cell.

member of the cone bipolar pair (CBb_1) is believed to be depolarizing and excitatory, and the other (CBb_2) is believed to be hyperpolarizing and inhibitory. Turning on a spot in the on-beta cell's receptive field center should depolarize CBb_1, delivering excitation, and simultaneously hyperpolarize CBb_2, withdrawing inhibition. Turning off the spot or turning on an annulus in the surround should cause the opposite response: withdrawal of excitation by CBb_1 and delivery of inhibition from CBb_2. For the off-beta cell, one member of the cone bipolar pair (CBa_1) is believed to be hyperpolarizing and excitatory, and the other (CBa_2 is believed to be depolarizing and inhibitory. Turning off a spot in the center should cause excitation from CBa_1 and withdrawal of inhibition from CBa_2.

This "push-pull" hypothesis, which stems directly from the microcircuitry illustrated in Figure 13, might have several advantages for a cell designed to detect local contrast at high spatial resolution. First, it would allow a cell to fire at high frequencies under some conditions and be totally supressed under others. This may be what enables ganglion cells such as the on-beta (detecting local brightness) and the off-beta (detecting local darkness) to operate over such a wide range of spike frequencies (0–700hz; Kuffler 1953). The push-pull mechanism should also quicken the beta's
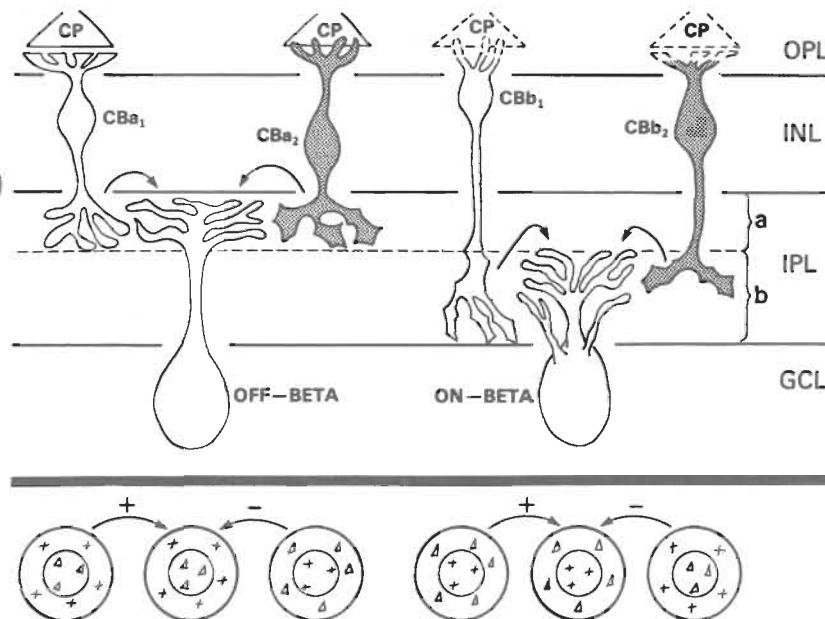

Figure 14 Push-pull mechanism for generating photopic receptive fields of on- and off-center beta ganglion cells. CP, cone pedicle. Further explanation in text. Reprinted from McGuire et al (1983c).

response to *changes* in contrast and thus may contribute to one of the beta's notable physiological attributes, "briskness" of response.

Figure 15 shows that under mesopic illumination the beta ganglion cell receptive field still has a center and an antagonistic surround, both of which are rod-driven (Barlow et al 1957, Kaplan et al 1979). The operative pathway suggested in Figure 16 is the one from the rod spherules to adjacent cone pedicles (Kolb 1979, Nelson 1977). A dim spot (below the cone threshold) causes a photocurrent to flow from rods into the cone pedicle. This current may activate the horizontal cell mechanism contained in the pedicle for generating the center-surround fields of cone bipolars and thence the center-surround receptive fields of beta cells. This might be the mechanism by which the center-surround organization, so crucial to the beta cell's spatial resolution, is maintained even in dim illumination.

After an hour or so in total darkness, the beta cell's sensitivity increases still further (Figure 15), to the point where a single photon can cause several extra impulses (Barlow et al 1971). But now spatial resolving power is sacrificed as the receptive field center enlarges by two-fold and the antagonistic surround drops out (Figure 15; Barlow et al 1957, Enroth-Cugell & Robson 1966, Kaplan et al 1979). The primary pathway suggested for this condition is no longer rod → cone → cone bipolar, but rod → rod bipolar → AII amacrine (Figure 16). The depolarization evoked in the AII by a spot (Nelson et al 1976) may spread via gap junctions to the CBb_1 axon terminals, causing them to excite the on-beta cell. The on-beta cell's enlarged receptive field center would correspond in diameter to the aggregate field
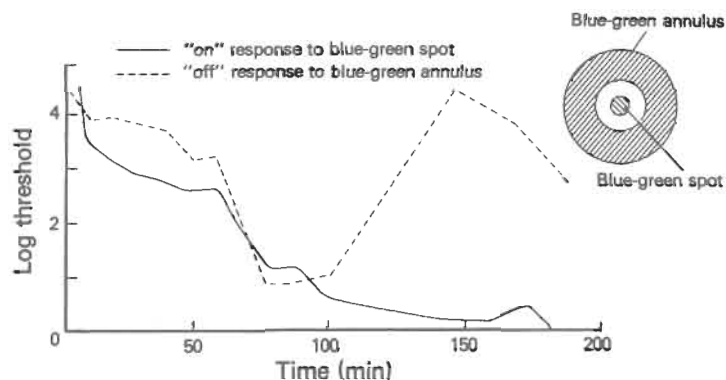

Figure 15 Thresholds of on-center ganglion cell to flashes of blue-green light during dark adaptation. Stimuli 380 msec in duration focused on *hatched areas* of inset diagram. Cones are responsible for the early sharp fall in threshold (first 10 min). Rods take over at between 10 and 30 min in both center and surround (see Barlow et al 1957). Threshold falls for both center and surround until about 100 min; thereafter, center threshold continues falling while surrounded threshold rises sharply. [Condensed from Figure 2 of Barlow et al (1957).]

of all the AII cells that feed it (Sterling & Megill 1983). It could, perhaps, be even a little larger than this, because the AIIs are interconnected by gap junctions. The antagonistic surround is lost from the beta cell apparently because it is conveyed from the outer plexiform layer by the cone bipolar dendrites, which under complete dark adaptation may carry no signal.

The same depolarization of the AII that excites the on-beta ganglion cell may suppress the off-beta cell by two mechanisms. The depolarized lobular appendage of the AII, as it is probably glycinergic, may cause postsynaptic inhibition via its contact with off-beta dendrites (Kolb 1979) and presynaptic inhibition via its contacts with the axon terminal of CBa_1 (Figure 16; McGuire et al 1983b, Sterling & Megill 1983). Because for both types of beta cell the push-pull arrangement is sacrificed in the dark, one would anticipate a loss in temporal as well as spatial resolution, and this is in accord with the physiological observations of Kaplan et al (1979). The circuitry in Figure 16 is also in accord with the reported effects of strychnine, a glycine blocker, on beta cell receptive fields (Kirby 1979, Saito 1981).

The two rod pathways discovered by Famiglietti, Kolb, and Nelson thus may serve different functions, and one wonders whether there are mechanisms
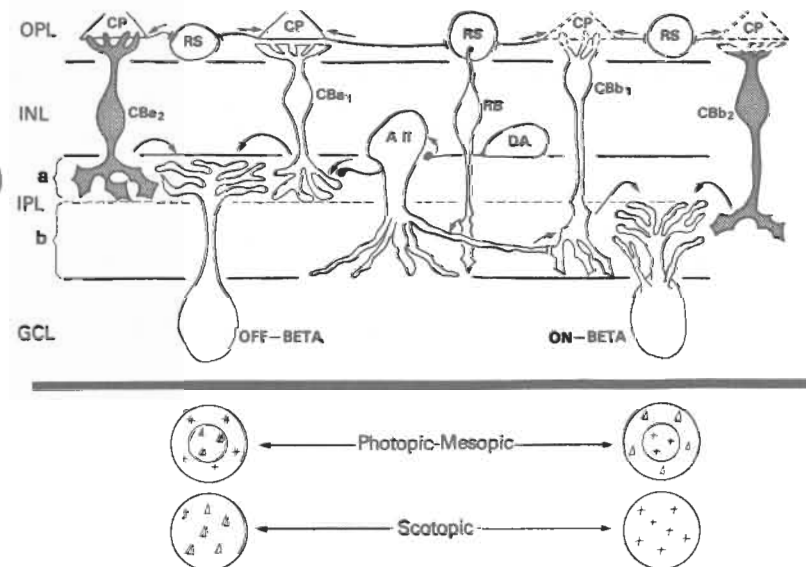

Figure 16 Thirteen neuron circuit (11 types shown; 2 horizontal cell types omitted for clarity) that may generate the receptive fields of on- and off-center beta ganglion cells in states of light and dark adaptation. Further explanation in text. CP, cone pedicle; RS, rod spherule; OPL, outer plexiform layer; INL, inner nuclear layer; CB, cone bipolar; RB, rod bipolar; DA, dopamine amacrine; AII, AII amacrine; GCL, ganglion cell layer.

nisms to regulate which pathway is active. It would not be surprising if the rod → cone pathway serving mesopic vision were switched off at the end of dark adaptation and the rod → AII pathway were switched on. The patency of the rod → cone pathway might be regulated by the B-horizontal cell as described above (Horizontal Cells, Physiology). The rod bipolar → AII pathway might be regulated by the dopamine amacrine. One would not expect the AII to be totally suppressed by dopamine at photopic levels because the AII can carry a cone signal (Figure 7). However, the rod bipolar pathway into or out of the AII might be regulated by dopamine in a more specific fashion (Sterling & Megill 1983).

CONCLUSION

Hubel & Wiesel proposed in 1962 a hierarchical structure for the cat visual system. A particular property, they argued, is established at one level, sharpened at successively higher levels, and generalized to a larger region of visual field. Their idea developed from studies of single units at the third through sixth levels (ganglion cells to complex cells in area 17). The studies reviewed here strongly support their concept as applied to the first through third levels (receptors to ganglion cells). In regard to simple and complex cortical cells, the hierarchical model has been strongly criticized (Stone et al 1979). However, if area 17 is anything like the retina, it probably contains many discrete cell types connected in specific ways. These probably do not form a single simple-to-complex hierarchy but many parallel hierarchies to further abstract and generalize the "qualitative contexts" relayed there from the many types of retinal ganglion cells. Anatomical and physiological evidence grows that a single sublayer of area 17 does have many discrete types (Davis & Sterling 1979, Solnick et al 1983, Hamos et al 1983), and new "contexts" apparently are created in the domains of orientation (Hubel & Wiesel 1962) and spatial frequency (Movshon et al 1978). What is needed to identify the continuation of the retinal hierarchies into area 17 is more detailed knowledge of the cortical cell types and their circuitry (Gilbert 1983, this volume).

Strong concepts have emerged to guide research on microcircuitry of the cat retina. It is now believed that cell types are discrete and number roughly 60. Each type is believed to have a particular transmitter, set of connections, and mosaic distribution. As knowledge of circuitry becomes very detailed, hypotheses regarding function emerge. These hypotheses are quite specific and testable; whether they are correct seems less important than that they can be read directly from the circuitry. Powerful technologies to extend our knowledge of circuitry in cat retina exist and are still developing. We may expect, in addition to the approaches already noted, to have monoclonal

antibodies specific for particular cell types (Sterling & Lampson 1983). Further, since neural activity is strongly reflected in oxidative metabolism and this can be recognized at the electron microscope level (Wong-Riley et al 1978), it may be possible to determine directly by electron microscopy which pathways are active under particular conditions. Where concepts and methods are strong, one may expect progress to be rapid. At a recent meeting of the Society for Neuroscience, D. H. Hubel declared, "The good old days are right now." Those who work on the cat retina will not argue.

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