The rise in cyclic AMP in NRK fibroblasts undergoing density dependent inhibition of growth has been found to be associated with an increase in adenylate cyclase activity (*9*). The rise in cyclic GMP in BALB 3T3 cells is likewise associated with increased guanylate cyclase activity (*10*), and this rise could be responsible for the increase in cyclic GMP. We have also measured cyclic GMP and guanylate cyclase activity in transformed NRK and transformed BALB 3T3 cells growing in serum-containing medium. Many transformed 3T3 and NRK cells show greatly diminished guanylate cyclase activity (*10*). Also, NRK cells transformed by the Kirsten, Moloney, or Harvey strains of murine sarcoma virus have very low cyclic GMP (*10*). Thus transformed cells can grow rapidly with diminished cyclic GMP levels. Seifert and Rudland reported that the addition of serum to resting serum-starved 3T3 cells causes a transient rise in cyclic GMP (*3*). We have failed to detect any rise in cyclic GMP after addition of serum to cells maintained in plasma. More recently Moens *et al.* reported that cyclic GMP levels do not rise in Swiss 3T3 cells undergoing density dependent inhibition of growth in serum (*11*). Our results cannot be directly compared with those of Seifert and Rudland and Moens *et al.* since there are differences in experimental design and in methodology. Some of these are as follows. (i) They washed their cells prior to extraction; we do not wash cells to prevent possible changes in cyclic nucleotide levels due to this manipulation. (ii) They used direct radioimmunoassay without succinylation; we have been unable to reliably measure cyclic GMP levels without the enhanced sensitivity and specificity of succinylation. (iii) Moens *et al.* used a different strain of 3T3 cells. (iv) Moens *et al.* allowed cells to undergo contact inhibition of growth in serum, whereas we used plasma that is deficient in some of the growth factors found in serum (*5*).

All in all, our data are inconsistent with the proposal that cyclic GMP promotes growth and opposes the action of cyclic AMP (*2, 3*). The role of cyclic GMP in cultured fibroblastic cells remains obscure.

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12. We thank Dr. D. Gospodarowicz for suggesting the use of plasma to arrest the growth of BALB 3T3 cells and for the BALB 3T3 clone B used in these experiments.

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Independence of "On" and "Off" Responses of Retinal Ganglion Cells

Abstract. *Recordings of action potentials from retinal ganglion cells that are stimulated repetitively demonstrate two properties: (i) variability introduced during the stimulus is not evident in the response that occurs at stimulus offset and (ii) variability in the* ON *response shows a different temporal structure than variability in the dark. Our findings demonstrate that these responses are generated independently.*

There are two responses to every visual stimulus: one after a light is introduced and one after it is withdrawn. During the time that the stimulus is present, the firing rate of a ganglion cell may be either higher or lower than its firing rate was in the dark. After stimulus offset the firing rate is again modified, usually in the direction opposite to the response during the stimulus (*1*). While the ON response is generally considered to reflect the cell's response to the stimulus, there is some controversy about the origin and significance of the OFF response (*2, 3*). Many researchers tacitly assume it to be a reflection of the same process that generates the ON response, and group the two together for analysis (*4*). We have found that the ON and OFF responses are manifestations of two independent processes; in addition, there are separate ON mechanisms that correspond to different parts of the receptive field.

If the same stimulus is repeated on a regular schedule, the number of spikes (action potentials) that are elicited varies from presentation to presentation; we have examined the statistical properties of this variability and its correlation with the variability that is exhibited by the maintained discharge. It is important to realize that these statistics are derived from total numbers of spikes and are not necessarily related to the statistics derived from the variability of interspike intervals.

Table 1. Correlation matrix for 39 stimulus presentations to the center of the receptive field of an off-center unit. The stimulus was a 0.562-mm diameter spot. Correlations are between all pairs of lists of the numbers of spikes in each of the 1-second bins. The mean and variance (σ^2) of the number of spikes in each bin are also presented.

List	1	2	3	4	5
1	1.00	.86	.09	.84	.85
2		1.00	.04	.82	.87
3			1.00	.03	−.11
4				1.00	.80
5					1.00
	Number of spikes in each bin				
Mean	38.7	38.7	24.1	65.6	46.4
σ^2	13.7	13.9	8.9	88.8	42.7

We used platinum-iridium microelectrodes to make extracellular recordings of action potentials from the isolated retinas of goldfish (*Carassius auratus*) (*5*). Data consisted of the total number of action potentials that occurred in each of five successive 1-second bins. (A bin is an interval of time during which spikes are counted.) The stimulus was a flash of deep red monochromatic light (680 nm or longer) coincident with the third bin. This regimen was repeated every 30 seconds and generated five lists, each consisting of the total number of spikes in the corresponding bin for each of at least 30 repetitions of the same stimulus. Lists 1 and 2 correspond to firing before the stimulus and represent the maintained discharge; list 3 is the ON response; and lists 4 and 5 are OFF responses.

We computed a matrix of the correlations between all pairs of lists; a typical matrix (Table 1) was derived for stimulation to the center of an off-center cell (*6*). These correlations express relations between the changes about the means of each of the lists. The most striking feature of this matrix is that there is a uniformly high correlation between any two lists in which there was no stimulus, and a low correlation between list 3 (that included the stimulus) and any other. The failure of the OFF response to show a lower correlation with maintained firing cannot simply be ascribed to a lack of response at OFF; the absolute magnitude of the OFF response (measured as the difference from maintained) in this case is larger than that of the ON response (see means in Table 1).

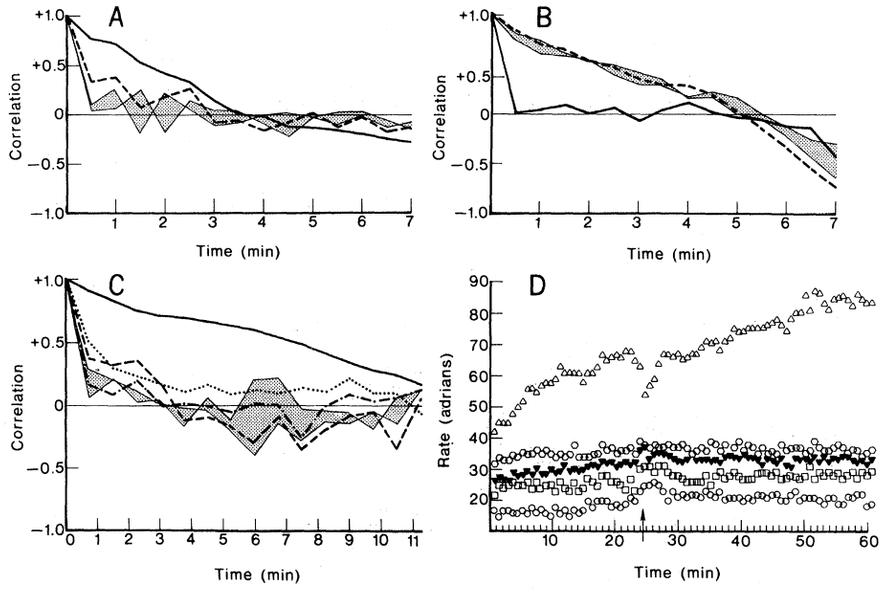

Fig. 1. (A) Autocorrelation functions for 42 stimulus presentations to the entire receptive field of an off-center cell. (This unit showed no antagonistic surround.) The shaded area represents the spread between the functions derived from the two maintained discharge lists; the ON function is denoted by the solid line; the first OFF function (list 4) is denoted by the dashed line. (B) Autocorrelation functions for 30 stimulus presentations to the center of an on-center cell. Stimulus was 0.562 mm in diameter. The symbols are the same as those in (A). (C) Autocorrelation functions for 49 pairs of stimulus presentations to an on-center cell. These functions were derived from the latter portion of the data presented in (D) (commencing after 24 minutes). Symbols for maintained discharge and stimulation to the center are the same as for (A); for stimulation to the surround, the ON is represented by the dotted line and the OFF by the dot-dash line. (D) Time course of responses of an on-center cell to repeated sequential presentations of stimuli to the surround and the center. The first data point was taken 20 minutes after the dissection. Maintained discharge (solid triangles) was taken as the average of the two successive seconds that preceded the stimulus to the surround. The surround was stimulated with an annulus whose inner diameter was 1.2 mm and outer diameter was 3.0 mm; ON responses to this stimulus are shown as circles, OFF responses as hexagons. This stimulus was followed 5 seconds later by a stimulus to the center of the field, a 0.562-mm diameter spot. This ON response is shown by open triangles, the OFF response by squares. The electrode was manipulated slightly at 24 minutes to improve the recording (arrow).

Thirty matrices derived from the stimulation of eight different on-center units and eight different off-center units show the same features: correlations are high between lists representing maintained discharge and between the firing rates before and after stimulation, while the firing rate during stimulation is less correlated with the firing rates in the dark. Six matrices showed patterns that varied in one aspect or another from the above description.

In order to verify that the differences in correlation that we observed were not simply due to the temporal sequence of the data collection, we calculated autocorrelation functions (7) from sequential half-second bins with no stimulation. For all seven cells analyzed in this manner the autocorrelation functions were flat for delays up to 15 seconds, indicating that correlation remains constant over time periods somewhat longer than each data sample.

Both the ON and OFF responses are functions of the stimulus, for both are graded with light intensity; however, the above data show that the two responses are generated independently. The lower correlation between the ON and any other list, relative to the correlations between firing rates in the dark, indicates that a different variability is expressed in the presence of the stimulus. However, the lack of a similar effect for the OFF response demonstrates that this noise is not also present in the OFF mechanism. It cannot, therefore, result from a change in the sensitivity of the receptors themselves, but must be a special property of ON systems, regardless of whether they are excitatory or inhibitory.

In order to examine further the temporal differences that might exist between the sources of variability in the ON mechanism and other random processes in the retina, we calculated autocorrelation functions for each of the five lists. We treated each list as an independent variable in time (although all five were running concurrently) that we sampled at a discrete interval of 30 seconds. Figure 1, A and B, shows typical autocorrelation functions derived for stimulation of another off-center cell and an on-center cell, respectively. In each case the autocorrelation function for the ON list (solid lines) is distinctly different from those autocorrelation functions that are derived from either maintained (lines bounding the shaded area) or OFF (dashed lines). There does not appear to be any relation between the specific form of the autocorrelation function and either the type of cell or the particular list that is analyzed; what is significant is that the autocorrelation functions for firing in the dark (for a given sample) are generally similar to each other and different from that for the ON response.

Since the ON and the OFF responses are generated by different mechanisms, the question of whether these two mechanisms might be the spatially antagonistic center and surround of the receptive field is raised. To test for this, we modified our experimental paradigm so that each cycle included two stimulus flashes presented 5 seconds apart. The first flash was an annulus designed to excite the surround mechanism; the second was a small spot like that used in the first experiment. Only units with an active surround were used, so that if the ON response to the spot was excitatory, the ON response to the annulus was inhibitory, or vice versa. We calculated the autocorrelation functions for the two lists that preceded the first stimulus, and for each of the ON and OFF lists. An example is shown in Fig. 1C. As in Fig. 1, A and B, the autocorrelation function of the ON response for the center of this unit is different from any other function. The ON response for the annulus (dotted line) also produces a unique function, while the functions for firing in the dark all follow essentially the same pattern. If the two mechanisms we had called the ON and OFF mechanisms in the center corresponded to the spatially antagonistic center and surround mechanisms, we would have expected a pairing of the autocorrelation functions derived from the ON of the center with the OFF of the surround (dot-dash line), and another pairing for the OFF of the center with the ON of the surround. That is, the two excitatory mechanisms should share one origin, and the two inhibitory mechanisms should share another. This is apparently not the case.

Under some conditions the independence of certain responses may be observed directly in the raw data. Figure 1D shows the ON and OFF responses to a flashed annulus and a flashed spot (the autocorrelation functions in Fig. 1C were derived from the last 60 percent of the data in Fig. 1D). Clearly, the ON response to the spot (open triangles) is changing independently from the other firing rates; however, the more sensitive analysis provided by autocorrelation is required to discern the

subtle differences between the variability in the ON responses to the annulus (circles) and the variability of the firing rates in the dark.

We have shown that ON response mechanisms have variability (noise) that is not shared by other mechanisms; our data also show that this noise is not simply an uncorrelated component that is added to the variability present in the dark. If an uncorrelated variance were added to an existing variance, the variance of the sum would be larger than either alone. In all the cells we have investigated, we have observed no systematic tendencies for the variance to go either up or down during the stimuli (in Table 1, for example, the variance happens to drop during the stimulus). Among the number of mathematically indistinguishable ways that this may be accomplished are the following. (i) A noise component may be introduced with the stimulus and added to the noise in the dark; however, to maintain a relatively constant variance in both conditions, the two components must be negatively correlated. (ii) If the noise that is added during the stimulus is not correlated with the noise in the dark, then the noise in the dark must be attenuated during the stimulus (*8*). The independence indicated by the different appearances of the autocorrelation functions leads us to prefer the second hypothesis (*9*).

In summary, we propose that ON and OFF information is generated in the retina by independent mechanisms, each of which contains its own source of variability. General theories of receptive field organization must account for this duplicity of ganglion cell operation. In addition, our method of analysis should be useful for investigating the relations between different receptor systems or different spatial components of the receptive field.

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References and Notes

1. We use the terms ON response to refer to the number of spikes that are produced during illumination, and OFF response to refer to the number of spikes that are produced during the second after offset of the stimulus. By maintained discharge we mean firing in the periods that precede the stimulus.
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4. This may be an explicit averaging, as in J. Stone and M. Fabian, *Vision Res.* **8**, 1023 (1968); H. Ikeda and M. J. Wright, *ibid.* **12**, 1465 (1972); more often there is a comparison of ON responses with OFF responses [for example, I. Abramov and M. W. Levine, *ibid.* **15**, 791 (1975); N. W. Daw, *J. Physiol. (Lond.)* **197**, 567 (1968); P. Gouras, *Science* **168**, 489 (1970); T. N. Wiesel and D. H. Hubel, *J. Neurophysiol.* **29**, 1115 (1966)]. It is also inherent in any method in which sinusoidal modulation of the stimuli is used.
5. Our methods are virtually identical to those described → M. W. Levine and I. Abramov, *Vision Res.* **15**, 777 (1975).
6. We classify the response type according to whether the excitatory response (increased firing rate relative to the maintained discharge) occurs at ON or OFF. Thus, an off-center unit is one that is inhibited during stimulation by a small, centered spot of light and fires at OFF; an on-center unit is the opposite.
7. An autocorrelation is the correlation of a signal at every time within some interval with the same signal delayed by some fixed amount. The autocorrelation function is the autocorrelation as a function of this delay time.
8. One might wish to consider the possibility of two or more components present in the dark, one of which is suppressed by the stimulus. All of the above arguments are valid, with the simple substitution of the word OFF for ON. In fact, this is equivalent to adding a negatively correlated component at ON.
9. This is most similar to the speculations of Granit (*2*).

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Cross-Cultural Differences in Simple Taste Preferences

Abstract. *A population of Indian laborers who show high preferences for sour and bitter tastes has been studied. Their judgments of taste intensity and pleasantness of sweet and salty stimuli are in accord with European population estimates, which suggests that dietary history may alter preferences for simple taste stimuli without affecting the gustatory system.*

It has been assumed that our pattern of taste preferences is part of our genetic composition. Sweetness is a pleasant taste, saltiness may be pleasant at low levels but unpleasant at higher ones, and sourness and bitterness become increasingly unpleasant as the concentrations increase. These taste preferences have been studied only with model aqueous systems, and generalizations to food preferences should be made with caution. The complexities and nuances of foods, and one's expectations about taste qualities, preclude any such simple classification once cognitive factors are taken into account. Evidence for the dichotomy of taste preferences for aqueous solutions derives from a long history of psychophysical studies, in which the subject is asked to judge either whether the taste is pleasant, neutral, or unpleasant (*1*), or the degree of such pleasantness and unpleasantness (*2–4*), or to rank tastes in order of pleasantness (*5*). The results of the studies obtained with Western populations agree with each other and confirm the striking division of the taste world into two categories with *sweet* referring to a pleasing aspect, and *bitter* and *sour* referring to a displeasing one.

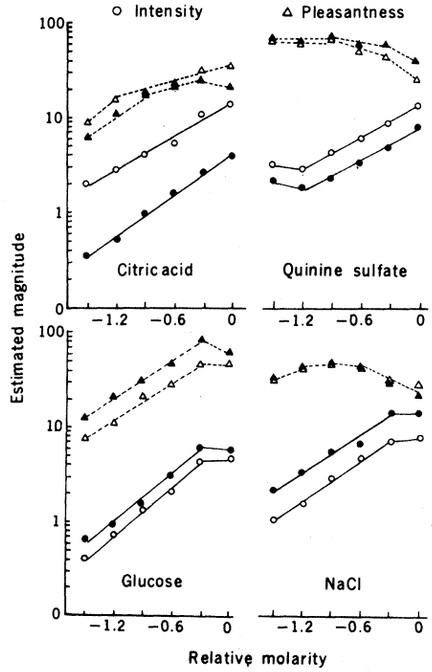

Fig. 1. Rated taste intensity and taste pleasantness for four compounds. The coordinates are log-log. The data, obtained by the method of line matching, are from a group of laborers from the Karnataka region of India. Solid markers are of judgments made after lunch and open markers are of judgments made after fasting.

Studies with Indian medical students from St. John's Medical College, Bangalore, India (*6*), which we conducted by standard psychophysical techniques confirmed that the sweet taste is pleasant, that salty is both pleasant and unpleasant, whereas sour and bitter are primarily unpleasant. In fact, the curve relating taste pleasantness of glucose solution exhibited the same maximum preference level (1.0*M* glucose) as did studies with U.S. testers in various other experiments (*3, 7*).

We find different preferences among illiterate Indian laborers from the Karnataka region in India. These laborers subsist on a sparse diet (1200 to 1500 calories) that contains many sour foods. The tamarind fruit, which tastes extremely sour and slightly sweet, is chewed as a confection, and another major dish, lentil soup, is flavored with tamarind fruit to produce a fairly sour dish. As a general rule their diet more strongly emphasizes sour tastes than do Western diets.

Because many of the individuals in this group of laborers were illiterate, we tested