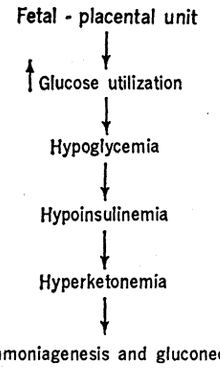

Fig. 1. Postulated sequence whereby glucose utilization by the fetal-placental unit alters metabolic response to starvation in midpregnancy in humans. The hyperketonemia resulting from lack of insulin may be mediated through increased lipid mobilization.

1 and 2 of the fast and was significantly elevated in the pregnant group on day 3. This increase was primarily due to an elevation in urinary ammonia excretion which rose to concentrations twice those observed in nonpregnant controls. In view of the comparable concentrations of urinary urea and creatinine in the two groups it is unlikely that the increase in glomerular filtration rate observed in pregnancy was responsible for the augmented excretion of total nitrogen and ammonia.

Total weight loss during the fast was 3.1 ± 0.4 kg (mean $\pm$ S.E.) in the nonpregnant group and 3.2 ± 0.2 kg in the pregnant subjects.

The current data demonstrate that the response of circulating glucose, insulin, and ketone acids to total starvation is exaggerated and accelerated in human subjects during the second trimester of pregnancy. The striking decline in plasma glucose to hypoglycemic concentrations could be attributed to overutilization of glucose or underproduction of glucose from endogenous precursors, or both. The normal to increased rates of protein dissolution suggest that maternal gluconeogenic mechanisms are intact. Moreover, in view of the interdependence of renal ammoniagenesis and gluconeogenesis (*14*), the elevation in urinary ammonia excretion is consistent with an augmentation in renal gluconeogenesis. Thus fasting hypoglycemia appears to be a consequence of continuous glucose consumption by the conceptus. That the marked reduction in plasma glucose is in turn responsible for the hypoinsulinism is suggested by the direct correlation between plasma glucose and insulin concentrations and the fact that insulin and glucose concentrations reach a simultaneous plateau at 36 hours.

With respect to the hyperketonemia of pregnancy, the importance of placental diabetogenic, contrainsulin factors has been postulated in both man (*5*) and laboratory animals (*15*). That such is not the case in midpregnancy in humans is suggested by the absolute hypoinsulinism in the pregnant group. The heightened ketonemia of pregnancy is thus more readily explained on the basis of the reduction in plasma insulin concentrations. Supporting this conclusion is the demonstration that acetoacetate and β-hydroxybutyrate concentrations were higher in the pregnant group so long as plasma insulin concentrations were significantly below those of nonpregnant controls (Table 1). However, when plasma insulin declined in the nongravid group after 84 hours of starvation to the concentration observed in pregnant women, ketone acid concentration in blood rose to virtually identical levels in the two groups. These effects of the lack of insulin on ketosis may be mediated through increased mobilization of free fatty acids. Finally, because ketonuria in starvation is dependent on the concentration of blood ketones and in turn influences the rate of ammonia excretion (*14*), hyperketonemia is the likely explanation for the heightened excretion of ammonia in the gravid state.

The sequence of events postulated to account for the altered fuel-hormone response to starvation in human subjects in the second trimester of pregnancy is shown schematically in Fig. 1. A similar concept has previously been advanced on the basis of observations in fasted gravid rats (*3*) and in postabsorptive women in the third trimester of pregnancy (*1*). However, the demonstration of hyperinsulinemia in those situations suggests a role for contrainsulin factors which appears to be of less importance in human midpregnancy.

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Centrifugal Effects in the Avian Retina

Abstract. *Electrical stimulation of the centrifugal fibers to the avian retina can disturb the balance between the excitatory and inhibitory system within the receptive fields of individual retinal ganglion cells. Although the mechanisms may vary from one unit to another, the effect is always to make them fire more readily and to a wider range of visual inputs.*

The bird is the only vertebrate for which there is conclusive evidence of an efferent retinal projection (*1*). The cell bodies of the centrifugal neurons are collected in the isthmo-optic nucleus, and their axons run forward together in the isthmo-optic tract, joining the optic nerve at the chiasma. Their endings terminate chiefly on the amacrine cells, which in the bird retina are probably genuine interneurons linking bipolars and ganglion cells, and are therefore well situated to modulate the flow of information through the retina. These isthmo-optic neurons compose the efferent limb of a local feedback

system which receives an input through the tectum from a given area of the retina and relays back to that same region of the eye. Little is known about the function of this system. Enhanced oscillations of the local electroretinogram have been observed to follow section of the optic tract, an effect ascribed to interruption of the efferent system (*2*), but one which is very difficult to interpret. This report describes the effects of these centrifugal fibers on the normal visual responses of individual retinal ganglion cells.

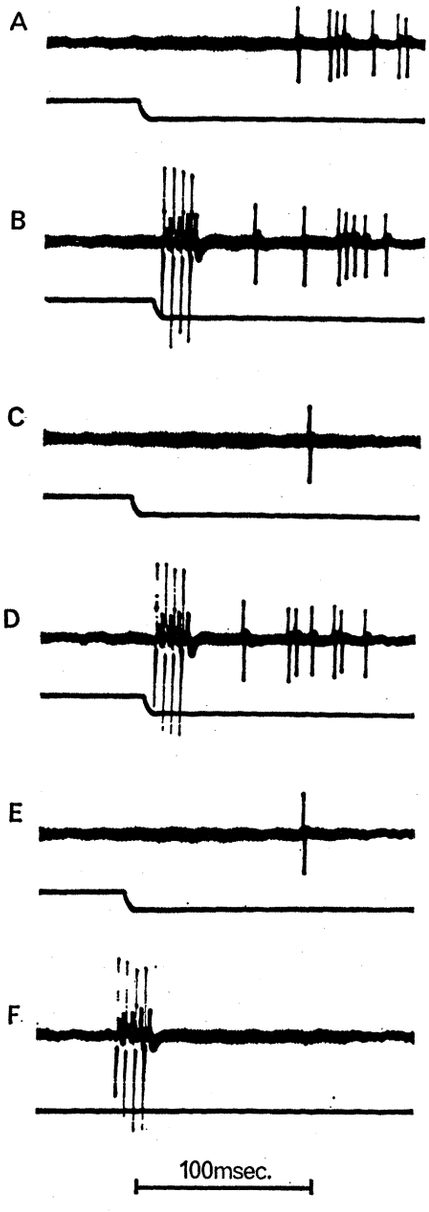

Fig. 1. Responses of an on-off retinal unit to repeated visual stimuli and activation of the isthmo-optic tract. A 2° spot flashed on the center of the field produced vigorous firing (A), which was only slightly affected by stimulation of the isthmo-optic tract (B). The visual stimuli were then repeated every 3 seconds, and subsequent off responses showed considerable habituation. Traces C, D, and E show consecutive responses after habituation had become established. In D, stimulation of the tract brought out an off response, but on its own, such stimulation produced no firing (F). Stimuli to the tract each consisted of a train of four pulses (durations, 0.5 msec) at a frequency of 200 per second. Spot luminance, 50 cd/m^2; background luminance, 6 cd/m^2.

Experiments were done on decerebrated domestic chicks, 2 to 14 days old, which were placed in a stereotaxic instrument, immobilized with a mixture of tubocurare and gallamine triethiodide, and artificially respired. The animal faced a translucent screen on which were projected a variety of visual images. Single retinal units were isolated by means of a technique similar to that of Kuffler (*3*), and their receptive fields were plotted with small spots of light turned on and off with an electromechanical shutter. These fields consisted of a central excitatory region surrounded by a purely inhibitory area. Stimulation of the surround usually reduced the response at the center but did not itself give rise to any discharge. Nearly 80 percent of the retinal ganglion cells fired at both the on and the off of light flashed at the center, and most others responded only at the on. About one-third of the on-off units were directionally selective, firing vigorously during movements of spots in one particular direction through the field but remaining silent during the reverse motion. After the receptive fields had been plotted and the class of the retinal unit established, the visual stimulation was combined with electrical activation of the isthmo-optic tract. To make interpretation of the results easier, it was necessary to open the feedback loop and so effectively isolate the efferent part of the system. Preliminary recordings of single unit activity in the isthmo-optic nucleus showed that there is little activity in the efferent system without visual stimulation. Thus, when the feedback loop was opened by severing the isthmo-optic tract proximal to the stimulation point, it was not removing a tonic influence on the retina.

Activation of the isthmo-optic tract in the absence of visual stimulation has never been observed to evoke firing in the retinal ganglion cells. Since these retinal units are quiescent unless presented with suitable visual stimuli, any such efferent influence would have been readily noticed. In addition, whenever it was effective, stimulation of the tract always increased the visual responses of retinal units and was never observed to depress them. The efferent effects which are described here have been observed in each of the three main types of retinal ganglion cell mentioned above, and were most readily seen when the normal visual responses of these cells had been reduced by habituation or surround inhibition. In all cases the effect of stimulating the centrifugal fibers was to emphasize the center response.

The visual responses of most retinal ganglion cells habituate if the stimulus presentations follow one another too frequently, and in some units activity disappears almost completely. Figure 1 shows one such unit, whose center was stimulated with a 2° spot at

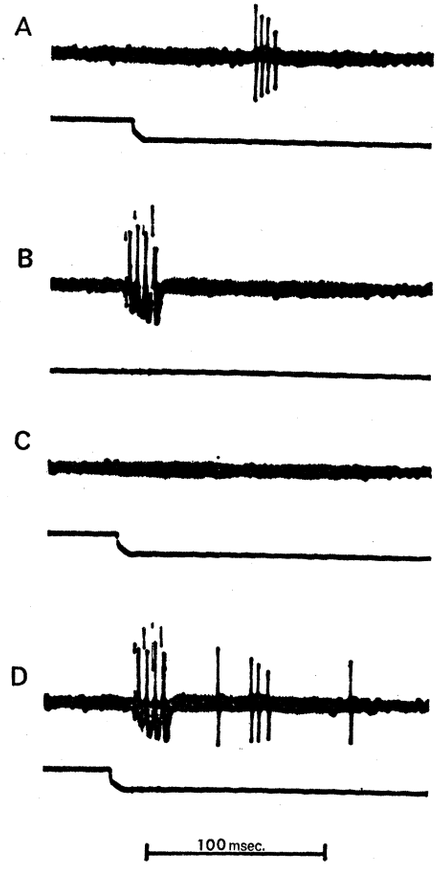

Fig. 2. Responses of an on-off retinal unit to large-field illumination and activation of the isthmo-optic tract. A 1.5° spot flashed on the center of the field produced a brief, high-frequency off discharge (A). Stimulation of the isthmo-optic tract on its own with a train of four pulses (durations, 0.5 msec) at a frequency of 200 per second, produced no firing (B). Illumination of the whole screen (area, 40° by 40°) gave negative responses (C), but simultaneous stimulation of the tract uncovered off firing (D). Spot luminance, 50 cd/m^2; background luminance, 6 cd/m^2.

3-second intervals. The initially vigorous off discharges show severe habituation after only a few presentations, but they are restored almost to their former level by electrical stimulation of the isthmo-optic tract. On the other hand, when the center responses were vigorous—as when the interval between stimuli was greater than 10 seconds—then stimulation of the tract had only a small effect, mainly that of reordering the discharge (compare traces A and B). It is unlikely that the efferents influence habituation per se, particularly since their effects are only transient, the succeeding responses continuing to show weak firing (for example, trace E). This suggests that habituation is merely a somewhat arbitrary means of reducing the responses of retinal ganglion cells to a level where the centrifugal effects can be revealed. The on responses of this particular unit showed less habituation and little response to the tract stimulation. The on and off systems of individual retinal units are often very different in their susceptibilities to repeated visual stimuli, and not all habituated responses were restored by efferent stimulation. However, a negative result in these experiments must be interpreted with caution because it was not possible to guarantee that the whole tract was activated.

Because of their powerful inhibitory surrounds, most retinal ganglion cells fire weakly when the whole screen is flooded with light. Usually, the best on-off responses result when illumination is restricted to the excitatory center, and any encroachment onto the surrounding area reduces the discharges.

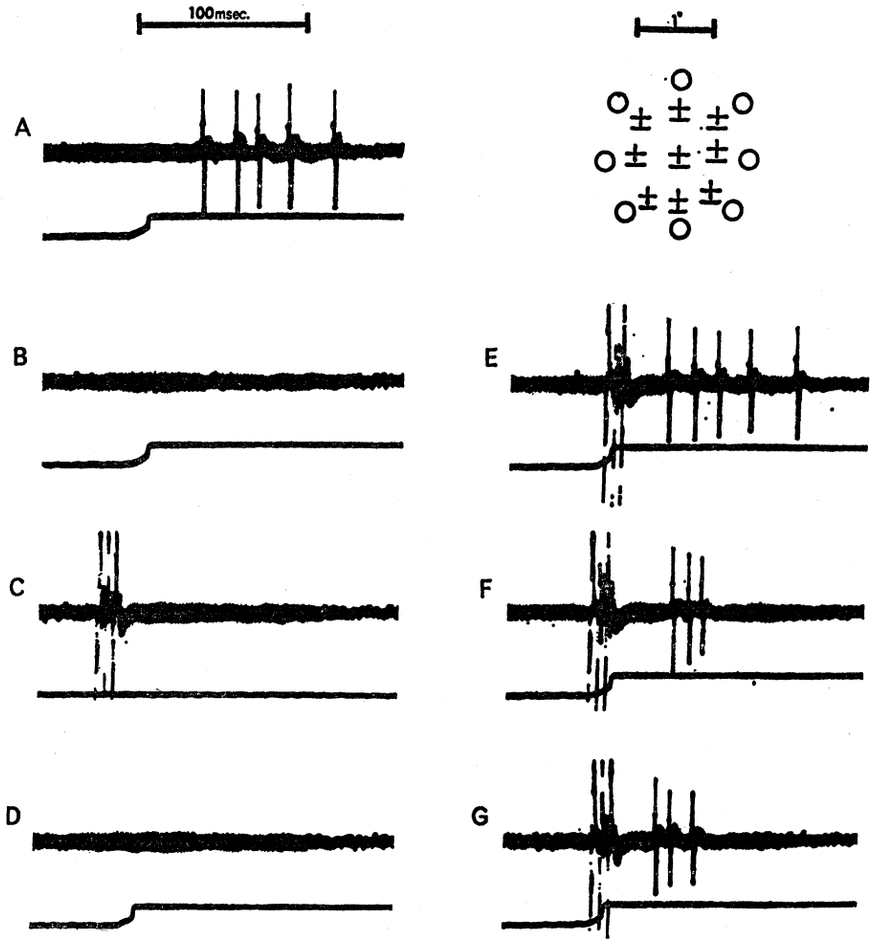

Fig. 3. Responses of an on-off retinal unit to spots and small annuli, and activation of the isthmo-optic tract. (Inset) The receptive field as plotted with 0.5° spots; ± indicates on-off firing, ○ indicates no response. (A) On response to a centered 1.5° spot. Negative responses to (B) the on of a 2.2° unlimited annulus, (C) tract stimulation with a train of three pulses (durations, 0.5 msec) at a frequency of 200 per second, (D) illumination of the whole screen (area, 40° by 40°). Stimulation of the tract had little effect on the response to a centered 1.5° spot (E), but uncovered on-responses to the 2.2° annulus (F) and large-field illumination (G). Background luminance, 6 cd/m²; spots, annuli, and large-field flash, 50 cd/m².

Figure 2 shows the off responses of an on-off unit which remains silent when the whole field is flashed. Combining activation of the isthmo-optic tract with the large-field flash, however, brings out an off response. The overall effect of the centrifugal input is to render the retinal ganglion cell less selective in its responses to visual inputs. When the center and its surrounding area are stimulated independently of one another by means of spots and annuli, it becomes clear that the efferent input is uncovering the normal center response and not inducing novel, excitatory responses in the surround. Thus, annuli with large internal diameters—and hence little chance of inadvertently activating the center—successfully inhibit center responses, yet on their own, they do not give rise to any firing even during tract stimulation.

There are two separate mechanisms which could mediate these efferent effects: selective facilitation of the central excitatory system or suppression of the surrounding inhibitory system (that is, disinhibition). If the Rodieck and Stone model of the receptive field (*4*) applies to the avian retinal ganglion cells, then these excitatory and inhibitory systems will be coextensive in the central area, with the balance in favor of excitation. If the two systems are not spatially separate, then it is very difficult to distinguish facilitation from disinhibition by means of the extracellular recording techniques employed here. However, the effects of tract stimulation can vary widely from one ganglion cell to another, and at least some of the variability is due to differences in the emphasis on center and surround mechanisms. Thus, in the unit shown in Fig. 3, tract stimulation induces firing during large-field illumination but has little effect on the center responses (compare traces A and E). The failure of the tract stimulation to augment the center responses is not due to saturation effects since it was equally unsuccessful when the luminance of the test flash was low and the firing weak. The most likely target for the efferent input in this unit, therefore, is the inhibitory system which dominates the surround. By suppressing this inhibitory surround, the efferents indirectly increase the excitability of the retinal ganglion cells by a process of disinhibition. This finding invites comparison with the well-known loss of inhibitory surrounds in cat retinal ganglion cells during dark adaptation

(*5*). It is also interesting that disinhibition has been tentatively invoked to explain similar changes in the receptive fields of some frog retinal ganglion cells (*6*). The absence of any response to the tract input at the field center might be due to the restricted area involved. It has been shown that spatial summation is very important in the inhibitory systems of goldfish retinal ganglion cells, to the extent that many complex properties were missed in earlier studies which had employed only small spots for activation (*7*).

There are other retinal units whose responses to efferent stimulation are a complete contrast with the above, showing enhanced firing to centered spots but remaining quiescent when the whole field is illuminated. In such cases, the centrifugal fibers probably facilitate the excitatory systems which dominate the center of the receptive field.

Closer investigation of these centrifugal effects reveals an increase in the size of the receptive field centers. In order to give prominence to this effect, the surround was activated with an unlimited annulus whose inner margin bordered the excitatory center of the field more closely than was usual in these experiments. In the unit shown in Fig. 3, the annulus came within 0.5° of the center, and gave typical surround responses: flashing the annulus on its own produced no discharge, but when combined with illumination of the center it completely suppressed the normal center responses. As expected, tract stimulation brought out a response to a large-field flash, but in addition, it evoked a response when the annulus alone was flashed. Thus, by suppressing the inhibitory surround, the efferent input uncovers activity from an otherwise silent area, the effect being to increase the apparent extent of the field center. Similar changes have been reported at various levels in the cat visual system (*8*).

It is difficult to assess the importance of light scatter onto the center in such experiments, and a number of precautions were taken to minimize it (*9*). If scatter was a major factor in these experiments, then it is likely to have a similar significance in the normal vision of the animal. However, some such expansion of the field center might be expected if the excitatory and inhibitory systems overlap in the boundary regions between the center and the surround, a feature of the Rodieck and Stone proposals. The excitatory field would then extend beyond the center boundaries defined with visual stimuli and would be revealed in its entirety only after an appropriate disturbance in the balance between the excitatory and inhibitory systems. In suppressing the inhibitory system (or facilitating the excitatory system), the centrifugal input could extend the apparent field center.

A number of controls were carried out to discount the possible influence of changes in accommodation and the size of the pupil, eye movements, and circulatory adjustments. In the bird, accommodation can be relaxed and the pupil dilated with drugs similar to curare (*10*), and the general muscle relaxant used here, a mixture of tubocurare and gallamine triethiodide, was very effective. Microscopic observations of the pupil failed to reveal any changes, and several experiments done with artificial pupils gave essentially the same results. Eye movements were less than 20 minutes of arc per hour, and although occasional drifts followed tract stimulation, they were always small (rarely more than 10 minutes of arc) and of longer latency (several hundred milliseconds) than the effects here described. It was therefore unlikely that eye movement affected the results in any essential way. Nonetheless, considerable care was used in the selection and positioning of spots and annuli so that such small movements could be tolerated. Arterial blood pressure was monitored continuously throughout the experiments, and although it was sensitive to tract stimulation on occasions, the results showed no associated effects.

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9. Luminance gradients between spots and background were always 1 log unit or less. Retinoscopy was used to make the initial selection of suitable supplementary lenses to focus the eye on the screen, but the final choice was made after recordings were obtained from a retinal ganglion cell. A range of lenses was then tried in order to find the one which gave the most vigorous responses to small spots and the smallest field plot.
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Pineal Function and Oviposition in Japanese Quail: Superior Cervical Ganglionectomy and Photoperiod

Abstract. *Bilateral ablation of the superior cervical ganglia appears to deprive the pineal body of sympathetic innervation. Although this procedure presumably interrupts the neural circuit for transmission of optic information to the pineal, oviposition rates of ganglionectomized females exposed to stimulatory (15-hour) or to nonstimulatory (4-hour) daily photoperiods do not differ from those of the controls.*

Pineal organs extend from or occur within the dorsal roof of the brain, specifically the diencephalon, of almost all vertebrates examined. There is great diversity in the origin and organization of these structures, indicative perhaps of diverse functions. The function of the pineal body of birds is obscure, although there is some evidence from gallinaceous species that it may be a gland producing a progonadal agent in very young birds and an antigonadal agent in older birds (*1*). Interpretations of function of the avian pineal are strongly influenced by assumptions regarding pineal function in mammals, where it is generally held that the pineal acts to suppress gonadal function (*2*), although proof of this contention remains equivocal (*3*).

The effect of light (or the absence of light) on the gonads of mammals is believed to be mediated to some extent by the pineal; light information is re-