to-noise ratio of the cones which at maximum equals that set by photon noise, that is, $CM\sqrt{N}$, where M is the modulation transfer function of the optics, C is the grating contrast, and N is the mean number of photons absorbed by each cone (*1*). N is proportional to luminance, the cone inner segment area, and $(t/F_{number})^2$. This leads (*1*) to an expression for the minimum possible undersampling given approximately by $\nu_s/\nu_o \simeq [k - 0.13 \ (d/d_c)^2]^{1/2}$, where $k = (\ln C\sqrt{N})/3.56$. We have approximated the point spread function by a Gaussian (*1*), that is, the angular width $\Delta\rho$ of the point spread function at the cone output is related to the cone inner segment diameter $\Delta\rho_r$ and the half-width diameter of the optical spread function $\Delta\rho_o$, both in angular terms, such that $\Delta\rho^2 = \Delta\rho_r^2 + \Delta\rho_o^2$. $N \simeq 10^4$ photons in bright light for man, rats, and cats, but for snakes, $N \simeq 10^5$, assuming, in all cases, an integration time of 30 m/sec and a maximum luminance of 10^4 cd/m^2. The discrepancy between N for snakes and N for the other animals is greatly exaggerated here because we have neglected the huge Stiles-Crawford effect due to the wide inner segments of snake cones. Furthermore, undersampling is advantageous in the presence of a significant Stiles-Crawford effect because this effect raises the signal-to-noise level of the optical image at intermediate frequencies (at the expense of higher frequencies). The maximum contrast normally encountered in nature is ~0.25.

7. If certain retinal regions are devoted exclusively to detecting and locating moving objects, aliasing distortion may be of minor concern. It is possible to have nearly 50 percent undersampling without suffering any aliasing distortion at the level of ganglion cells. This requires having more cones than ganglion cells, with the retina wired so that ganglion cells can only detect frequencies below their anatomical sampling frequency ν_g, where the cone sampling frequency obeys $2\nu_s = \nu_o + \nu_g$. Thus, the cones can undersample by an amount $2(\nu_s/\nu_o) = 1 + \nu_g/\nu_o$ with an alias-free signal at the ganglion cell level. The cat eye (Table 1) is consistent with this strategy because $\nu_o \simeq 30$ cycles per degree (cpd), $\nu_s \simeq 20$ cpd, and $\nu_g \simeq 10$ cpd. The information within the spatial frequency band ν_g to ν_s need not be discarded but can be used in parallel for detection and location of moving objects.
8. Information theory determines the total number of different scenes an eye can distinguish [A. W. Snyder, S. B. Laughlin, D. G. Stavenga, *Vision Res.* **17**, 1163 (1977)]. We subtract from this total the number of scenes produced by frequencies above and then find the image quality that maximizes this difference (*17*).
9. S. B. Laughlin, *Z. Naturforsch. Teil C* **36**, 910 (1981).
10. The spatial correlation of the object world depends on the distribution and size of objects that reflect the majority of light and has an approximately exponential falloff for naturally occurring scenes (*9*). We argue that the cone grain has a definite functional role (*1*) or there would be fewer cones. Thus, to determine the approximate optical image quality, we choose a class of natural scenes that tests the limiting performance of spatial vision for a given cone matrix. Such scenes can be characterized by a correlation function about equal to the cone spacing, or, more precisely, the width at half-height equals the center-to-center cone separation. Most naturally occurring scenes of interest to an animal are considerably more correlated than this and thus have less high-frequency energy. However, it is only those natural scenes of interest which are comparatively uncorrelated that limit the amount of undersampling, since they suffer aliasing distortion. In other words, if the above assumptions are prejudiced, it is against too much undersampling, so that the unbroken curve in Fig. 1 may be slightly lower. This leads to the same expression for ν_s/ν_o as in (*6*), but with $k = 0.32$, or reduced by about 0.58 from detection theory (*17*).
11. The greater the signal-to-noise ratio across the cones, the less undersampling is desirable. The signal-to-noise ratio is increased by extending the neural integration time and by removing correlation between neurons by having dissimilar spectral cone types (*17*).
12. M. Land and A. W. Snyder [*Vision Res.* **25**, 1519 (1985)] measured an optical modulation transfer function of 35 percent at the anatomical resolution frequency ν_s. W. S. Jagger (*ibid.*, p. 729) demonstrates that oversampling does not occur in the cane toad eye and that adjacent receptors are resolvable through the natural optics.
13. In the developing kitten eye, optical and retinal organization varies so as to preserve optimal sampling over a twofold change in eye size (A. Hughes and R. O. L. Wong, in preparation) and a range of improving image quality. The adult retinal organization is discussed by A. Hughes [*Exp. Brain Res.* **42**, 196 (1981); in *Progress in Retinal Research*, N. N. Osborne and G. J. Chader, Eds. (Pergamon, Oxford, 1985), vol. 4, pp. 243–313].
14. A. B. Carlson, *Communication Systems* (McGraw-Hill, New York, 1968).
15. According to J. I. Yellot, Jr. [*Science* **221**, 382 (1983); *Vision Res.***22**, 1205 (1982); *ibid.* **24**, 281 (1984)], cone undersampling is the unavoidable consequence of "fixed optical components" preventing image quality from being matched over a nonuniform retina. There is no known theoretical constraint supporting this contention [A. Hughes, in *Visual Neuroscience*, J. Pettigrew, K. Sanderson, W. R. Levick, Eds. (Cambridge Univ. Press, Cambridge, in press), chap. 5]. The snake eye, with its uniform cone mosaic, is an exception to his claim. He further postulated that cones "assume an optimally irregular arrangement that avoids Moiré distortion of high frequency and minimizes sampling noise for low frequencies," but this has been disputed [A. S. French, A. W. Snyder, D. G. Stavenga, *Biol. Cybern.* **27**, 229 (1977); J. Hirsch and R. Hylton, *Vision Res.* **24**, 347 (1984); T. R. J. Bossomaier, A. W. Snyder, A. Hughes, *ibid.* **25**, 145 (1985)].
16. A. Hughes, in *Handbook of Sensory Physiology*, F. Crescitelli, Ed. (Springer, New York, 1977), vol. 7, part 5, pp. 613–756.
17. T. R. J. Bossomaier and A. W. Snyder, in preparation.
18. G. Westheimer, in *Handbook of Sensory Physiology*, D. Jameson and L. M. Hurvich, Eds. (Springer, New York, 1977), vol. 2, part 4, pp. 170–187.
19. W. H. Miller, *ibid.*, vol. 7, part 6A, H. Autrum, Ed. (Springer, New York, 1977), pp. 69–143.
20. F. W. Campbell and R. W. Gubisch, *J. Physiol. (London)* **186**, 558 (1966).
21. G. Østerberg, *Acta Ophthalmol. Suppl.* **6**, 1 (1935).
22. J. A. M. Jennings and W. N. Charman, *Vision Res.* **21**, 445 (1981).
23. R. H. Steinberg, M. Reid, P. L. Lacy, *J. Comp. Neurol.* **148**, 229 (1973).
24. J. G. Robson and C. Enroth-Cugell, *Vision Res.* **18**, 159 (1978).
25. W. Krause, *Int. Monatsh. Anat. Physiol.* **12**, 46 (1895).
26. We thank W. S. Jagger for confirming earlier measurements of P for the garter snake (Table 1). G. Westheimer suggested using information theory to determine the optimum sampling efficiency.

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Technical Comments

The Sympathochromaffin System and the Pituitary-Adrenocortical Response to Hypoglycemia

Mezey *et al.* (*1*) reported that, in rats, the β-adrenergic antagonist propranolol blocked the plasma ACTH response to insulin injection, and they suggested that insulin stimulates ACTH release by a mechanism in which catecholamines of peripheral origin act directly on the anterior pituitary. Their finding that direct application of insulin to pituitary cells in vitro did not evoke ACTH release is consistent with in vivo evidence that the counterregulatory responses, including sympathochromaffin activation and cortisol secretion, which follow insulin injection are the result of decrements in plasma glucose, not of insulin itself (*2*). There is, however, substantial evidence that peripheral catecholamines do not play a critical role in the pituitary-adrenocortical response to plasma glucose decrements in humans. First, administration of propranolol, with or without the α-adrenergic antagonist phentolamine, did not reduce the plasma cortisol response to insulin-induced hypoglycemia (*3*), to the late decrement in plasma glucose that follows glucose ingestion (*4*), or to the decrement in plasma glucose that results from suppression of glucagon secretion in the postabsorptive state (*5*) in humans. Second, patients with diabetes who had deficient epinephrine secretory responses to plasma glucose decrements exhibited plasma cortisol increments during hypoglycemia that were similar to those of patients with normal epinephrine responses (*6*). Third, normal increments in plasma cortisol in response to intravenously administered 2-deoxy-D-glucose, which is thought to produce cellular glucopenia, occurred in patients with cervical spinal cord transections and no sympathochromaffin response (*7*). Fourth, elevations of epinephrine (*8*) or of norepinephrine (*9*) to plasma concentrations that spanned their respective physiologic ranges did not stimulate cortisol secretion in normal humans. Although none of the human studies cited assessed ACTH secretion as such, stimulation of cortisol secretion is a direct function of the plasma ACTH level and is the only action of ACTH of established biologic importance. Thus, the suggestion of Mezey *et al.* from their studies in rats does not appear to apply to humans.

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REFERENCES AND NOTES

1. E. Mezey *et al.*, *Science* **226**, 1085 (1984).
2. G. B. Boli *et al.*, *N. Engl. J. Med.* **311**, 1214 (1984).
3. R. A. Rizza, P. E. Cryer, J. E. Gerich, *J. Clin. Invest.* **64**, 62 (1979); D. A. Popp, S. D. Shah, P. E. Cryer, *ibid.* **69**, 315 (1982); D. A. Popp, T. F. Tse, S. D. Shah, W. E. Clutter, P. E. Cryer, *Diabetes Care* **7**, 243 (1984).
4. T. F. Tse, W. E. Clutter, S. D. Shah, P. E. Cryer, *J. Clin. Invest.* **72**, 278 (1983).
5. S. G. Rosen, W. E. Clutter, M. A. Berk, S. D. Shah, P. E. Cryer, *ibid.* **73**, 405 (1984).
6. G. Bolli *et al.*, *Diabetes* **32**, 134 (1983); N. H. White *et al.*, *N. Engl. J. Med.* **308**, 485 (1983).

7. R. G. Brodows, F. X. Pi-Sunyer, R. G. Campbell, *J. Clin. Invest.* **52**, 1841 (1973).
8. W. E. Clutter, D. M. Bier, S. D. Shah, P. E. Cryer, *ibid.* **66**, 94 (1980).
9. A. B. Silverberg, S. D. Shah, M. W. Haymond, P. E. Cryer, *Am. J. Physiol.* **234**, E252 (1978).

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Mezey *et al.* (*1*) reported that insulin-induced hypoglycemia stimulated ACTH secretion of normal magnitude in rats with two types of brain lesions (hypophyseal stalk transection and medial basal hypothalamic destruction), either of which "removes all central input to the pituitary. . . ." Because treatment with propranolol blocked the ACTH response in such lesioned rats the authors concluded that the ACTH response was driven by systemic elevations in catecholamines. We are puzzled by these results and wonder if, indeed, the separation of the influence of the brain from the pituitary was as complete as the authors intended it to be. Hypothalamic lesions that separate the anterior medial basal hypothalamus from the rest of the brain have been reported to inhibit basal activity in the adrenocortical system (*2*) and to abolish (*3*) or very markedly inhibit (*2, 3*) the corticosterone (and presumably the ACTH) response to insulin-induced hypoglycemia. In those studies histological verification of the lesion was carefully and stringently performed. Moreover, medial basal hypothalamic ablation inhibited the rise in corticosterone after hypoglycemia as did pharmacological blockade of hypothalamic input to the corticotrope with chlorpromazine-Nembutal-morphone (*4*). In the report by Mezey *et al.*, initial ACTH levels in lesioned rats were as high as in unlesioned controls, and the response to hypoglycemia was not blunted. There is another report in which rats with hypothalamic lesions were preselected for their capacity to respond to ether stress; in this selected, responsive group of rats, hypoglycemia induced by large doses of insulin caused a rise in plasma ACTH of normal magnitude (*5*). These results suggest that in the complete absence of central nervous system input to the pituitary there is a minimal response of the adrenocortical system to insulin-induced hypoglycemia in rats, whereas in the presence of some input, the response may be normal. Furthermore, when 2-deoxyglucose was used to produce intracellular glucopenia and a resultant activation of the adrenocortical and sympathochromaffin systems, the magnitude of the corticosterone response to this stimulus was not affected by prior splanchnic nerve transection, which markedly diminished the norepinephrine and abolished the epinephrine responses (*6*). We think that this evidence favors the possibility that the lesions made in the study by Mezey *et al.* did not abolish all communication between brain and pituitary and that the increase in ACTH secretion resulting from insulin-induced hypoglycemia may not be mediated by catecholamines of peripheral origin in the rat.

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REFERENCES AND NOTES

1. E. Mezey *et al.*, *Science* **226**, 1085 (1984).
2. M. Karteszi *et al.*, *ibid.* **111**, 535 (1982).
3. T. Aizawa and M. A. Greer, *Endocrinology* **110**, 1693 (1982).
4. T. Aizawa *et al.*, *Metabolism* **30**, 996 (1981).
5. J. Weidenfeld *et al.*, *Exp. Brain Res.* **48**, 306 (1982).
6. C. Sun *et al.*, *Endocrinology* **105**, 307 (1979).

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It is generally accepted that corticotropin-releasing factor, and perhaps vasopressin and cholecystokinin, participate in the central regulation of pituitary ACTH release. Recently, we (*1*) proposed that under certain circumstances (for example, insulin hypoglycemia) peripheral catecholamines may also affect ACTH secretion. Dallman and Greer question the validity of our results and interpretations and suggest that we did not abolish all communication between brain and pituitary. They indicate that they found in their studies—in which "histological verification of the lesions was carefully and stringently performed"—that hypothalamic lesions inhibit basal activity in the adrenocortical system and abolish corticosterone's response to insulin (*2–4*). We controlled histologically just as stringently as they did for the completeness of lesions. Furthermore, dopamine levels were almost undetectable in the posterior pituitary when insulin stress was administered to animals whose pituitary stalk was transected (sham 11.69 ± 0.55, $n = 6$; lesioned 0.78 ± 0.38; $n = 9$; values in nanograms per milligram of protein). Only those animals showing complete lesions were used in our studies. Other forms of stress, such as ether administration, acute immobilization, and 0.3 ml of 4 percent Formalin injection, which are believed to act through central mechanisms to release ACTH, did not raise plasma ACTH immunoreactivity in animals with similar lesions. Unlike Dallman and Greer, Vermes *et al.* (*5*) and Rivier *et al.* (*6*) found plasma ACTH immunoreactivity was the same in rats that had undergone hypothalamic deafferentation as in sham-operated rats (Vermes *et al.*, control 140 pg/ml, lesioned 130 pg/ml; Rivier *et al.*, control 500 pg/ml; lesioned 600 pg/ml). Greer himself (*2*) reported that plasma ACTH levels were the same in sham-operated animals and in animals with anterolateral deafferentation (sham 77 pg/ml, lesioned 70 pg/ml). Thus, there is considerable disagreement among investigators.

In the paper cited by Dallman and her coworkers (*3*), animals were subjected to medial basal hypothalamic lesioning and tested 4 days later. In our studies, insulin was injected 36 hours after the lesions were made. In their study, insulin injection increased plasma corticosterone levels approximately two- to threefold. We found similar changes in ACTH levels. The basal corticosterone levels in Dallman's lesioned animals were greatly reduced in contrast to those in ours. We performed our studies (*1*) only 36 hours after making lesions because we were concerned about the ability of corticotrophs to respond after chronic deprivation of releasing factor and the possibility of rapid revascularization. The markedly reduced basal corticosterone levels found by Dallman's group 4 days after hypothalamic lesioning may reflect infarction of the anterior pituitary, despite their assertion that the blood supply to the pituitary was intact.

We did not state in our report (*1*) that our lesioned animals had an ACTH secretion of normal magnitude. In fact, the lesions do seem to reduce the response to insulin somewhat. This suggests that insulin may act centrally as well as through peripheral mechanisms to release ACTH. We believe that the criticisms of Dallman and Greer are unjustified and are inconsistent with their own published data. We believe that our data show that insulin in part stimulates ACTH release by a mechanism that involves the action of peripheral catecholamines on the anterior pituitary.

While our studies in rats may have relevance to humans, we did not say that our data could be directly extrapolated to any other species. It is evident that there is no way to clearly prove or disprove our hypothesis in humans, and the examples given by Cryer do not eliminate the possibility that peripheral catecholamines participate in the regulation of ACTH release.

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REFERENCES AND NOTES

1. E. Mezey *et al.*, *Science* **226**, 1085 (1984).
2. T. Aizawa and M. Greer, *Endocrinology* **110**, 1693 (1982).
3. M. Karteszi *et al.*, *ibid.* **111**, 535 (1982).
4. T. Aizawa *et al.*, *Metabolism* **30**, 996 (1981).
5. I. Vermes *et al.*, *Neurosci. Lett.* **27**, 89 (1981).
6. C. Rivier *et al.*, *Endocrinology* **110**, 272 (1982).

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