5′-GGTGAAGCTGTTCATCACGTGC-3′; probe 2 (splice junction) = 5′-AGTTAAAGGTAC*ACG-CAAAAGATAC-3′ (the asterisk represents the splice junction); probe 3 (intron, noncoding, 73 to 95 nucleotides from 5′ splice site) = 5′-GGTGCAAGCAAAACCTTGGCTGC-3′; probe 4 (intron, ORF, 239 to 258 nucleotides from 5′ splice site) = 5′-GTCCCGTTCTTAACCATTTC-3′. The sequence of the *nrd*B gene has been described (*9*).

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The Inversion of Sensory Processing by Feedback Pathways: A Model of Visual Cognitive Functions

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The mammalian visual system has a hierarchic structure with extensive reciprocal connections. A model is proposed in which the feedback pathways serve to modify afferent sensory stimuli in ways that enhance and complete sensory input patterns, suppress irrelevant features, and generate quasi-sensory patterns when afferent stimulation is weak or absent. Such inversion of sensory coding and feature extraction can be achieved by optimization processes in which scalar responses derived from high-level neural analyzers are used as cost functions to modify the filter properties of more peripheral sensory relays. An optimization algorithm, Alopex, which is used in the model, is readily implemented with known neural circuitry. The functioning of the system is investigated by computer simulations.

NUCLEI IN THE THALAMUS TRANSMIT information received from the senses to appropriate centers in the neocortex. These thalamic relays are also affected by reafferent neural pathways emanating from the neocortex and the brainstem reticular formation. The function of these feedbacks has long been a puzzle to neurophysiologists. In the visual system the cortex exhibits a variety of neural maps that preserve to some extent the retinotopic character of the stimulus: neighboring neurons represent neighboring points in sensory space. At the same time, feature-analyzing networks will tend to transform the initially retinotopic pattern into one in which codes are substituted for particular sensory features. Thus, at the cortical level, we know that single neurons express by their activity very specific features of the visual input and may be presumed to form part of feature analyzing systems (*1*). In the present model we propose a mechanism whereby central coded responses are able to recreate peripheral retinotopic activity. Both corticofugal fibers and brainstem afferents to the dorsal lateral geniculate nucleus (dLGN) play a role in this process.

In the mammalian visual system the dLGN is more than a passive relay between the retina and the visual cortex. The corticofugal fibers make up a large fraction of all inputs into the dLGN (*2*). In addition, fibers from centers in the brainstem and midbrain reticular formation are synaptically connected to neurons in the dLGN (*3*).

Figure 1 shows the connections between neurons in the dLGN, the perigeniculate nucleus (PGN), visual cortex, and afferents from the retina and reticular formation. Circles represent populations of neurons. The diagram shows the retinal afferents to geniculate relay cells (G) and interneurons

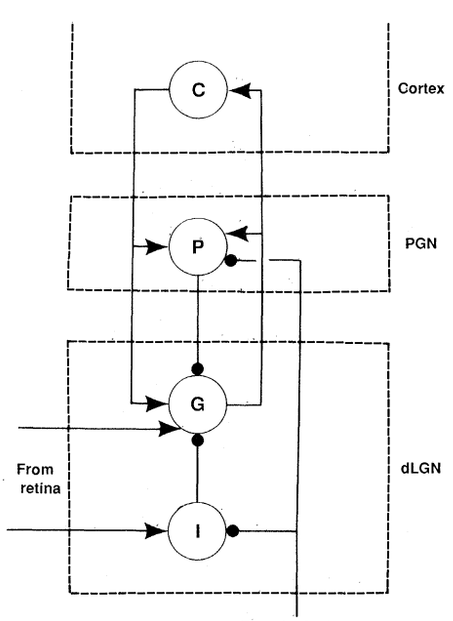

Fig. 1. Neural connectivity in the mammalian visual system. G, relay cells in dLGN; I, interneurons in dLGN; P, cells in PGN; C, cells in visual cortex. Open circles represent populations of neurons. Arrows represent excitatory synapses and filled circles represent inhibitory synapses.

(I). Fibers ascending from the dLGN to the cortex make collateral connections with PGN cells (P), and corticofugal fibers synapse with PGN cells on their way back to the dLGN (*4*). PGN cells are inhibitory on relay cells in the dLGN and receive diffuse inputs from the brainstem reticular formation. We have taken these inputs to be inhibitory (*2*). Unlike the corticofugal fibers, which are retinotopically arranged, afferents from the reticular formation, at least those emanating from the locus coeruleus, appear to be diffusely distributed over the dLGN (*5*).

Visual information is evidently modified on its way to the cortex, and the modifications carry with them information derived from higher level cortical analyzers and the presumably more global information from the reticular core.

Visual centers in the cortex also exhibit reciprocal innervation (*6*), and are affected by reafferents from the reticular formation (*7*). The mammalian visual pathway, after the retina, thus appears as a succession of mutually interacting centers, which are also subjected to the global influence of the reticular core.

Figure 2A illustrates the mechanism by which inverse sensory processing may be achieved through feedback. This was discussed in earlier versions of the model (*8*). Here, an array $\{x\}$ is incident on a sensory relay (a) that passes the information in modified form $\{y\}$ to a set of analyzers (b). The responses of these analyzers form a new array $\{r\}$ whose components reflect the presence of particular features in $\{y\}$. Responses are calculated as inner products between $\{y\}$ and static templates, and are multiplied by coefficients that define the sensitivities of the analyzers (*9*). All responses are summed in (s), producing a scalar quantity ρ. The summation is nonlinear, so that ρ is sensitive to the emergence of a single component of $\{r\}$, rather than to a superposition of many weaker responses. This is accomplished, for example, by adding the responses raised to a power greater than one.

Modification of $\{x\}$ proceeds by an iterative optimization process. Maximizing the global feedback ρ will have the following consequences:

1) If $\{x\}$ has some initial resemblance to one of the features defined by the analyzers and if the sensitivities of the analyzers are all the same, the pattern should converge on that feature. Missing parts of the pattern will be completed and extraneous features suppressed.

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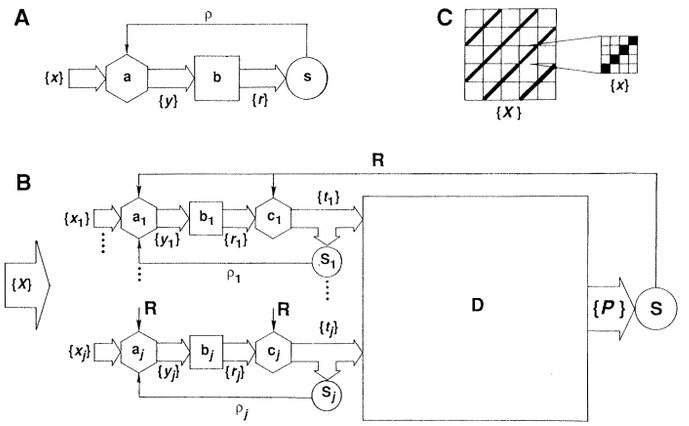

Fig. 2. Information flow in the model. (**A**) Single-stage system. Input array $\{x\}$ is incident on a relay, a, transmitting the modified information $\{y\}$ to analyzers in b. Responses in the array r are summed in s; the global response ρ provides feedback to a. (**B**) Hierarchic system. Subfields $\{x_1\}, \ldots, \{x_j\}$ of input array $\{X\}$ are transmitted by relays $a_1, \ldots, a_j$ to analyzers $b_1, \ldots, b_j$. Second level relays $c_1, \ldots, c_j$ transmit the modified responses $\{t_j\}$ to global analyzers in D. Responses $\{t_j\}$ and $\{P\}$ are summed nonlinearly in s_j and S to produce the responses ρ_j and R, respectively. (**C**) Visual field $\{X\}$ and subfields $\{x\}$.

2) If the input is featureless and if one of the analyzers has an enhanced sensitivity, the input pattern should converge on the feature selected by the more sensitive analyzer.

3) If the input is featureless and if the sensitivities of the analyzers are all the same, the system will exhibit initial "frustration," an unstable condition that is resolved by the presence of noise. Again, $\{y\}$ will converge on a single feature.

The hierarchic system shown in Fig. 2B is patterned after the mammalian visual system and uses structures similar to those in Fig. 2A as building blocks. Here $\{X\}$ represents input over the entire visual field, as contained in the activities conveyed to the dLGN by the optic nerve. The field is divided into subfields that correspond roughly to the areas "seen" by a typical complex cell in the visual cortex (*1*). Each subfield is made up of an array of pixels (Fig. 2C). Activities in the pixels of the jth subfield form the pattern $\{x_j\}$. The relay a_j transforms $\{x_j\}$ into $\{y_j\}$, which it transmits to the feature analyzers in b_j. The responses of these analyzers form the array $\{r_j\}$. In a second stage of modification, $\{r_j\}$ is transformed in c_j to $\{t_j\}$. These transformed responses are summed in s_j, and the scalar results ρ_j are returned to the relays a_j. The same arrays are also transmitted to a set of global analyzers in D that "see" the responses from the entire visual field and form the output array $\{P\}$. The components of $\{P\}$ are again summed nonlinearly in S, generating the global response R. The same R is used in all relays c_j and—together with the responses ρ_j—in all relays a_j. Optimizations are carried out in the relays a_j and c_j, modifying the components of their inputs so as to maximize the scalar feedbacks they receive.

We draw the following analogy to the visual system: a_j may represent a group of relay neurons in the dLGN whose activities are received by the cortical analyzers in b_j. In the optimization algorithm, arrays $\{y\}$ are stored and updated iteratively. The corticofugal fibers may serve this storage function by returning these arrays to the thalamic relays. Unit D in Fig. 2B represents higher cortical analyzers that are sensitive to large portions of the visual field. Finally, a global response R emanates from the brainstem and is diffusely transmitted to the thalamus and areas in the cortex.

In many optimization problems a single scalar function $F(y_1, \ldots, y_N)$, called the cost function, is to be maximized or minimized by choosing the best set of parameters $y_1, \ldots, y_N$. When multiple extrema exist, simple hill-climbing algorithms are generally inadequate. Iterative procedures are often used, in which one parameter at a time is changed by small increments. In a procedure introduced by Metropolis *et al.* (*10*), a stochastic algorithm decides acceptance or rejection of a particular step and thus avoids trapping in secondary extrema. The method has recently been developed further and applied to various optimization problems (*11*).

Alopex (*12*), the optimization algorithm we use here, was first designed to aid in the experimental determination of visual receptive fields (*13*). It differs from other algorithms in that the cost function is computed after all parameters are changed synchronously. Also, the changes, which are always accepted, depend on the recent history of the system.

Different forms of the Alopex algorithm have been used (*8, 13, 14*). They all have the following in common. The parameters y_i determining the cost function F are changed simultaneously by small amounts that are determined in part by noise, in part by the cross-correlation between the previous change in the parameter, and the change in the cost function. Noise is represented by an effective temperature that can be lowered gradually to improve convergence. In the version of Alopex used in the present work, the relays a_j and c_j in Fig. 2B are considered filters that modify the components of the afferent arrays. We write for the nth iteration of the process:

$$y_i^{(n)} = k_i^{(n)} \cdot x_i^{(n)} \tag{1}$$

where the filter coefficient $k_i^{(n)}$ is a slowly changing variable

$$k_i^{(n)} = k_i^{(n-1)} + \delta_i^{(n)}$$

and

$$\delta_i^{(n)} = \begin{cases} +\delta \text{ with probability } p_i^{(n)} \\ -\delta \text{ with probability } [1 - p_i^{(n)}] \end{cases} \tag{2}$$

and

$$p_i^{(n)} = 1/[1 + \exp(-\Delta_i^{(n)}/T)] \tag{3}$$

where

$$\Delta_i^{(n)} = [y_i^{(n-1)} - y_i^{(n-2)}] \cdot [F^{(n-1)} - F^{(n-2)}] \tag{4}$$

In this formulation the filter coefficients execute random walks with a superimposed bias that tends to maximize F. Trapping in local maxima is avoided by the presence of noise. More detailed descriptions of Alopex algorithms, including choice of parameters, have been presented elsewhere (*8, 13, 14*).

In Fig. 3 we present a neuronal circuit patterned after known connectivity in dLGN. The proposed circuit is made up of three relay cells G_1, G_2, G_3 in the dLGN: one ON- (G_1) and one OFF-response cell (G_3) whose inputs x_1 and x_3 are proportional to the rates of increase and decrease of a retinal stimulus, respectively, and a sus-

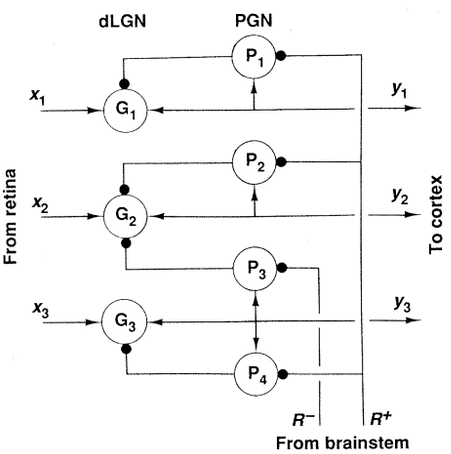

Fig. 3. Proposed connectivity of afferents and reafferents to dLGN. x_1, x_2, x_3: retinal afferents; y_1, y_2, y_3: thalamocortical fibers and corticothalamic returns; R^+, R^-: brainstem afferents to PGN; dLGN relay cells: G_1 (ON response), G_3 (OFF response), and G_2 (sustained response).

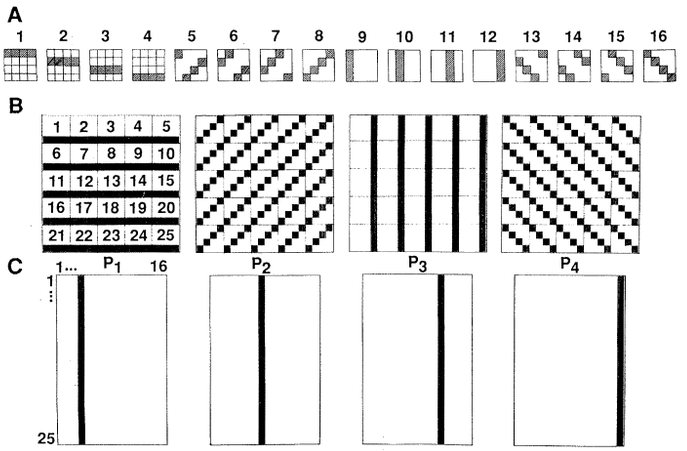

Fig. 4. Templates of feature and pattern analyzers. (**A**) Sixteen features defined by analyzers b_j in Fig. 2B. (**B**) Global patterns P_1–P_4 in visual space defined by templates in D. (**C**) Templates to detect visual patterns in (B). Each row represents one of 25 subfields, each column one of 16 features as defined in (A). Blank elements in templates are zeroes, shaded elements are ones.

tained cell G_2, whose input x_2 is proportional to the retinal stimulus. These three relay cells form one element in a retinotopically arranged array. The thalamocortical axons of G_1, G_2, G_3, carrying the modified inputs y_1, y_2, y_3, make collateral excitatory connections as shown with four PGN cells (P_1–P_4). Excitatory, retinotopically arranged corticofugal fibers return to the dLGN, where they synapse again with relay cells. PGN cells produce recurrent inhibition on dLGN relay cells. Ascending fibers from centers in the brainstem reticular formation make inhibitory connections with PGN cells.

The putative circuit in Fig. 3 uses some of the known anatomical features shown in Fig. 1. We have retained the excitatory collateral inputs of thalamocortical fibers to neurons in the PGN and the inhibitory action of PGN cells on dLGN relay cells; the double arrows from dLGN to cortex in Fig. 3 indicate retinotopic excitatory corticothalamic feedback. Ascending fibers from the brainstem reticular formation are shown to be inhibitory on PGN cells.

We have further assumed that the inhibitory reafferents from the reticular formation contain two distinct pathways, one signaling an increase (R^+), the other a decrease (R^-) in activity at a particular brainstem center. Whereas the retinal afferents, thalamocortical, and corticothalamic connections are distinct for every element in the dLGN, we assume that all returns from the brainstem to the thalamic neurons are the same.

The circuitry in Fig. 3 satisfies qualitatively the Alopex optimization conditions of Eqs. 1 to 4 for each of the three signals to be relayed to the cortex, except for the fact that the probabilistic function $p_i^{(n)}$ (Eq. 3) is here replaced by a step function. The necessary nonzero temperature that determines $p_i^{(n)}$ may be due to inherent randomness of neural responses (*15*).

As an example, the activity of the relay cell G_2 will have a substantial increase only when an increase in x_2 is accompanied by activity in R^+ (which inhibits P_2, thus disinhibiting G_2). We see that, in general, the pattern of changes in x_1, x_2, x_3 is more likely to be transmitted to the cortex whenever it is correlated with input on the R^+ line, and blocked when R^- is activated. The short-term memory contained in the cumulative values of the filter coefficient $k_i^{(n)}$ in Eq. 2 can be expressed in terms of the preceding activity $y_i^{(n-1)}$. For the case of a stationary stimulus $\{x_i\}$, we obtain from Eqs. 1 and 2

$$y_i^{(n)} = y_i^{(n-1)} + \delta_i^{(n)} \cdot x_i \qquad (5)$$

This expression illustrates the function of the retinotopic feedback $y_i^{(n-1)}$ in our model.

In our computer simulation of the hierarchic system (Fig. 2B), we have chosen a visual field made up of 25 subfields, each of which consists of 16 pixels (Fig. 2C). Each of the 25 units b_j contains 16 analyzers defined by the templates shown in Fig. 4A. These were chosen to represent linear features of different orientations and locations within a given subfield, analogous to simple cortical fields (*1*). The responses $\{r_j\}$ of these analyzers are again modified by an Alopex process in c_j, and the modified outputs, 400 in all, go to a bank of global analyzers in D.

We have chosen four global patterns shown in visual space in Fig. 4B. Templates shown in Fig. 4C are designed to give maximal responses for the corresponding patterns in Fig. 4B. Here, the rows represent the 25 different subfields and the columns the responses of the 16 analyzers in Fig. 4A.

We carried out computer simulations under all three conditions: (i) sustained sensory inputs $\{X\}$ of partial patterns; (ii) featureless inputs with enhanced sensitivity on one of the analyzers; and (iii) featureless input without detection bias. In all cases we observed convergence on a response pattern at the second level and enhancement of the corresponding visual pattern at the first level. The system readily converged on the preferred pattern under conditions (i) and (ii), and somewhat more slowly, as expected, under condition (iii).

In Fig. 5 we show the results of a run under condition (ii). The global analyzers selected the four patterns shown in Fig. 4B by using the templates shown in Fig. 4C. Sensitivity of analyzer P_4 was set at twice that of the others. The initial pattern $\{X\}$ was featureless. Figure 5E shows the global response R (top trace) and the four analyzer responses P_1–P_4 as function of iteration number. The modified stimulus pattern $\{Y\}$ and the response array $\{T\}$ are shown (Fig. 5, A through D) after 2000 and 4000 iterations. Convergence on the preferred stimulus is evident at both the visual and the higher level representation.

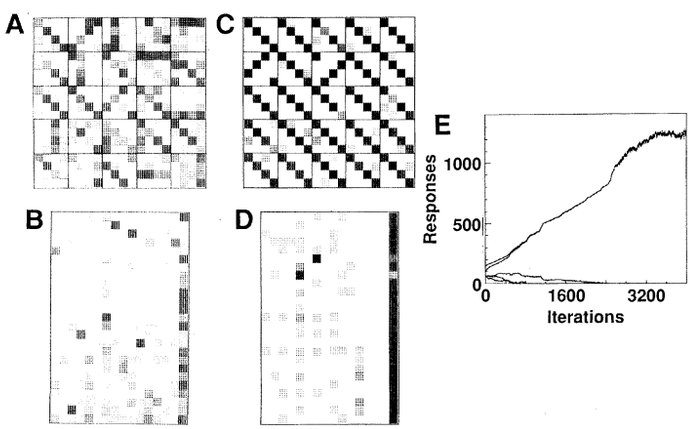

Fig. 5. Computer simulation of two-stage system with initially featureless input and heightened sensitivity of analyzer for pattern P_4 in Fig. 4. (**A** and **B**) Modified stimulus $\{Y\}$ and response array $\{T\}$ after 2000 iterations; (**C** and **D**) same after 4000 iterations; (**E**) global response R (top trace) and pattern responses P_1–P_4 versus iteration number.

We have shown that optimization processes, in which responses derived from higher level analyzers act as cost functions, are able to modify stimulus patterns at peripheral sensory stations through inversion of sensory processing. The existence of such feature-specific feedback could in principle be demonstrated by physiological studies. The Alopex process is iterative and inherently slow and may supplement other suggested cognitive mechanisms (*16*). The present model is not concerned with the formation or the functioning of neural analyzers, how-

ever. Many mechanisms for learning and pattern recognition have been proposed (*17*) and may be incorporated into this model. Central analyzers in our model are no longer the last neuronal processing stage. Instead, their responses are directed peripherally, where they select, modify, or generate stimulus patterns.

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Localization, Secretion, and Action of Inhibin in Human Placenta

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Inhibin is a gonadal glycoprotein hormone that regulates the production of follicle-stimulating hormone (FSH) by the anterior pituitary gland and exhibits intragonadal actions as well. The present study shows that inhibin-like immunoreactivity (inhibin-LI) is present in cells of the cytotrophoblast layer of human placenta at term and in primary cultures of human trophoblasts. Human chorionic gonadotropin (hCG) stimulated secretion of inhibin-LI from these cultured placental cells. This effect was mimicked by 8-bromo–cyclic adenosine monophosphate (8-bromo–cAMP), forskolin, and cholera toxin, suggesting that the mechanism of hCG induction of placental inhibin-LI secretion is cAMP-dependent. Incubation with an antiserum that binds the α-subunit of human inhibin increased the secretion of hCG and gonadotropin-releasing hormone–like immunoreactivity (GnRH-LI) from trophoblast cells in culture, suggesting a local tonic inhibitory action of endogenous inhibin on hCG and GnRH-LI release. The action of inhibin on hCG secretion may partially require the presence of placental GnRH, as suggested by evidence that a synthetic GnRH antagonist partially reverses the hCG increase induced by inhibin immunoneutralization. Results suggest paracrine roles for both inhibin and GnRH in the regulation of placental hCG production.

THE PLACENTA SYNTHESIZES AND SECRETES protein and peptide hormones that are active both in the maternal-fetal compartment and within the placenta. Human chorionic gonadotropin (hCG) is the polypeptide hormone that regulates progesterone production from corpus luteum and placenta (*1*); a placental gonadotropin-releasing hormone (GnRH) has been proposed as a local modulator of hCG secretion (*2*). Because peptides participate in the mechanism of control of hormonogenesis in the chorionic system (*3*), the presence of inhibin-like bioactivity and immunoreactivity in rabbit and human placenta at term (*4, 5*) suggests a possible role for inhibin in the endocrinology of pregnancy. Inhibin, a heterodimeric protein with α and β subunits, has been isolated from porcine and bovine follicular and ram rete testis fluids; it selectivity inhibits the release of follicle-stimulating hormone (FSH) from the pituitary (*6*). The amino acid structure of porcine, bovine, and human inhibin has been determined from complementary DNA (cDNA) sequences (*7*). We have also identified the human inhibin α-chain messenger RNA (mRNA) in a term placental cDNA library (*8*). The aim of the present study was to localize placental inhibin and explore its local action and regulation.

To determine where inhibin-like immunoreactivity (inhibin-LI) is present in placental cells, we conducted immunohistochemical localization studies on immersion-fixed samples of three fresh human placentas collected at term. Indirect immunofluorescence staining (*9*) with antiserum to porcine inhibin-α-(1–25)-Gly-Tyr revealed numerous immunoreactive cells in the placental villi (Fig. 1). These appeared to be localized in the central (cytotrophoblast) layer of the villi. When the antiserum was adsorbed with rat synthetic corticotropin-releasing factor (CRF) or GnRH, other peptides present in cytotrophoblasts (*2, 3, 10*) did not interfere with staining for inhibin-LI. The antisera used to detect inhibin-LI in human placenta were used previously to stain porcine and rat ovarian follicular granulosa cells, which are widely acknowledged to be the principal site of inhibin production in the female. Trophoblasts produce placental hormones (*1*), and cytotrophoblast cells show intense positive staining for GnRH, CRF, and somatostatin (*2, 3, 10*).

To study the regulation of inhibin secretion from the placenta, we developed a monolayer primary culture of human trophoblasts. Placenta collected from pregnancy at term was minced, rinsed, and dissected

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