geted deletion of the gene show early loss of hair cells (*7*, *8*), but a careful electron microscopic investigation is still needed to establish how far these hair cells can proceed in their differentiation. At least one molecular marker specific for hair cells, myosin VIIA, is expressed in immature hair cells in the homozygous mutants, which suggests that some differentiation can occur in the absence of *Pou4f3* (*9*). *Pou4f3* seems to be required for the continued differentiation and survival of hair cells at early stages, as well as for the long-term maintenance and repair of hair cells in adults (as shown by the Israeli family).

The *POU4F3* transcription factor joins myosin VIIA and diaphanous as molecules that, when defective, can result in nonsyndromic progressive hearing loss. All have been reported in the past few months (*10*, *11*). Two mitochondrial mutations, in the 12*S* rRNA and $tRNA^{Ser(UCN)}$ genes, also predispose to age-related hearing loss (*12*, *13*). The A1555G mutation of the 12*S* rRNA gene may be particularly common as a cause of progressive hearing loss in some populations, even in the absence of exposure to aminoglycosides, a drug to which carriers of this same mutation are extremely sensitive (*14*). Many human syndromes show late-onset progressive hearing loss as one of the manifestations, and some of the genes responsible have been identified (*15*, *16*). Furthermore, many inbred mouse strains progressively lose cochlear function, and a start has been made in localizing the relevant genes (*17*). Mice lacking the nociceptin receptor show an increased susceptibility (compared with wild-type mice) to noise-induced hearing loss shortly after exposure to a loud sound, implicating this receptor in the cochlea's protective or recovery mechanisms (*18*). Finally, various growth factors and similar agents can protect laboratory mammals when administered together with an otherwise damaging drug or noise.

All these observations suggest that time is running out on progressive hearing loss, and that a molecular understanding and intervention strategy may be closer than we think.

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TRANSCRIPTION

Promoter Logic

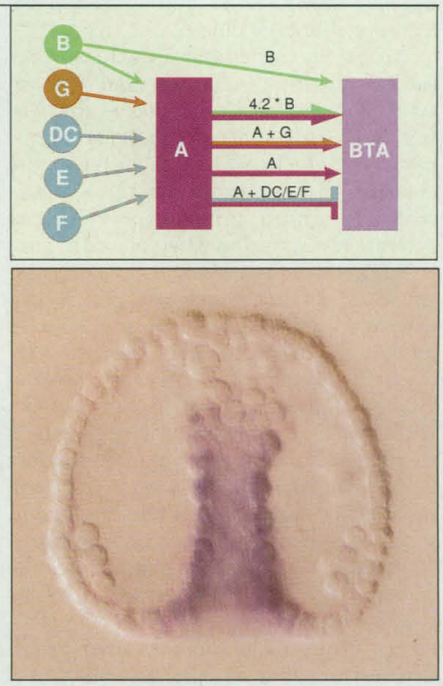
Gregory A. Wray

As animal embryos develop, genes are transcribed in strikingly complex patterns. Single genes can be expressed in several distinct domains, each of which is precisely delineated in space, time, and by level. Not surprisingly, a complicated regulatory apparatus is needed to exert this degree of control. The regulatory regions for animal genes (called promoters) typically span a few hundred to several thousand bases of DNA. Scattered through these promoters can be dozens of regulatory elements of various kinds that act as binding sites for distinct transcription factors (*1*). In some promoters, regulatory elements are grouped into "modules," each of which drives a discrete portion of the overall expression profile of the gene or prevents transcription at inappropriate times and places.

The presence of a particular regulatory element within a promoter reveals very little about how it influences the expression of a given gene. Instead, extensive experimental analyses are needed to decipher how the various regulatory elements within a promoter work together to modulate transcription. To do this, a normal or modified region of a promoter is fused to a reporter gene and introduced into an embryo, where it is exposed to the shifting array of transcription factors that modulate the expression of the endogenous gene. The resulting pattern of reporter gene expression can reveal, for instance, whether a particular regulatory element can activate or repress transcription at a specific time and place. Because of the complexity of most promoters, multiple experiments of this kind are needed to gain even a rough overview of how an expression pattern is generated.

In spite of considerable investigation of the function of animal promoters, general principles have remained frustratingly elusive. There is little logic apparent in the organization of regulatory elements, and even less in the way that they interact to regulate gene expression. The same regulatory element may activate transcription in one promoter and repress it in another, and the consequences of experimentally combining regulatory elements is rarely predictable. Furthermore, comparisons among the handful of well-characterized promoters have not yet revealed many functional similarities (*1*). Evidently, there are many ways to switch a gene on or off or to modulate levels of transcription. The impression one gets is that each promoter is a haphazard and unique assemblage of regulatory elements—able to get the job done, but not elegantly.

It therefore comes as a surprise to discover a promoter that operates in a logical



A genetic computer. The promoter of *Endo16* acts like a logic circuit (**top**) to determine expression of the gene (**bottom**).

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manner. On page 1896 of this issue (*2*), Yuh and colleagues report that the *Endo16* promoter of the sea urchin *Srongylocentrotus purpuratus* works remarkably like a tiny analog computer: Regulatory inputs from several promoter modules depend on a single module to integrate their status and in turn communicate directly with the basal transcription apparatus to produce a finely tuned response.

In the sea urchin embryo, transcription of *Endo16* commences shortly after gastrulation in all endodermal cells (see the figure) and remains active into late larval stages, by which time it is restricted to the midgut. This seemingly straightforward expression profile is driven by a promoter that consists of more than 30 regulatory elements dispersed through ~2.3 kb of upstream sequence (*3*). As in some other promoters, these protein binding sites are organized into distinct functional modules: three (A, B, and G) are capable of activating expression, and three (DC, E, and F) repress expression in cells that are adjacent to the gut. What makes the *Endo16* promoter so interesting, however, is the multifunctional, integrating role of module A.

Yuh *et al.* carried out an extensive series of quantitative assays that demonstrate how module A operates as the central processing unit of the *Endo16* promoter (see the figure). Its eight regulatory elements have several functions. *Transcriptional activation*: module A alone can activate transcription when one of its sites is bound by SpOtx, a homeodomain transcription factor. *Synergism*: when two other sites within module A interact with module B, transcription increases precisely by a factor of 4.2 over the level of module B alone. *Repression*: another site within module A interacts with module F to repress transcription in inappropriate cells. *Integration*: yet another site within module A interacts with the basal transcription apparatus. In this way, module A integrates and directly communicates the status of the rest of the promoter to the basal transcription apparatus. Furthermore, other experimental observations demonstrate that module A is absolutely required for modules DC, E, F, and G to have any effect on transcription.

To test their understanding of the *Endo16* promoter, Yuh and colleagues wrote a computer model that simulates these regulatory interactions. With the model, they made predictions about the consequences of specific promoter manipulations on transcription levels that were then tested experimentally. That these predictions were largely confirmed demonstrates not only an unusually complete understanding of how a particular promoter functions, but also the degree to which the *Endo16* promoter operates as an analog device. The "program" that runs this tiny computer is directly encoded in DNA as regulatory elements; its inputs are single molecules whose composition varies in time and among various cells of the embryo, and its output is a precise level of transcription.

Are other promoters equally logical? This is not the image that emerges from the literature. Many promoters appear either to have a simpler organization or to operate less logically than that of *Endo16*. On the other hand, few promoters have been examined with the many precise quantitative assays that were carried out by Yuh and colleagues. As the authors point out, only one of the eight regulatory elements within module A is concerned with spatial regulation. Nonquantitative assays would have completely missed most of the functions that the other seven elements encode. Some other promoters, such as the *even-skipped* promoter of *Drosophila*, have a clear modular organization (*4*) and may prove to operate through a single, integrating module as does *Endo16*.

Recasting the genome as thousands of simple computational devices has important implications for thinking about the evolution of genetic pathways. Little is known about how promoter structure and function evolve. To some extent, this is because the kinds of clear structure-function relations that guide our understanding of how proteins and morphology evolve are simply lacking for promoters. The results of Yuh and colleagues offer hope that the seemingly haphazard operation of animal promoters might become more comprehensible to developmental and evolutionary biologists alike.

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LIQUID CRYSTALS

Chiral Order from Achiral Molecules

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Chirality, the handedness of matter, and ferroelectricity, resulting from macroscopic electric polarization, are properties that had been believed to exist independently from each other. However, liquid crystals show a remarkable interplay between these phenomena, a fact that has great technological significance for display devices. Up to now, these ferroelectric displays use liquid crystals, which need to possess a chiral molecular structure. But in 1996, Niori *et al.* reported that a similar ferroelectric switching was observed in a liquid-crystalline phase formed by achiral molecules with a bow-shape resembling the form of a banana (*1*). Even though the molecules are achiral, these materials are able to form macroscopic chiral domains and, as Link *et al.* reported in a recent paper in *Science*, exhibit a spontaneous breaking of achiral symmetry in a bulk liquid crystal (*2*).

Max Born introduced the idea of creating a polar fluid as early as 1916 (*3*) in order to explain the formation of a nematic phase by dipolar interaction between the permanent dipoles of rodlike molecules. Although the proposed mean-field model was able to predict a transition from an isotropic phase to an anisotropic one, it had two major deficiencies. First, the dipolar interaction of the permanent dipoles of molecules forming nematic phases is too weak to produce a phase transition at room temperature, where it occurs. Worse, nematic phases are also formed by molecules that do not possess a permanent dipole at all. Second, the resulting anisotropic order of dipoles is such that, on average, the dipoles point in the same direction, so that an inherently ferroelectric fluid was predicted, but such a polar order was never found experimentally in nematic liquid-crystalline phases. Actually, the rod-shaped molecules exhibit a preferred parallel orientation, and even when the molecules bear a permanent dipole, there are, on average, as many dipoles pointing "up" as there are dipoles pointing "down."

According to this picture of the nematic phase, it was accepted for a long time that macroscopic polar order could not exist in liquid-crystalline phases in general. However, this view had to be revised when Meyer *et al.* (*4*) showed by a simple symmetry argument that layered liquid-crystalline

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