This pattern could imaginably be brought about by competitive interactions operating a switch whose position would be determined by the relative concentrations of the *Ubx* and *Antp* products — which are in turn determined by the segmentation genes.

The second remarkable point about the experiments is that they worked at all. *Ubx* is an extremely large and complex locus which Kornfeld and Hogness have shown gives rise by differential splicing to at least five different proteins whose correct expression normally depends upon a 40-kilobase 5′ control region called *bxd*. Krasnow was therefore surprised that he was able to get intelligible results from a simplified system in culture. Indeed, so far he has investigated only one of the five Ubx proteins, UBX Ib, specific binding sites for which have been identified in Hogness's laboratory by Phil Beachy, with Krasnow and Elizabeth Gavis, by footprinting *in vitro*. These sites, which were used in Krasnow's CAT plasmids, consist of TAA repeats of which a minimum of four are required to bind the UBX protein. Two of these repeated sequences occur downstream of the start sites of both *Ubx* and *Antp*, and *Antp* also has two upstream — an unusual arrangement that in the case of *Ubx* has been shown to be conserved in two distantly related *Drosophila* species. With the availability of a functional assay for the interactions of these developmental regulatory proteins with DNA, the activities of the other *Ubx* products, as well as the products of other segmentation and selector genes, and the significance of the unusual organization of the UBX Ib binding sites, are open to investigation.

## Regulatory interactions

Indeed, the success of these experiments opens up the possibility of directly testing the importance of interactions between regulatory proteins, and perhaps of DNA looping, in gene regulation in development. For example, interactions between regulatory proteins that bind to different parts the huge *bxd* control region may provide an explanation for some highly suggestive observations, made by Steve Helfand (now at Yale University, then in Hogness's laboratory), that as increasingly large deletions are made from the 5′ end of the *bxd* region, expression of *Ubx* becomes progressively lower (Helfand, personal communication). This could be explained by cooperative binding interactions of transcriptional activators to repeated upstream sites. But although the *bxd* region does contain TAA repeats, it is not yet known whether they are required for correct *Ubx* expression, nor is the identity of the proteins binding to the *bxd* region known. Conversely, a recent paper by Weinzierl *et al.*[9] on mutations in the coding regions of *Ubx* suggests a perhaps testable hypothesis about the relationship of *Ubx* structure to the function of its products as gene regulatory proteins. Their observation was as follows.

Between the exon encoding the homoeobox at the 3′ end of *Ubx* and the major coding portion of the 5′ exon lie two so-called microexons, both of which are present in the major *Ubx* transcript (Kornfeld and Hogness) but one or both of which are absent from less abundant messenger RNAs. Weinzierl *et al.* examined the effect of a nonsense mutation in the second of the microexons on the phenotype of the fly embryo. Such a mutation would terminate translation before the homoeobox, and the effect on the epidermis and embryonic nervous system is identical to that of two other mutations destroying the reading frame of all transcripts. During differentation of the adult central nervous system, however, where *Ubx* is normally also expressed, the mutation has no effect. Although it is possible that this is because adult differentation of the central nervous system is less sensitive to the loss of the *Ubx* product, the more interesting possibility is that the mutant microexon is normally spliced out of the adult neural transcript so that the mutation has no effect in this tissue.

It would follow from this that the regulatory protein would have subtly different properties in the two tissues; and Weinzierl *et al.* provocatively remark that the microexons encode short stretches of amino acids separating the homoeo domain from a second conserved domain and might be expected to affect the functional properties of the protein.

Experiments reported by Mark Ptashne (Harvard University) on *ersatz* looping in bacteriophage λ and the lambdoid phage 434 suggest how. The λ repressor has a flexible stretch of amino acids separating its DNA-binding domain from the carboxyl domain that mediates the protein–protein interactions necessary for dimerization and cooperative binding (see refs 7 and 8), and when its adjacent binding sites are artificially separated will bind cooperatively and cause the intervening DNA to loop out; 434 repressor, which is otherwise similar, has no flexible 'neck' and in analogous experiments fails to induce loops. Further speculation is clearly premature at this stage. □


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# George Khoury (1943–1987)

**GEORGE Khoury died on 25 April after several years of battle with lymphoma. He attributed several of his near-miraculous remissions from disease to his own "good protoplasm". He had that and much, much more.**

**Khoury's reputation as a molecular biologist began in the early 1970s among a small group of workers who pioneered the use of simian virus 40 as a model for eukaryotic transcription and replication. He made the first transcription map of an animal virus, demonstrating the use of restriction enzymes in such mapping studies. This mapping subsequently enabled him to discover that simian virus 40 transcripts are not encoded by contiguous stretches of DNA, an important clue that paved the way for the discovery of RNA splicing. His group at the National Institutes of Health in Bethesda described for the first time the functioning of a eukaryotic *trans*-acting transcriptional regulatory element, the viral T antigen. These results showed that the T antigen acts as a negative regulator of its own messenger RNA synthesis.**

**More recently, his group showed that the T antigen is a positive regulator of late messenger RNA biogenesis. His work also showed the essential role of splicing in the maturation and export of messenger RNA precursors from the cell nucleus. He pioneered the molecular-biological characterization of the human pavovaviruses BK and JC, and in the early 1980s he and colleagues discovered transcriptional enhancer techniques.**

**For those who knew George Khoury there were other sides of his character that were as important as his creative, prolific scientific output. He showed by example that even in the heat of intense competition, generosity was preferable to pettiness; that acts of kindness and integrity accrue to one's name far more than do long lists of publications. When others would criticize a colleague, he would invariably muster a more charitable response. He showed that setbacks can be greeted with equanimity. His examples set a standard to be emulated.**

**In recent years, he became a critical catalyst in the renaissance of molecular biology at Princeton University, his alma mater. The declining energies of his last weeks were spent largely to ensure that colleagues who depended on him would be taken care of. He died three days before the announcement of his election to the US National Academy of Sciences.**

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