Cyclic AMP Control of Gene Expression in *Escherichia coli*: the Work of Ira Pastan

**Regulation of Inducible Enzyme Synthesis in *Escherichia coli* by Cyclic Adenosine 3′,5′-Monophosphate**

(de Crombrugghe, B., Perlman, R. L., Varmus, H. E., and Pastan, I. (1969) *J. Biol. Chem.* 244, 5828–5835)

**Regulation of *Lac* Messenger Ribonucleic Acid Synthesis by Cyclic Adenosine 3′,5′-Monophosphate and Glucose**

(Varmus, H. E., Perlman, R. L., and Pastan, I. (1970) *J. Biol. Chem.* 245, 2259–2267)

**Purification of and Properties of the Cyclic Adenosine 3′,5′-Monophosphate Receptor Protein Which Mediates Cyclic Adenosine 3′,5′-Monophosphate-dependent Gene Transcription in *Escherichia coli***

(Anderson, W. B., Schneider, A. B., Emmer, M., Perlman, R. L., and Pastan, I. (1971) *J. Biol. Chem.* 246, 5929–5937)

Ira Harry Pastan was born in Winthrop, Massachusetts in 1931. He attended Tufts College where he received his B.S. in 1953 and then went on to Tufts Medical School and earned his M.D. in 1957. After 2 years as an intern and assistant resident at the Yale University School of Medicine’s Grace-New Haven Hospital, Pastan joined the National Institutes of Health (NIH) as a clinical associate in the Clinical Endocrinology Branch. His intention was to pursue a career in clinical medicine or clinical research.

At the NIH, Pastan cared for patients with endocrine disorders and studied the mechanism of action of thyroid-stimulating hormone (TSH). He enjoyed research so much that when his 2 years as a clinical associate were over, he decided to pursue a career in basic research. He remained at the NIH and became a postdoctoral fellow with Earl Stadtman, whose work was featured in a previous *Journal of Biological Chemistry* (JBC) Classic (1). Pastan worked on microbial biochemistry with Stadtman for the next 2 years and then returned to the Clinical Endocrinology Branch in 1963 as a senior investigator to begin his own studies.

At first, Pastan went back to working on the mechanism of TSH action. He soon expanded his efforts to include other peptide hormones and cyclic AMP, the second messenger that had just been discovered by Earl Sutherland, as discussed in a previous JBC Classic (2). Pastan started studying the mechanism of action of cyclic AMP using the thyroid gland but decided to switch to *Escherichia coli* because he thought it would be easier to study the problem in a simpler organism.

In the mid-1960s, it was known that glucose repressed inducible enzyme synthesis in *E. coli* and that cells growing on glucose had low levels of cyclic AMP, whereas starved cells had high cyclic AMP levels. This suggested to Pastan that cyclic AMP might be involved in regulating the synthesis of inducible enzymes. To set about proving this hypothesis, Pastan and his colleagues examined the effects of cyclic AMP on a wide variety of inducible enzymes and transport proteins. This is the subject of the first JBC Classic reprinted here. They found that cyclic AMP overcomes the glucose repression of the synthesis of several inducible enzymes including β-galactosidase, galactokinase, glycerokinase, and thymidine phosphorylase. From these results, Pastan concluded, “Since glucose lowers the intracellular concentration of cyclic AMP in *E. coli*, we propose that the intracellular level of cyclic AMP regulates the rate of
synthesis of many inducible enzymes in *E. coli* and other microorganisms and that glucose lowers the rate of synthesis of these enzymes by decreasing the intracellular level of cyclic AMP.”

Following up on these findings, Pastan began to investigate the mechanism by which cyclic AMP and glucose alter the rate of enzyme synthesis. Several groups had suggested that glucose repression was mediated through a reduction in the rate of *lac* mRNA formation, but no one had been able to directly measure *lac* messenger levels or synthesis rates during glucose repression. In the second JBC Classic reprinted here, Pastan and his colleagues describe hybridization assays for the measurement of synthesis rates of *lac* messenger RNA and demonstrate that cyclic AMP and glucose alter the rates of β-galactosidase mRNA production.

Pastan eventually discovered that the stimulation of inducible enzyme synthesis requires the interaction of cyclic AMP with a protein he named the cyclic AMP receptor protein (CRP). In the final JBC Classic reprinted here, Pastan and his colleagues describe the purification and properties of this protein.

Pastan later found that cyclic AMP produces an allosteric change in CRP, which increases the affinity of the receptor for DNA sequences in the promoters of many genes. This results in the initiation of transcription and an increase in gene activity. This was the first example of positive control of gene expression. Prior to these studies, the major mechanism of gene regulation was thought to be repression.

In 1970 Pastan was appointed Chief of the newly established Laboratory of Molecular Biology in the National Cancer Institute, a position he continues to hold. He changed the focus of his research from basic to clinical to develop new approaches to cancer treatment. More information on Pastan’s cancer research can be found in his JBC Reflections (3).

Pastan has received many awards and honors in recognition of his contributions to science, including the NIH G. Burroughs Mider Lectureship (1973) and the Pierce Immunotoxin Award (1988). He was elected to both the National Academy of Sciences and the American Academy of Arts and Sciences.¹

Harold E. Varmus, Pastan’s postdoctoral fellow and coauthor on two of these Classic papers, has also had a very successful career. After his time in Pastan’s lab, Varmus became a postdoctoral fellow with J. Michael Bishop at the University of California, San Francisco. During this time, Varmus and Bishop performed the research that would result in their 1989 Nobel Prize in Physiology or Medicine for the discovery of the cellular origin of retroviral oncogenes. Varmus later became the Director of the National Institutes of Health (1993–2000) and then President of the Memorial Sloan-Kettering Cancer Center in New York City (2000 to present).

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¹ Biographical information on Ira Pastan was taken from Ref. 3.
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