

Hsie A W & Puck T T. Morphological transformation of Chinese hamster cells by dibutylryl adenosine cyclic 3':5'-monophosphate and testosterone. *Proc. Nat. Acad. Sci. US* 68:358-61, 1971.

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Chinese hamster ovary cells growing randomly in a compact, multilayered-colony were converted into a monolayer of elongated fibroblast-like cells when treated with dibutylryl cyclic AMP and testosterone suggesting a role of cyclic AMP in regulating cell shape and malignant conversion. [The SCI® indicates that this paper has been cited in over 560 publications since 1971.]

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"As a graduate student with Howard V. Rickenberg at the department of bacteriology (later changed to microbiology and now biology), Indiana University, Bloomington, I studied the role of phosphoenolpyruvate carboxykinase (PEPCK) in carbohydrate metabolism in *Escherichia coli*. I isolated a mutant (AB257^{pc-1}) which formed high levels of PEPCK and other catabolic enzymes, such as beta-galactosidase and tryptophanase, when grown in a medium containing glucose as the sole source of carbon exhibiting the glucose effect or catabolite repression. The observation that the addition of glucose-6-phosphate severely repressed the formation of beta-galactosidase in this glucose-resistant mutant, AB257^{pc-1}, led us to suggest the possible role of glucose-6-phosphate in catabolite repression.¹ A hypothesis proposing the regulatory role of adenosine 3':5'-monophosphate (cyclic AMP) as a 'derepressor' on catabolite repression was advanced by Ira Pastan and his colleagues.² This hypothesis was supported by subsequent analysis of AB257^{pc-1} by Rickenberg and his colleagues,³ who showed that AB257^{pc-1} is defective in cyclic AMP phosphodiesterase, an enzyme which hydrolyzes cyclic AMP to 5'-AMP.

"I undertook my postdoctoral work with Theodore T. Puck, of the University of Colorado Medical Center, to learn somatic cell genetics. Initially, I studied the biochemistry and genetics of auxotrophic mutants of Chi-

nese hamster ovary (CHO) cells. In the spring of 1970, my interest in the role of cyclic AMP in cellular function and the boredom of mutant characterization led me to investigate whether cyclic AMP or its derivatives would enable CHO cells to utilize lactose as a sole source of carbon, and to study the hypothetical mammalian equivalent of the lac operon. In my first experiment to determine the toxicity of N⁶,O²-dibutylryl cyclic AMP to CHO cells, I found that after seven days incubation in the presence of 0.3-1.0 mM of dibutylryl cyclic AMP, CHO cells were converted from a randomly growing, compact, epithelial-like (transformed) morphology to a contact-inhibited, elongated, fibroblast-like (normal) form.⁴ This was consistent with the reports that some tumors and transformed cells are defective in the cyclic AMP system; treatment with dibutylryl cyclic AMP apparently restores the normal behavior of the transformed (CHO) cells. Thus, cyclic AMP may play a role in regulating two fundamental biological processes: cellular morphogenesis and malignant conversion. These implications may have stimulated the later explosive research by various investigators in the continued search for the role of cyclic nucleotides in carcinogenesis. Similar findings concerning the effects of cyclic AMP have been made by others using other cell types.

"Meanwhile, Puck observed that steroid hormones, such as testosterone, caused effects similar to those produced by dibutylryl cyclic AMP, but they were less pronounced. Testosterone exerted a synergistic effect with dibutylryl cyclic AMP. I remember well the fine reception of these preliminary findings (with Charles A. Waldren)⁴ at the annual meeting of the American Society of Cell Biology in 1970 and the full paper (with Puck) in 1971. In 1980, I received the Distinguished Alumni Service Award from Indiana University partly in recognition of this work.

"Looking back 14 years, I am indebted to my mentors Puck and Rickenberg, who provided the environment, foresight, and encouragement to make my work possible and interesting."

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