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Razin A & Riggs A D. DNA methylation and gene function. *Science* 210:604-10, 1980.
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Control of gene activity by DNA methylation has been recognized as a logically attractive possibility. Recent experiments suggest that DNA methylation is a key element in the hierarchy of control mechanisms that govern vertebrate gene function and differentiation. On the basis of these experiments, a model for the establishment and maintenance of a differentiated state is presented. [The *SCI*® indicates that this paper has been cited in over 660 publications.]

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It was the fall of 1977 when I arrived at the City of Hope in Duarte, California, for a sabbatical year with Art Riggs. I had been working for several years on DNA methylation in prokaryotes and had just moved to eukaryotic systems, employing novel analytical methods that John Sedat and I developed during his stay in my laboratory in Jerusalem. Riggs was also interested in DNA methylation, having postulated its function in X-chromosome inactivation and differentiation.[1]

Over lunch, on my second day in Duarte, I discussed with Riggs new ideas that we both had on the biological function of DNA methylation. We agreed that the time had come to publish an article that would summarize the available data on DNA methylation and draw a general model that would serve us in designing future experiments. However, it was a very busy year. Riggs had just finished cloning the first chemically synthesized gene, somatostatin, and became immediately engaged in cloning the human insulin gene. I found myself busy in developing the first site-specific mutagenesis method using chemically synthesized oligonucleotides.[2] So, the planned article had to wait until the fall of the next year, when I wrote a very crude draft and left it with Riggs upon my return to Israel. In December Riggs came to Jerusalem for three weeks, and a semifinal draft was ready by the time he left. It took, however, another year until the article was finally published, partly because the manuscript was misplaced in the *Science* editorial office.

In retrospect, it was rather fortunate that the birth of this article took so long. Several very crucial experiments were published in 1978 and 1979 that allowed us to construct a detailed model that associates DNA methylation patterns, their change during differentiation, and gene activity. A collaborative effort by Howard Cedar, me, and our students, together with work done in several other laboratories, resulted in the verification of the theory presented in our paper.

Many laboratories in the US and Europe have published numerous reports supporting the predicted model. As an example, the inactivation of the X chromosome has been shown unequivocally to be associated with DNA methylation. Over the past five years, hundreds of papers have been published that demonstrate, in one way or another, the association of DNA methylation and gene activity. This burst of publications relating to our article seems to explain the high rate of citation that it has received.

Our article was sufficient to cover the entire field of DNA methylation in 1980; however, by 1984 it required an entire book.[3] As an example of the revolution made in biological thinking by the realization of the importance of DNA methylation in gene activity, I should mention the recently published paper on the association of DNA methylation in genomic imprinting.[4]

1. **Riggs A D.** X-inactivation, differentiation and DNA methylation. *Cytogenet. Cell Genet.* 14:9-11, 1975. (Cited 245 times.)
2. **Razin A, Hirose T, Itakura K & Riggs A D.** Efficient correction of a mutation by use of chemically synthesized DNA. *Proc. Nat. Acad. Sci. USA* 75:4268-72, 1978. (Cited 95 times.)
3. **Razin A, Cedar H & Riggs A D, eds.** *DNA methylation: biochemistry and biological significance.* New York: Springer-Verlag, 1984. 392 p.
4. **Swain J L, Stewart T A & Leder P.** Parental legacy determines methylation and expression of an autosomal transgene: a molecular mechanism for parental imprinting. *Cell* 50:719-27, 1987.

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