

This Week's Citation Classic

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Stent G S & Brenner S. A genetic locus for the regulation of ribonucleic acid synthesis. *Proc. Nat. Acad. Sci. US* 47:2005-14, 1961.
[Medical Research Council Unit for Molecular Biology, Cavendish Laboratory, Cambridge, England]

Some amino acid auxotrophs of *E. coli* continue to synthesize ribosomal RNA during amino acid starvation, in contrast to others which stop such synthesis as soon as they are deprived of the required amino acid. Conjugation experiments showed that there exists a locus, RC, on the bacterial chromosome whose abnormal, or 'relaxed,' allele causes less stringent control by amino acids over ribosomal RNA synthesis than its normal, or 'stringent,' allele. [The *SCF*[®] indicates that this paper has been cited in over 535 publications since 1961.]

Gunther S. Stent
Department of Molecular Biology
University of California
Berkeley, CA 94720

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"In 1961, Jacob and Monod had just revolutionized thinking about the mechanism of control of gene expression by publishing their operon model.¹ According to that model, the formation of specific classes of messenger RNA, and hence the quality of protein synthesis, is controlled by various metabolites which act at special regulatory genetic sites.

"So when I spent most of my 1961 sabbatical leave with Sydney Brenner at the Cambridge Medical Research Council (MRC) Unit for Molecular Biology, it seemed an obvious question to ask whether such special regulatory sites account also for the control of the overall rate of ribosomal RNA synthesis, and hence for the quantity of protein synthesis. This overall rate was known to depend on the presence of amino acids, because auxotrophic mutants requiring an amino acid for growth stop synthesizing not only protein but also ribosomal RNA as soon as they are deprived of that amino acid. Inasmuch as the amino acid could be shown to exert this regulatory role catalytically rather than stoichiometrically,^{2,3} it was plausible to suppose that it acted as an inducer of RNA syn-

thesis. Accordingly, I set out to try to find operon theory-like regulatory sites involved in the amino acid-mediated control of ribosomal RNA synthesis, by isolating mutant strains of *E. coli* defective in normal ribosomal RNA control. Before I had got very far in my mutant hunt, Brenner pointed out to me that at least one such defective strain was already available, namely *E. coli* K12 strain 58-161, whose amino acid auxotrophs continue ribosomal RNA synthesis at a near-normal rate in the absence of the required amino acid.⁴

"Brenner and I then decided to cross Hfr donor variants of 58-161 to normal F⁻ recipients, in order to see whether the abnormal regulatory behavior of that strain might be attributable to some mutant locus on the *E. coli* chromosome. Since the facilities for bacterial genetics were quite poor at the MRC Unit (then still located in a hut in the courtyard of the Cavendish Physics Laboratory), I got nowhere in my crosses. Finally, in desperation I took the train down to London every morning to do the crosses in William Hayes's lab at the Hammersmith Hospital, with the help of Hayes's associate, Royston Clowes. And within a week or so, I had my first recombinants which showed that the phenotypes of normal (or 'stringent') and defective (or 'relaxed') control of ribosomal RNA synthesis are indeed attributable to different alleles of a genetic locus, which we designated as RC (now known as *relA*), situated somewhere between the *xyl* and *gal* genes.

"I imagine that the brief paper in which we published this simple finding came to be frequently cited only after 1969 when Gallant and Cashel⁵ discovered that changes in intracellular concentrations of a hitherto unknown nucleotide tetraphosphate, which they designated 'magic spot,' are associated with the overall rate of RNA synthesis, and that the 'stringent' and 'relaxed' alleles of the RC locus have a differential effect on 'magic spot' levels. For this finding held out the promise of leading to an understanding of the control of the initiation of transcription by RNA polymerase. I have not followed these latter-day developments but it is my impression that, 'magic spots' notwithstanding, the problem of the overall control of bacterial RNA synthesis still remains to be fully solved.⁶

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