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Maaløe O & Hanawalt P C. Thymine deficiency and the normal DNA replication cycle. I. *J. Mol. Biol.* 3:144-55, 1961.
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The paper introduces the novel concept that, once initiated, a round of DNA replication will run to completion in the absence of protein synthesis. To start a new round, *de novo* protein synthesis is required. [The *SCI*® indicates that this paper has been cited in over 530 publications since 1961.]

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"Our Institute of Microbiology at the University of Copenhagen was established in 1958, and since that time we have received numerous visitors from the US. Phil Hanawalt was one of them. He had just finished his PhD work at Yale University when he came over to work with me in November 1958. At first he continued doing radiation studies with strain 15T⁻ of *Escherichia coli*. Nothing striking happened until one day, looking at Phil's latest results, I experienced the only true flash of scientific intuition I can recall: somehow his results suggested to me that a round of replication might be autonomous in the sense that protein synthesis was needed to start the round but not to run it to completion. It is well known that '...chance only favours the prepared mind,' and I'm sure that in this case the element of preparedness was a keen awareness that a culture of bacteria must be viewed as a population of cells representing all stages in cycles such as the DNA replication cycle.

"The concept of autonomy in a round of replication was tested in various ways. In the paper discussed here the phenomenon of 'thymineless death' (a characteristic of the strain we worked with) was important. We could show that, in an exponentially growing population, a small fraction (two to three percent) of the cells were immune to thymineless death and that this fraction probably represented cells that had completed a round of replication but not initiated a new round. Incubation with thymine, but without arginine and uracil (strain 15T⁻ requires both for growth), for 40-60 minutes caused the entire population of cells to accumulate in the 'immune state.' Presumably, this long period was needed for cells that had just started a round of replication to complete it. We use the term 'run out' experiment to describe this course of events.

"In the succeeding paper,[1] the analysis was pushed further by means of autoradiography of whole cells labeled in various ways by ^{3}H-thymine. We could show that if cells more or less double their DNA content in the absence of protein synthesis, they do not initiate a new round of replication until protein (and mass) synthesis has caught up with replication. The studies presented in our two papers in the *Journal of Molecular Biology* have inspired much subsequent work on DNA replication *in vivo*.[2,3]

"In my own laboratory, the 'run out' type of experiment has also been used to study RNA and protein synthesis *in vivo*. The antibiotic rifampicin has been useful for studying run-out of RNA synthesis,[4,5] and the growth rate of polypeptide chains has been estimated by pulse-chase labeling with radioactive amino acids."[6]

1. **Hanawalt P C, Maaløe O, Cummings D J & Schaechter M.** The normal DNA replication cycle. II. *J. Mol. Biol.* 3:156-65, 1961. (Cited 150 times.)
2. **Lark K G, Repko T & Hoffman E J.** The effect of amino acid deprivation on subsequent deoxyribonucleic acid replication. *Biochim. Biophys. Acta* 76:9-24, 1963. (Cited 335 times.)
3. **Bird R E, Louarn J, Martuscelli J & Caro L.** Origin and sequence of chromosome replication in *Escherichia coli*. *J. Mol. Biol.* 70:549-66, 1972. (Cited 160 times.)
4. **Pato M L & von Meyenburg K.** Residual RNA synthesis in *Escherichia coli* after inhibition of transcription by rifampicin. *Cold Spring Harbor Symp.* 35:497-504, 1970. (Cited 170 times.)
5. **Molin S.** Ribosomal RNA chain elongation rates in *Escherichia coli*. (Kjeldgaard N C & Maaløe O, eds.) *Control of ribosome synthesis: proceedings of the Alfred Benzon Symposium IX*. Copenhagen: Munksgaard, 1976. p. 333-9.
6. **Ingraham J L, Maaløe O & Neidhardt F C.** *Growth of the bacterial cell*. Sunderland, MA: Sinauer Associates, 1983. p. 310.

