The Meselson–Stahl Experiment

DNA replication occurs before every cell division. The mechanism by which DNA copies are synthesized is similar in all living organisms. After the two strands have separated, each serves as a template for the synthesis of a complementary strand. (In other words, each of the two new DNA molecules contains one old strand and one new strand.) This process, referred to as semiconservative replication, was first demonstrated in an elegant experiment reported in 1958 by Matthew Meselson and Franklin Stahl (**Figure 1**).

In this classic work, Meselson and Stahl took advantage of the increase in density of DNA labeled with the heavy nitrogen isotope ^{15}N (the most abundant nitrogen isotope is ^{14}N). After *E. coli* cells were grown for 14 generations in growth media whose nitrogen source consisted only of $^{15}NH_4Cl$, the ^{15}N-containing cells were transferred to growth media containing the ^{14}N isotope. At the end of both one and two cell divisions, samples were removed. The DNA in each of these samples was isolated and analyzed by CsCl density gradient centrifugation. (Refer to Biochemical Methods 2.1 for a description of density gradient centrifugation.) Because pure ^{15}N-DNA and ^{14}N-DNA produce characteristic bands in centrifuged CsCl tubes, this analytical method discriminates between DNA molecules containing large amounts of the two nitrogen isotopes. When the DNA isolated from ^{15}N-containing cells grown in ^{14}N medium for precisely one generation was centrifuged, only one band was observed. Because this band occurred halfway between where ^{15}N-DNA and ^{14}N-DNA bands would normally appear, it seemed reasonable to assume that the new DNA was a hybrid molecule, that is, it contained one ^{15}N strand and one ^{14}N strand. (Any other means of replication would create more than one band.) After two cell divisions, extracted DNA was resolved into two discrete bands of equal intensity, one made up of $^{14}N,^{14}N$-DNA (light DNA) and one made up of hybrid molecules ($^{14}N,^{15}N$-DNA), a result that also supported the semiconservative model of DNA synthesis.

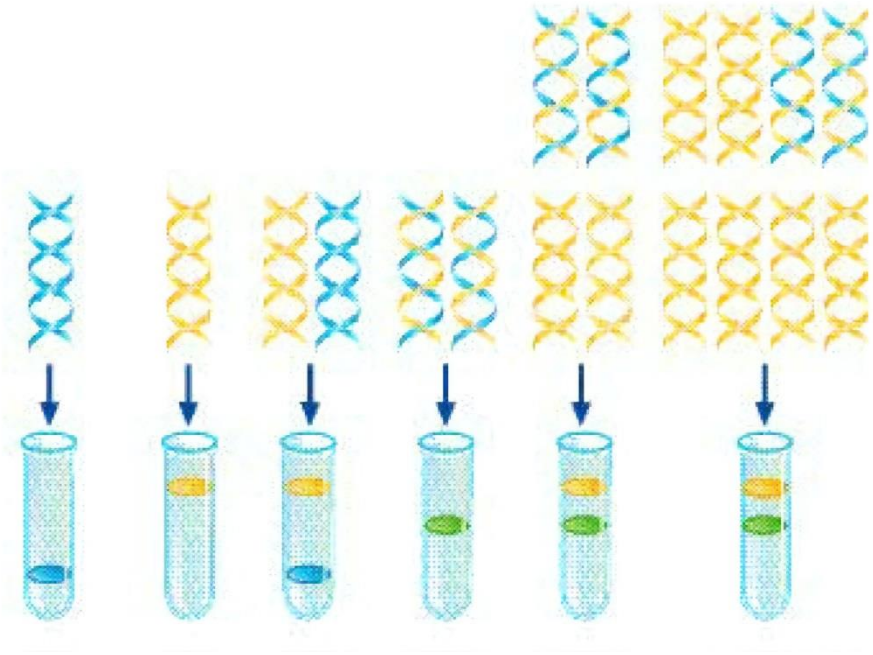

FIGURE 1

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CsCl centrifugation of *E. coli* DNA can distinguish heavy DNA grown in ^{15}N media (1) from light DNA grown in ^{14}N media (2). A mixture is shown in (3). When *E. coli* cells enriched in ^{15}N are grown in ^{14}N for one generation, all genomic DNA is of intermediate density (4). After two generations, half of the DNA is light and half is of intermediate density (5). After three generations, 75% of the DNA is light and 25% of the DNA is of intermediate density (6).