respectively, 1.0 (2 ovulations among 2 animals), 1.0 (4 among 4), 1.1 (6 among 5), 1.3 (15 among 12), and 1.5 (15 among 10). With the exception of one animal in the group receiving 500 I.U. of hCG that had four ovulations (2.9 percent of the animals ovulating), all animals showed only single (76.5 percent) or double (20.6 percent) ovulations.

The 41.7 percent ovulation rate with 500 I.U. of hCG is comparable to the 42.9 percent rate reported earlier (*8*) for animals that received the same amount of hCG with the dose being administered after 5 days of treatment with 5 mg of progesterone per day to mimic the luteal phase of the reproductive cycle.

The results indicate that a dose-response curve can be drawn for the ovulatory response of the squirrel monkey to hCG injection. Full responsiveness is reached by a dose of 250 I.U. of hCG, and the MED is between 100 and 250 I.U. This dose is considerably less than that commonly used with other nonhuman primates and suggests that the MED in humans might also be less than is commonly used clinically.

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β-Galactosidase and Selective Neutrality

A recent report (*1*) concluded that the observed amino acid composition of β-galactosidase from *Escherichia coli* is not ($P \simeq 10^{-24}$) the sole result of a selectively neutral evolutionary process with respect to (i) equal interchangeability among amino acids, (ii) base replacement at the gene level, and (iii) replacement drawn from a pool of amino acids at their natural abundances in proteins. Any one of these three hypotheses was by itself an adequate explanation of the amino acid composition of about 60 percent of the β-galactosidase molecule, but none was capable of explaining the composition of the remaining molecular structure.

Although individually each of the above hypotheses fails to explain fully the experimentally observed amino acid composition of β-galactosidase, together they, in principle, might. To illustrate, let us consider that an urn contains 1000 balls. Three investigators have three different hypotheses about them: all balls are white; all are red; and all are black. On emptying the urn it is found 200 are white, 300 are red, and 500 are black. All three hypotheses are strongly rejected, but it is obvious that a linear combination of the three explains the observations perfectly. The purpose of this note is to show that an explanation of this sort does not suffice for β-galactosidase.

All possible linear combinations of hypotheses (i) to (iii) were tested to see if any combination of the three would better explain the observed amino acid composition of β-galactosidase than each individually. Let n_{1i}, n_{2i}, and n_{3i} be the expected number of residues of the i^{th} (i = 1 to 20) amino acid type under each of the three hypotheses. Because there are 1021 residues in the protein, n_{1i} = 51.05 for all 20 amino acids, and the numerical values for n_{2i} and n_{3i} are in table 1 of (*1*). Denoting by f_1, f_2, and f_3 the fraction by which each hypothesis ($f_1 + f_2 + f_3 = 1$) contributes toward the expected composition, under the composite hypotheses this expected composition is given by

$$n_i = f_1 n_{1i} + f_2 n_{2i} + f_3 n_{3i}$$

The values of f_1, f_2, and f_3 which best explain the observed amino acid composition of β-galactosidase were determined by minimizing

$$\chi^2 = \sum_{i=1}^{20} \frac{(n_i - n_0)^2}{n_i},$$

n_0 being the observed number of residues of each amino acid. The best f_i were $f_1 = 0.34$, $f_2 = 0.34$, and $f_3 = 0.32$. The expected mole fraction of each amino acid under this best linear composite hypothesis was then calculated from the first equation above. The minimal value of χ^2 was 71.87, which, for 17 degrees of freedom, has an associated probability of 1.03×10^{-8}. The composite hypothesis is rejected. At the 1 percent level of significance, aspartic acid, glutamine, and leucine were present in excess of expectation, and cysteine and lysine were present in amounts below expectation. These five amino acids represent 237 residues and account for 68 percent of the χ^2 value of 71.87. The remaining 77 percent of the residues of the β-galactosidase molecule were in reasonable agreement with expectation.

The poor agreement with experiment, for a certain portion of the molecular structure of β-galactosidase, under each of the hypotheses individually, thus cannot be much improved by linear combinations of these hypotheses. For this portion they are wrong singly; they are wrong in combination. The biological significance of this result is that protein structure, at least that of β-galactosidase, and probably generally, is not simply the result of compositional optimization with respect to the conflicting requirements of the three hypotheses.

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