LETTERS TO THE EDITOR

The Relationship between Cell Growth and Generation Time

Dear Sir:

Linear cell growth (i.e., a constant growth rate) has been proposed as the characteristic form for individual cells of all kinds when grown in steady-state cultures on compounds of low molecular weight (1). A major question for this, or any other proposed cell growth pattern, is its relationship to the distribution of generation times; experimental generation time distributions must be consistent with cell growth patterns. This note presents a theoretical basis relating observed distributions of cell generation times to linear cell growth.

In order to demonstrate this relationship, we consider a cell population that obeys three simplifying assumptions, all based upon observations of cell growth:

(*a*) All cells have the same mass M at birth, and at division, $2M$. Cell masses actually vary at birth and at division, but this assumption is strictly true for the *average* cell mass.

(*b*) Each cell grows at a constant rate during the entire growth-duplication cycle. The available evidence only supports constancy over most of the cycle (1), with changes occurring near cell division.

(*c*) Growth rates of individual cells are described by a normal distribution. This assumption is in agreement with a hypothesis proposed earlier, that the growth rate of a cell is proportional to the number of its "uptake sites" involved in the binding, transport, or accumulation of compounds, and that the distribution of these sites is a truncated normal (1, 2). Some experimental support for this assumption is provided by the observations that cell volume distributions in synchronous cultures of *Escherichia coli* quickly approach a normal distribution of cell sizes and that this distribution is maintained until the beginning of the next round of cell division (3).

As shown in Fig. 1, these assumptions lead to a skewed distribution of generation times. For each cell, the change in mass M from birth to division depends upon its growth rate r and generation time τ;

$$M = r\tau$$

or

$$r = M\tau^{-1}. \tag{1}$$

Because M is constant, equation 1 shows that the *reciprocal* of the generation time, τ^{-1}, has the same distribution as that for growth rate r, assumed above to be normally distributed. This distribution of τ^{-1} is compatible with experimentally determined generation time distributions for bacteria, yeast, protozoa, and mammalian cells (2).

Theoretically, other cell growth patterns also would lead to the same generation time distribution under the first and third assumptions. For example, if cell mass increases

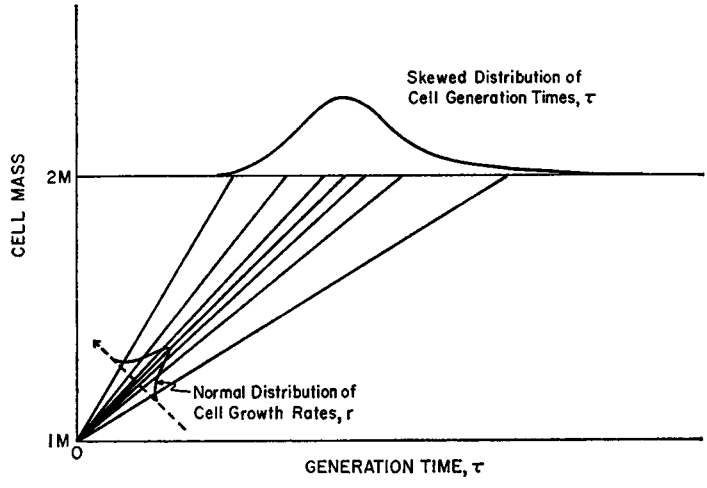

FIGURE 1 The relationship between linear cell growth and the generation time distribution. The straight lines indicate the increase in cell mass for individual cells as a function of time, from the mass at birth M to the mass at division $2M$. The frequency distribution of cell growth rates is indicated by the normal distribution on the dashed line base. The frequency distribution of generation times is drawn just above the horizontal line labeled $2M$.

exponentially with time t according to

$$M = M_0 e^{rt},$$

then, since mass doubles at time τ,

$$r = \tau^{-1} \ln 2,$$

and again the distributions of r and τ^{-1} have the same form. This result is contrary to earlier expectations that exponential growth leads to a lognormal distribution (4). More generally, the normal distribution of the reciprocal of generation time occurs for any cell growth pattern in which the variables r and τ occur as the product $r\tau$, such as $(r\tau)^2$ or higher powers, or in polynomials or transcendental functions.

While the assumptions for equation 1 are oversimplified, they lead to a demonstration of the source of the asymmetry observed in generation time distributions of linearly growing cells; and although the relationship in equation 1 may be more descriptive than causal, it contains the elements of a heuristic model for the development of more sophisticated models.

The relationship between linear cell growth and the normal distribution of the reciprocal of generation time enhances the credibility of both: observations of linear cell growth in bacteria, yeast, and protozoa are matched by corresponding observations of normal distributions of τ^{-1} for each, as expected. The same generation time distribution also has been observed for green monkey kidney cells (5), but the pattern of cell growth has not yet been unequivocally demonstrated for mammalian cells in steady-state cultures.

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Reactivity of Purine and Pyrimidine Bases toward Singlet Oxygen

Dear Sir:

Despite extensive studies of photodynamic reactions (1) involving nucleic acids and their component bases, there is presently only a limited understanding on the molecular level of the mechanism of this process. This reaction, which requires a dye, visible light, and molecular oxygen, produces appreciable destruction of guanine moieties and, to a smaller extent, thymine moieties in nucleic acids, most probably by some oxidative pathway (2). A large number of efficient sensitized oxidations of organic compounds are initiated by dye sensitization. The active species is presently believed to be an excited form of molecular oxygen, singlet oxygen $O_2(^1\Delta_g)$, formed by energy transfer from an excited molecule of sensitizer (S) to ground state molecular oxygen (3):

$$S + h\nu \rightarrow S^*,$$

$$S^* + O_2(^3\Sigma_g) \rightarrow S + O_2(^1\Sigma_g^+ \text{ and/or } ^1\Delta_g).$$

For this reason it has been suggested that singlet oxygen may be the active intermediate in aerobic photodynamic reactions (4).

F. R. Hallett et al. (5), tested this hypothesis by reacting a large number of purine and pyrimidine compounds with singlet oxygen generated by chemical reaction of NaClO and H_2O_2. A good correspondence between the reactivity of these compounds in photodynamic reactions and reactions with chemically produced singlet oxygen was found; however, interpretation of the results of this study was somewhat complicated because of side reactions between the substrates and chemical species other than singlet oxygen present in the solution, and rigorous pH control could not be accomplished by this method. For instance, the reactivity of different bases toward chemically produced singlet oxygen apparently decreases with the increase in pH, in direct contradiction to the experimental observations in the photodynamic effect.

The purpose of this study was to determine the sensitivity of nucleic acid components towards singlet molecular oxygen generated *externally* by microwave discharge of an oxygen stream (6). This procedure offes the advantage of a cleaner system, free of interferences due to side reactions.