NONTHRESHOLD MODELS OF THE SURVIVAL OF BACTERIA AFTER IRRADIATION

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1. Introduction

The purpose of this paper is to investigate a certain class of nonthreshold models for the survival of the bacteria *E. coli* following exposure to X-ray and ultraviolet radiation. The threshold or multihit model contains two assumptions —that the effect of radiation is a process of accumulation of hits or irreversible structural defects in the cell and that death occurs when exactly n hits have accumulated. Woodbury [17] suggested a general method of modifying the model to include the possibility of repair during the irradiation period. Although the purport of the method is clear, some of the generality has to be abandoned to resolve the conflict between the first two sets of equations on p. 77 of [17]. The second assumption in the threshold model is retained, changing its form slightly so that the cell will die if more than n unrepaired hits have been accumulated at the end of the dose.

A fruitful approach to threshold problems in general has been suggested by L. LeCam and developed by Puri [13] in connection with a situation in which a host is infected with a parasite which multiplies and eventually kills the host. If we call the underlying process, be it the accumulation of hits in a cell or parasites in a host, $\{X(s): 0 \leqq s \leqq t\}$, where t is the time interval considered, then the LeCam-Puri approach is that the probability of dying in a time period $(s, s + \tau)$ is proportional to $\tau g(X(s)) + o(\tau)$, where g may be, for example, the identity function. It follows that the probability $S(t)$ of surviving a time t is of the form $f(X(s): 0 \leqq s \leqq t)$, for example, $\exp\left\{-\int_0^t X(s)\,ds\right\}$. In a seminar given at the University of California in 1967, the author applied this approach to radiation problems and showed that repair could be incorporated quite naturally in this context.

For the present purposes this approach is too general. In most cases the

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radiation damage is accumulated almost immediately and repair, if any, takes place after irradiation. For these cases, it appears natural to consider only the class of survival models for which $f(X(s): 0 \leqq s \leqq t)$ depends only on $X(t)$, the total amount of damage after the dose. This is equivalent to a suggestion of Haynes [8] that a cell with k hits following irradiation has some probability $0 \leqq Q(k) \leqq 1$ of survival. If hits are accumulated in a Poisson process, it follows that both the multihit and multitarget models, which have been used extensively in the past [1], [11], [16] are special cases of the preceding. Properties of the theoretical model are discussed, in particular the property that the rate parameter of the Poisson process and the function $Q(k)$ are not jointly identifiable.

In the second half of the paper, the idea is developed that the bacteria survive because of enzyme systems which are capable of repairing structural defects [8]. The general model is interpreted in terms of repair and a more specific model is proposed based on Harm's ideas [6]. In a series of experiments, Harm has shown that *E. coli* can survive large doses of ultraviolet radiation if the exposure is at a low dose rate. The implication is that repair takes place during the irradiation period. Harm has suggested also that certain configurations of lesions on the chromosome may be more difficult to repair, particularly defects at approximately the same location on opposing strands. The enhanced survival for low dose rate exposure is then the result of the continual repair of the DNA molecule during the radiation period which minimizes the chances of overlapping structural defects. The mathematical model based on these ideas is shown to agree well with the empirical data for high dose rate survival and to predict "liquid-holding recovery". For low dose rate exposure with the largest total dose, there is some indication of an interaction between the radiation and the repair mechanism.

In a further application of this model, the interaction between X-ray and ultraviolet radiation is considered as in the experiments of Haynes [7]. It was shown that the previous application of X-ray altered the shape of the ultraviolet survival curve. A similar effect was observed by reversing the order of radiation. In general, there appears to be a synergism between the two types of radiation. By postulating that the presence of X-ray structural defects may block the repair of ultraviolet damage, a mathematical model is constructed. The predictions of this model compare favorably with the empirical data.

2. Mathematical description of the model

A cell is exposed to a dose d (ergs/mm^2) of radiation. During the radiation period a number of events occur in the cell. An event may be the absorption of a photon in the case of ultraviolet radiation or the initiation of a chain of ionizations in the case of X-ray or hard radiation. The number of these primary events is assumed to be Poisson distributed with a mean ηd, where η is some unknown constant. At the site of each primary event a certain amount of damage is formed. In the case of ultraviolet radiation, it may be reasonable to say that

one lesion or abnormal photoproduct is formed randomly and independently with probability π at each primary event, so that the number of lesions formed in a cell would have a Poisson distribution with mean λd where, $\lambda = \eta\pi$. The probability $Q(n)$ that a cell will survive n lesions is assumed to be independent of the dose which caused the lesions. In general, it will depend on many factors including the experimental conditions, the presence of a repair mechanism in the cell and any delay in replication which the n lesions may produce. The probability that a cell will survive a dose d of ultraviolet light is evidently

$$S(d) = \sum_{k=0}^{\infty} \frac{e^{-\lambda d}(\lambda d)^k}{k!} Q(k). \tag{1}$$

From biological considerations, it appears natural that the class should be restricted by

$$\begin{aligned} Q(k) &\geqq Q(k+1), \qquad k = 0, 1, 2 \cdots, \\ Q(0) &= 1, \\ \lim_{k\to\infty} Q(k) &= 0. \end{aligned} \tag{2}$$

That is, the chance that a cell will survive cannot increase as the number of lesions increases; the cell will survive if no lesions are present and the cell is certain to die if the number of lesions exceeds all bounds. The class of survival curves satisfying both (1) and (2) will be called the class A.

The first observation is that the class contains the multihit survivor curve in the case

$$Q(k) = \begin{cases} 1 & k = 0, 1, \cdots, n-1, \\ 0 & \text{otherwise.} \end{cases} \tag{3}$$

It also contains the multitarget model. The multitarget model with m targets each with a mean number $\lambda d/m$ lesions has a survivor function

$$S(d) = 1 - \left(1 - \exp\left\{-\frac{\lambda d}{m}\right\}\right)^m. \tag{4}$$

By expanding the terms of (4), it follows that $S(d)$ is in the class A with parameters λ and

$$Q(j) = \sum_{k=1}^{m} (-1)^{k+1}\binom{m}{k}\left(\frac{m-k}{m}\right)^j. \tag{5}$$

We recognize $Q(k)$ to be the occupancy probability that out of m boxes in which k balls are distributed at random, at least one box will be empty. In general, any occupancy model where the lethal configuration becomes increasingly likely as the number of lesions increases will have a survivor function in the class A.

The second observation is that the class is equivalent to the class of multihit mixtures. Fowler [5] gives an example of fitting a multihit mixture to radiation survival data. A multihit mixture survivor function is of the form

$$S(d) = \sum_{j=1}^{\infty} p_j \sum_{k=0}^{j-1} \frac{e^{-\lambda d}(\lambda d)^k}{k!}, \tag{6}$$

where $p_j \geqq 0$, $j = 1, 2, 3, \cdots$, and $\sum_{j=1}^{\infty} p_j = 1$. Note that this class excludes the possibility of surviving an infinite number of lesions. By changing the order of summation, we have the result that $S(d)$ satisfies condition (1) with parameters λ and $Q^*(k)$, where $Q^*(k) = \sum_{j=k+1}^{\infty} p_j$. Since $Q^*(0) = 1$, $Q^*(k) \geqq Q^*(k+1)$ and $\lim_{k\to\infty} Q^*(k) = 0$, the function (6) is a member of the class A. Conversely, setting $p_{k+1} = Q(k) - Q(k+1)$, that is $Q(k) = \sum_{j=k+1}^{\infty} p_j$, $k = 0, 1, 2, \cdots$, and substituting in (1), it is evident, after changing the order of summation, that any member of the class is a finite multihit mixture.

Instead of assuming that the primary event causes only a single lesion, it may be assumed, more generally, that there will be a random and independent distribution of damage $X \geqq 0$, at each event. If the accumulation of damage is additive and if $Q(x)$, the probability that the cell will survive an amount x of damage, is restricted to be nonincreasing such that $Q(0) = 1$ and $\lim_{x\to\infty} Q(x) = 0$, then it can be shown that the class is not increased. This more general description of the class is not used here since the emphasis will be placed on the interpretation of ultraviolet survival data, where the simplifying assumptions leading to the class A may be approximately valid.

3. Properties of the theoretical model

Before considering the problem of estimating $Q(k)$ and λ from an empirical survivor function, it is important to know whether $Q(k)$ and λ are identifiable from a theoretical survivor function in the class A and for an arbitrary theoretical survivor function it is useful to have a criterion for deciding whether the function is in the class A.

PROPOSITION 1. *If $S(d)$ is a member of the class A with the parameters λ and $Q(k)$, then $S(d)$ and λ determine $Q(k)$ uniquely.*

PROOF. This result is contained in the work of Teicher [16] concerning general problems of identifiability. More directly, consider the function $S(d)e^{\lambda d}$. This is an entire function with a unique power series expansion. The coefficient $Q(k)\lambda^k/k!$ of d^k is therefore determined by $S(d)e^{\lambda d}$, and hence $S(d)$ and λ determine $Q(k)$ uniquely. This concludes the proof.

PROPOSITION 2. *If $S(d)$ is an arbitrary nonincreasing survivor function and $\mu > 0$, then the transform*

$$f(u, \mu) = \int_0^{\infty} \exp\left\{\frac{x(u-1)}{u}\right\} dF\left(\frac{x}{\mu}\right) \tag{7}$$

is analytic for $u \in C$, where $F(d) = 1 - S(d)$ and C is the interior of the circle with radius $\frac{1}{2}$ and center $\frac{1}{2}$ in the complex plane.

PROOF. Since $F(x/\mu) = 1 - S(x/\mu)$ is a distribution function, it has a Laplace transform $g(\theta)$ which is analytic for $\Re(\theta) > 0$. Since $f(u, \mu) = g((1-u)/u)$ and since the function $\theta = (1-u)/u$ is analytic in C and maps $C \to \Re(\theta) > 0$, the result follows.

PROPOSITION 3. *If $S(d)$ is an arbitrary nonincreasing survivor function and $\mu > 0$, then $f(u, \mu)$, $u \in C$, determines $S(d)$ uniquely.*

PROOF. For $\mu > 0$, arbitrary, $S(x)$ is determined by $S(x/\mu)$ which in turn is determined by its Laplace transform $f((1 + \theta)^{-1}, \mu)$, $\Re(\theta) > 0$. Since $(1 - u)/u$ is analytic in C and the mapping $C \to \Re(\theta) > 0$ is one to one, it follows that $f((1 + \theta)^{-1}, \mu)$, $\Re(\theta) > 0$, is determined by $f(u, \mu)$, $u \in C$, which concludes the proof.

THEOREM 1. *Let $S(d)$, $d > 0$ be an arbitrary nonincreasing survivor function and let $F(d) = 1 - S(d)$.*

A necessary and sufficient condition for the function $S(d)$ to be in the class A is that for some $\mu > 0$ function (7) has an analytic continuation which is a probability generating function (p.g.f.).

If the p.g.f. generates the quantities $\{\eta_k, k = 1, 2, \cdots\}$, then

$$S(d) = \sum_{k=0}^{\infty} \sum_{j=k}^{\infty} \eta_{j+1} \frac{e^{-\mu d}(\mu d)^k}{k!}. \tag{8}$$

PROOF. Let $S(d)$ be in the class A with parameters λ and $Q(k)$, then

$$\begin{aligned} S\left(\frac{x}{\lambda}\right) &= \sum_{k=0}^{\infty} Q(k) \frac{e^{-x}x^k}{k!}, \\ \frac{d}{dx} F\left(\frac{x}{\lambda}\right) &= \sum_{k=1}^{\infty} q_k \frac{e^{-x}x^k}{k!}, \end{aligned} \tag{9}$$

where $q_k = Q(k - 1) - Q(k)$, $k = 1, 2, \cdots$. The integral

$$f(u, \lambda) = \int_0^{\infty} \exp\left\{-\frac{x(1 - u)}{u}\right\}\left(\sum_{k=1}^{\infty} q_k \frac{e^{-x}x^k}{k!}\right) dx \tag{10}$$

converges for $u \in C$; hence $f(u, \lambda) = \sum_{k=1}^{\infty} u^k q_k$, $u \in C$. Since $q_k > 0$, $k = 1, 2, \cdots$ and $\sum_{k=1}^{\infty} q_k = 1$, $f(u, \lambda)$ has an analytic continuation which is a p.g.f. The second part of the theorem follows with $q_k = \eta_k$, $k = 1, 2, \cdots$.

Let $S(d)$ be a nonincreasing survivor function and suppose that for some $\mu > 0$, $f(u, \mu) = \int_0^{\infty} \exp\{-x(1 - u)/u\}\, dF(x/\mu)$ has an analytic continuation which is a p.g.f. Let $f(u, \mu) = \sum_{k=1}^{\infty} u^k \eta_k$. Then the function

$$S^*(x) = \sum_{k=0}^{\infty} \sum_{j=k}^{\infty} \eta_{j+1} \frac{e^{-\mu x}(\mu x)^k}{k!} \tag{11}$$

is in the class A. For this function $f^*(u, \mu) = \sum_{k=1}^{\infty} u^k \eta_k$ for $u \in C$. From Proposition 3 it follows that $S(x) = S^*(x)$, $x > 0$ so that $S(x)$ is in the class A.

COROLLARY 1. *If $S(d)$ is a member of the class A with parameters λ and $Q(k)$, then for each $\mu > \lambda$ there exists a $Q^*(k)$ satisfying condition (2) such that*

$$S(d) = \sum_{k=0}^{\infty} Q(k) \frac{e^{-\lambda d}(\lambda d)^k}{k!} = \sum_{k=0}^{\infty} Q^*(k) \frac{e^{-\mu d}(\mu d)^k}{k!}. \tag{12}$$

PROOF. Let $\mu > \lambda$. Since $S(d)$ is in the class A it is nonincreasing so that from Proposition 2, $f(u, \mu) = \int_0^{\infty} \exp\{-x(1 - u)/u\}\, d[1 - S(x/\mu)]$ is analytic,

$u \in C$. After integration, we have $f(u, \mu) = g(\lambda u/(\mu - u(\mu - \lambda)))$, $u \in C$, where $g(u) = f(u, \lambda)$ is a p.g.f. It follows that $f(u, \mu)$, $\mu > \lambda$, is the p.g.f. of a negative binomial mixture. Therefore, $S(d)$ is also in the class A with parameters μ and $Q^*(k) = \sum_{j=k}^{\infty} q_{j+1}^*$, $k = 0, 1, 2, \cdots$, where

$$\sum_{k=1}^{\infty} u^k q_k^* = g\left(\frac{\lambda\mu}{\mu - u(\mu - \lambda)}\right), \qquad |u| \leqq 1. \tag{13}$$

This concludes the proof.

For some purposes, it may be useful to have a relationship between $Q(k)$ and $Q^*(k)$ directly. From the equation in Corollary 1 after multiplying both sides by $e^{\mu d}$ and equating coefficients of d^k, it is easy to verify that

$$Q^*(k) = \sum_{m=0}^{k} Q(m)\binom{k}{m}\left(\frac{\lambda}{\mu}\right)^m\left(1 - \frac{\lambda}{\mu}\right)^{k-m}. \tag{14}$$

EXAMPLE 1. In the case $Q(k) = 1_{[k<n]}$, $S(d) = \sum_{k=0}^{\infty} Q(k)e^{-\lambda d}(\lambda d)^k/k!$ has the form of the classical n hit survival function. From the corollary, it follows that the function $S(d)$ has an infinite number of alternative representations in the class A with parameters $\mu > \lambda$ and $Q^*(k)$, where

$$Q^*(k) = \begin{cases} \displaystyle\sum_{j=k-n+1}^{\infty} \frac{\binom{j+n+1}{j}(\mu/\lambda - 1)^j}{(\mu/\lambda)^{j+n}}, & k \geqq n, \\ \displaystyle\sum_{j=0}^{n-1} \binom{k}{j}((\mu - \lambda)/\mu)^{k-j}(\lambda/\mu)^j, & k \geqq n, \\ 1 & k < n \text{ for all } \mu > \lambda. \end{cases} \tag{15}$$

Provided $\mu > \lambda$, $Q^*(k)$ is always positive and decreasing. This function may be a more acceptable explanation of the survival curve than the function $Q(k) = 1_{[k<n]}$ which implies that the cell survives with $n - 1$ lesions but not with n lesions. As an illustration, for the "5 hit" function $S(d) = \sum_{k=0}^{4} e^{-d}d^k/k!$ the equivalent $Q^*(k)$ are drawn for $\mu = 1, 2, 4, 10$ in Figure 1. Thus, a cell which appears to have a 5 hit survivor function may have a 50 per cent chance of surviving 50 lesions if the equivalent representation with $\mu = 10$ is used. In general if $S(d) = \sum_{k=0}^{\infty} Q(k)e^{-\mu d}(\mu d)^k/k!$, then it is necessary to know μ before we can determine $Q(k)$. An equivalent result in terms of multihit mixtures has been obtained by Teicher [16] and Dittrich [3].

It also follows from Theorem 1 that if $S(d)$ is in the class A with parameters μ and $Q(k)$ and if $q_k = Q(k - 1) - Q(k)$ for $k = 1, 2, \cdots$, then the factorial moments of the distribution $\{q_k: k = 1, 2, \cdots\}$ are given by

$$\begin{aligned} \mu_{[j]} &= \sum_{k=1}^{\infty} k(k + 1) \cdots (k + j)q_k \\ &= (j + 1)\int_0^{\infty} x^j S(x/\mu)\, dx, \qquad j = 0, 1, 2, \cdots. \end{aligned} \tag{16}$$

If μ is known and $Q(k)$ has some theoretical form depending on unknown parameters, it may be feasible to use a "method of moments" to estimate $Q(k)$.

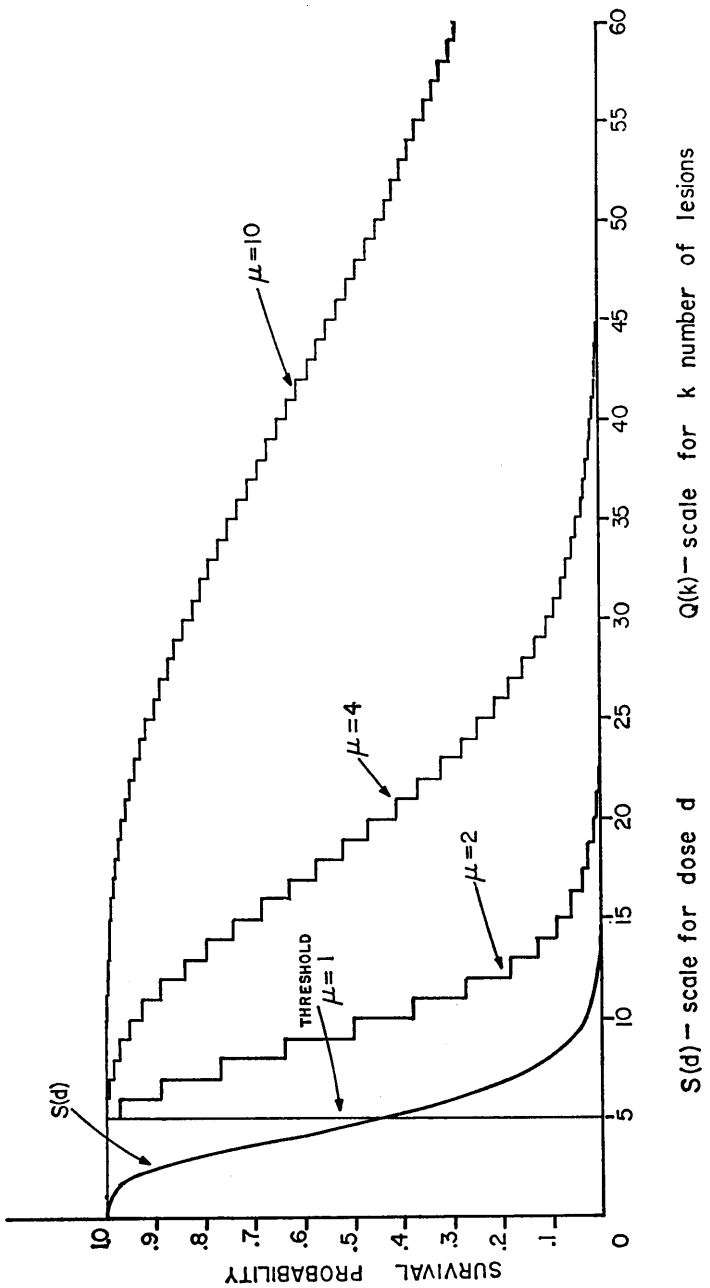

FIGURE 1

The 5 hit survival function $S(d) = \sum_{k=0}^{4} e^{-d} d^k/k! = \sum_{k=0}^{\infty} e^{-\mu d}(\mu d)^k/k!\, Q(k)$ with equivalent $Q(k)$ corresponding to $\mu = 1, 2, 4, 10$.

EXAMPLE 2. Suppose

$$Q(k) = \sum_{j=k}^{\infty} \frac{e^{-\theta}\theta^j}{j!}, \qquad \theta > 0,\ k = 0, 1, 2, \cdots, \tag{17}$$

then $\mu_{[0]} = \theta + 1$, and since $m_{[0]} = \int_0^\infty \hat{S}(x/\mu)\,dx$ is the sample analogue of $\mu_{[0]}$, $\hat{\theta} = \int_0^\infty \hat{S}(x/\mu)\,dx - 1$ is the "moment" estimate of θ.

Suppose that we have a survivor function which is known to be a member of the class A. Then we can ask if there is a smallest μ for which a representation in the class is possible.

PROPOSITION 4. *The only survivor function $S(d)$ which has a representation in the class A for all $\mu > 0$ is the function $S(d) = 1$, $d \geqq 0$.*

PROOF. The proof is by contradiction. Let $S(d)$ be a survivor function that has a representation in the class A for all $\mu > 0$ and such that $S(d_0) < 1$ for some $d_0 > 0$. Let $S(d) = \sum_{k=0}^{\infty} Q(k, \mu)e^{-\mu d}(\mu d)^k/k!$, and consider $S(d_0)$ in the limit as $\mu \to 0$. Then $S(d_0) \to \lim_{\mu\to 0} Q(0, \mu) = 1$ by the conditions of (2) and there is a contradiction. This concludes the proof.

PROPOSITION 5. *If $S(d)$ is in the class A for some $\mu > 0$, then there is a least value μ_0 for which a representation in the class is possible.*

PROOF. Let $S(d) = \sum_{k=0}^{\infty} Q(k, \mu)e^{-\mu d}(\mu d)^k/k!$. By Proposition 4, we know that there is number $\mu_0 > 0$ such that $S(d)$ has a representation for all $\mu > \mu_0$. It remains to be shown that $S(d)$ can be represented in the class with $\mu = \mu_0$. Let $\{\mu_n\}$ be a sequence of real numbers such that $\mu_n \downarrow \mu_0$ as $n \to \infty$ then from equation (14) we have

$$Q(k, \mu_n) = \sum_{m=0}^{k} Q(m, \mu_{n+1})\binom{k}{m}\left(\frac{\mu_{n+1}}{\mu_n}\right)^m\left(1 - \frac{\mu_{n+1}}{\mu_n}\right)^{k-m}. \tag{18}$$

Since $Q(k, \mu_{n+1})$ is a nonincreasing function of k for $\mu_{n+1} > \mu_0$, it follows from equation (18) that $Q(k, \mu_n) \geqq Q(k, \mu_{n+1})$ for all n so that $Q(k, \mu_n)$ is a nonincreasing function of n for each k. In particular, since $Q(k, \mu_n) \geqq 0$ for all n, the limit as $n \to \infty$ exists and this limit $Q(k, \mu_0)$ is a nonnegative nonincreasing function of k. Similarly, $Q(0, \mu_n) = 1$, $n = 1, 2, \cdots$, implies $Q(0, \mu_0) = 1$ and $\lim_{k\to\infty} Q(k, \mu_n) = 0$, $n = 1, 2, 3, \cdots$, implies $\lim_{k\to\infty} Q(k, \mu_0) = 0$, so that $\{Q(k, \mu_0), k = 0, 1, 2, \cdots\}$ satisfies the conditions of (2).

It has to be shown that

$$S^*(d) = \sum_{k=0}^{\infty} Q(k, \mu_0)\frac{\exp\{-\mu_0 d\}(\mu_0 d)^k}{k!} = S(d). \tag{19}$$

Let $S(d) = \sum_{k=0}^{\infty} Q(k, \mu_n)\exp\{-\mu_n d\}(\mu_n d)^k/k!$, $\mu_n > \mu_0$, then for each $\varepsilon > 0$, there exists a K such that $Q(k, \mu_n) < \varepsilon$ for all $k > K$, and since $Q(k, \mu_n)$ is nonincreasing in n for each k, it follows that $Q(k, \mu_0) < \varepsilon$ for all $k > K$. Finally, we have

$$\begin{aligned} &|S^*(d) - S(d)| \\ &\quad \leqq \left|\sum_{k=0}^{K}\left\{Q(k, \mu_0)\frac{\exp\{-\mu_0 d\}(\mu_0 d)^k}{k!} - Q(k, \mu_n)\frac{\exp\{-\mu_n d\}(\mu_n d)^k}{k!}\right\}\right| + 2\varepsilon. \end{aligned} \tag{20}$$

Since there are a finite number of terms in the summation and each converges to zero as $n \to \infty$, we have shown that $S(d) \to S^*(d)$ for each $d \geqq 0$. Since $S(d)$ is independent of n, it follows that $S(d) = S^*(d)$ for $d \geqq 0$. This concludes the proof.

PROPOSITION 6. *If $S(d)$ is a function of the class A, then the parameter μ is restricted by the following inequalities:*

$$\mu \geqq -S'(0), \tag{21}$$

$$\mu \geqq \frac{\int_0^\infty S(x)\,dx}{2\int_0^\infty xS(x)\,dx - \left(\int_0^\infty S(x)\,dx\right)^2}. \tag{22}$$

PROOF. For (21), let $S(d) = \sum_{k=0}^{\infty} Q(k)e^{-\mu d}(\mu d)^k/k!$. Then $S'(0) = -\mu(1 - Q(1))$. Since $0 \leqq Q(1) \leqq 1$, we have $-S'(0)/\mu \leqq 1$ or $\mu \geqq -S'(0)$.

For (22), since the variance of the q_k distribution must be nonnegative, from (16) we have

$$2\mu^2\int_0^\infty xS(x)\,dx - \mu\int_0^\infty S(x)\,dx - \left(\mu\int_0^\infty S(x)\,dx\right)^2 \geqq 0, \tag{23}$$

that is,

$$\mu\left\{2\int_0^\infty xS(x)\,dx - \left(\int_0^\infty S(x)\,dx\right)^2\right\} \geqq \int_0^\infty S(x)\,dx \tag{24}$$

or

$$\mu\left\{\int_0^\infty x^2\,dF(x) - \left(\int_0^\infty x\,dF(x)\right)^2\right\} \geqq \int_0^\infty x\,dF(x), \tag{25}$$

where $F(x) = 1 - S(x)$ is a distribution function. It follows that $\int_0^\infty x^2\,dF(x) - \left(\int_0^\infty x\,dF(x)\right)^2$ is positive provided the distribution function $F(x)$ is nondegenerate. The result then follows from equation (24).

If we consider T the lethal dose, a random variable for each cell, with distribution $P(T > d) = S(d)$, then (25) says that the Poisson rate of arrival of damage per unit dose cannot be less than $E(T)/\mathrm{Var}\,(T)$.

EXAMPLE 3. For the multihit class, $S(d) = \sum_{k=0}^{n-1} e^{-\lambda d}(\lambda d)^k/k!$, we have

$$\begin{aligned} -\int_0^\infty x\,dS(x) &= \int_0^\infty x\,\frac{e^{-\lambda x}(\lambda x)^{n-1}}{(n-1)!}\,dx = \frac{n}{\lambda}, \\ -\int_0^\infty x^2\,dS(x) &= \int_0^\infty x^2\,\frac{e^{-\lambda x}(\lambda x)^{n-1}}{(n-1)!}\,dx = \frac{n(n+1)}{\lambda^2}, \end{aligned} \tag{26}$$

so that from (21) and (22), $\mu \geqq n\lambda^2/n\lambda = \lambda$.

If $S(d)$ is identical to a multihit survivor function with parameter λ, then the only other possible representations of $S(d)$ in the class A have $\mu \geqq \lambda$.

From (26), it follows that the value of the parameter λ for which $S(d)$ has the multihit representation is given by

$$\lambda = \frac{\int_0^\infty S(x)\,dx}{2\int_0^\infty xS(x)\,dx - \left(\int_0^\infty S(x)\,dx\right)^2}, \tag{27}$$

and the value of the parameter n, the threshold number of lesions, is given by

$$n = \lambda \int_0^\infty S(x)\,dx. \tag{28}$$

By substituting the sample analogues of $\int_0^\infty S(x)\,dx$ and $\int_0^\infty xS(x)\,dx$, equations (27) and (28) can be used to provide estimates of n and λ. This procedure has been advocated by Kellerer [10].

DEFINITION 1. *In radiation biology, it is customary to plot* $\log S(d)$ versus *dose and consider the limiting slope of* $\log S(d)$ *as* d *increases. If there is such a limiting slope and the asymptotic tangent is extrapolated back to intersect the ordinate at* $\log(N)$, *then* N *is called the extrapolation number.*

DEFINITION 2. *If* $F(x)$ *is a positive nonincreasing function of* $x > 0$ *and if there exists* $0 < \rho < 1$ *such that* $F(x)/\rho^x$ *converges to a finite nonzero limit, say* N, *as* $x \to \infty$, *then* $F(x)$ *is asymptotic to* $N\rho^x$. *This is written as* $F(x) \sim N\rho^x$.

Let $S(d)$ be a member of the class A with parameters $Q(k)$ and λ, then

$$\frac{d}{dx}\log S(x) = -\lambda \frac{\sum_{k=0}^{\infty} (Q(k) - Q(k+1))e^{-\lambda d}(\lambda d)^k/k!}{\sum_{k=0}^{\infty} Q(k)e^{-\lambda d}(\lambda d)^k/k!}. \tag{29}$$

If $Q(k_0) = 0$ for some particular integer value k_0, then

$$\lim_{x\to\infty} \frac{d}{dx}\log S(x) = -\lambda. \tag{30}$$

Thus, the asymptotic slope of $\log S(d)$ is $-\lambda$. The extrapolation number N is given by

$$\lim_{x\to\infty} e^{\lambda x}S(x) = \lim_{x\to\infty} \sum_{k=0}^{k_0-1} \frac{Q(k)(\lambda x)^k}{k!}, \tag{31}$$

if $k_0 = 1$, $N = 1$. If $k_0 > 1$, the limit diverges to $+\infty$.

PROPOSITION 7. *If* $Q(k) > 0$ *for all* $k > 0$ *and if* $Q(k) \sim N\rho^k$ *for* $N > 0$ *and* $0 < \rho < 1$, *then* $S(x) \sim N \exp\{-\lambda(1-\rho)\}$.

PROOF. Let $Q(k) \sim N\rho^k$ for $N > 0$, $0 < \rho < 1$. Then $N = \lim_{k\to\infty} Q(k)/\rho^k$. Consider

$$\begin{aligned} S(x)\exp\{\lambda(1-\rho)x\} &= \sum_{k=0}^{\infty} Q(k)\frac{e^{-\lambda\rho x}(\lambda x)^k}{k!} \\ &= \sum_{k=0}^{\infty} \frac{Q(k)}{\rho^k}\frac{e^{-\lambda\rho x}(\lambda\rho x)^k}{k!}. \end{aligned} \tag{32}$$

This is $E(Q(X)/\rho^X)$, where X is a Poisson variable with mean $\lambda\rho x$. Let $\varepsilon > 0$; then there exists a K such that $|Q(k)/\rho^k - N| < \varepsilon$ for $k > K$. From (32) we have

$$(33)\qquad |S(x)\exp\{\lambda(1-\rho)x\} - N| \leqq \sum_{k=0}^{\infty}\left|\frac{Q(k)}{\rho^k} - N\right|\frac{e^{-\lambda\rho x}(\lambda\rho x)^k}{k!}$$
$$\leqq \sum_{k=0}^{K}\left|\frac{Q(k)}{\rho^k} - N\right|\frac{e^{-\lambda\rho x}(\lambda\rho x)^k}{k!} + \varepsilon$$
$$\leqq \max\left(N, \frac{1}{\rho^K}\right)\Pr(X \leqq K) + \varepsilon.$$

For x sufficiently large $\Pr(X \leqq K)$ is arbitrarily small so that we have $S(x)\exp\{\lambda(1-p)x\} \to N$ as $x \to \infty$. This concludes the proof.

EXAMPLE 4. In the case of the m target model where $S(d) = 1 - (1 - \exp\{-\lambda d/m\})^m$ it was shown in (4) that $Q(j) = \sum_{k=1}^{m}(-1)^{k+1}\binom{m}{k}((m-k)/m)^j$, $j = 0, 1, 2, \cdots$. It follows that

$$(34)\qquad \lim_{j\to\infty}\frac{Q(j)}{((m-1)/m)^j},$$

that is, $Q(j) \sim m((m-1)/m)^j$. From Proposition 7, we have $S(d) \sim m\exp\{-\lambda d/m\}$.

If $S(d)$ is hypothesized to be a multitarget survivor function, the asymptotic behavior of $S(d)$ can be exploited to provide quick estimates of m and λ. In practice, information on $S(d)$ is only available for a finite range of d and estimates of this type can be criticized for the assumption made that the asymptotic behavior of $S(d)$ can be deduced from the finite dose range.

4. The implications of repair for the general damage dependent survivor function

From this point, it is assumed that λ and $Q(k)$ are known and the theoretical survivor function is $S(d) = \sum_{k=0}^{\infty}(e^{-\mu d}(\mu d)^k/k!)Q(k)$. If repair can take place, a certain number of lesions formed will be removed. It is assumed that all lesions have been removed if the cell survives [8]. Let $M(d)$ be the mean number of lesions repaired after a dose d. This will be called the repair function. It is possible to observe experimentally the amount of new material incorporated into a cell following irradiation [9]. It is assumed that the amount of new material is proportional to $M(d)$. The problem is to relate $M(d)$ to $S(d)$. Since d is the mean number of lesions formed at dose d, Haynes [8] has suggested the rule

$$(35)\qquad M(d) = \log S(d) + \mu d.$$

The exact relationship between $M(d)$ and $S(d)$ depends on the mechanism of repair. To see this, first note that if the repair of all lesions is essential for survival, then $Q(k)$ is the probability that k lesions are removed from a cell which has k lesions after irradiation. It does not say anything about the probability $p(k, n)$ that n lesions are removed from a cell with k units of damage where $n < k$. Three general repair mechanisms are described before introducing

a specific model. These mechanisms are chosen so that $M(d)$ and $S(d)$ have a simple relationship and are intended to be examples of the diverse types of relationship possible.

4.1. *The minimum repair mechanism.* If the survivor function is $S(d) = \sum_{k=0}^{\infty} (e^{-\mu d}(\mu d)^k/k!)Q(k)$ and the cell is repairing a minimum of its damage, then given that it has k lesions it will repair all and survive with probability $Q(k)$ or repair none and die. Then the mean number of lesions repaired for a cell with k lesions is $kQ(k)$ and after a dose d the mean number of lesions repaired is

$$\begin{aligned} \min(d) &= \sum_{k=0}^{\infty} kQ(k) \frac{e^{-\mu d}(\mu d)^k}{k!} \\ &= \mu d \sum_{k=0}^{\infty} Q(k+1) \frac{e^{-\mu d}(\mu d)^k}{k!} \\ &= d(S'(d) + \mu S(d)). \end{aligned} \tag{36}$$

4.2. *Maximum repair mechanism.* If the cell is repairing a maximum of its damage, then given it has k lesions, it will repair all and survive with probability $Q(k)$ or repair $k-1$ lesions and die with probability $1 - Q(k)$. The mean number of lesions repaired is then $kQ(k) + (k-1)(1 - Q(k))$ and after a dose d the mean number of lesions repaired is

$$\begin{aligned} \max(d) &= \sum_{k=0}^{\infty} \{kQ(k) + (k-1)(1 - Q(k))\} \frac{e^{-\mu d}(\mu d)^k}{k!} \\ &= \mu d - 1 + S(d). \end{aligned} \tag{37}$$

4.3. *Mechanism with mixture of repair capacity.* Define the repair capacity of a cell at a particular time as the maximum number R of lesions it can remove regardless of the number of lesions present. Suppose that R is a random variable. For example, following irradiation the cell will have a certain number n of lesions. As each lesion is removed by repair there is a probability that an event may occur which will render the cell incapable of division. Let $1 - \eta_k$ be the probability that such an event occurs during the removal of the kth lesion, given that it has not occurred previously. Then the probability that a cell will survive n lesions is $\eta_1 \cdots \eta_n$. If $Q(n)$ is an arbitrary function in the class (2) then $\{\eta_k, k = 1, 2, \cdots\}$ can be chosen so that $Q(n) = \eta_1 \cdots \eta_n$, $n = 1, 2, \cdots$. That is, a survivor function in the class A can be interpreted as having arisen from this mechanism.

If the cell has n lesions the probability that it will repair k lesions is then $\eta_1 \cdots \eta_k(1 - \eta_{k+1})$ for $0 \leqq k \leqq n-1$, and $\eta_1 \cdots \eta_n$ for $k = n$. Further, since $\eta_1 \cdots \eta_k(1 - \eta_{k+1}) = Q(k+1) - Q(k) = q_k$, we have the mean number of lesions repaired in a cell with n lesions after irradiation is

$$0q_1 + 1q_2 + \cdots + kq_{k+1} + \cdots (n-1)q_n + nQ(n). \tag{38}$$

This is evidently equivalent to considering a repair capacity distribution with $\Pr(R = k) = q_{k+1}$, since if a cell has a repair capacity k it will repair a maximum

of k lesions and the mean number of lesions repaired for all cells with n lesions after irradiation is then given by (38).

It is also possible to consider that the probability of the successful removal of a lesion depends on the number of lesions remaining in the cell, but in general no simple relationship between $M(d)$ and $S(d)$ results from this mechanism.

Returning to (38), we have

$$0q_1 + 1q_2 + \cdots + (n-1)q_n + nQ(n) = \sum_{j=1}^{k} Q(j), \tag{39}$$

so that the mean number of lesions removed after dose d is then

$$\begin{aligned} \text{mix}\,(d) &= \sum_{k=1}^{\infty} \frac{e^{-\mu d}(\mu d)^k}{k!} \sum_{j=1}^{k} Q(j) \\ &= S(d) + \mu \int_0^d S(x)\,dx - 1. \end{aligned} \tag{40}$$

As a first example consider the 1 hit survivor function $S(d) = e^{-d}$. In the class A, $S(d)$ may have equivalent representations of the form

$$S(d) = e^{-d} = \sum_{k=0}^{\infty} Q(k) \frac{e^{-\mu d}(\mu d)^k}{k!}, \qquad \mu > 1. \tag{41}$$

For the case $\mu = 1$ the repair functions for $d \geqq 0$ are

$$\begin{aligned} &\text{Haynes rule} = 0, \\ &\min\,(d) \quad = 0, \\ &\max\,(d) \quad = e^{-d} - 1 + d, \\ &\text{mix}\,(d) \quad = 0. \end{aligned} \tag{42}$$

For the case $\mu > 1$ the repair functions for $d \geqq 0$ are

$$\begin{aligned} &\text{Haynes rule} = (\mu - 1)d, \\ &\min\,(d) \quad = de^{-d}(\mu - 1), \\ &\max\,(d) \quad = \mu d - 1 + e^{-d}, \\ &\text{mix}\,(d) \quad = (\mu - 1)(1 - e^{-d}). \end{aligned} \tag{43}$$

EXAMPLE 5. Harm [6] has shown that the function $\exp\{-d^2/\sigma^2\}$ approximates the empirical survivor function of *E. coli* B/*r*, following ultraviolet irradiation over the range 0 to 1500 ergs/mm^2. Using Harm's value of σ, and a value for μ given by Setlow [14], the repair functions are computed in Figure 2.

5. A particular model of the effect of ultraviolet radiation on *E. coli*

In the preceding theory a function $Q(k)$ was introduced. The value $Q(k)$ was defined to be the probability a cell would survive k lesions under some fixed experimental condition. This general formulation does not permit any inference to be made on the form of this function under different experimental conditions. In order to proceed further than the fitting of an isolated survivor function it is necessary to construct a more detailed model of the biological system. Such a model is described below.

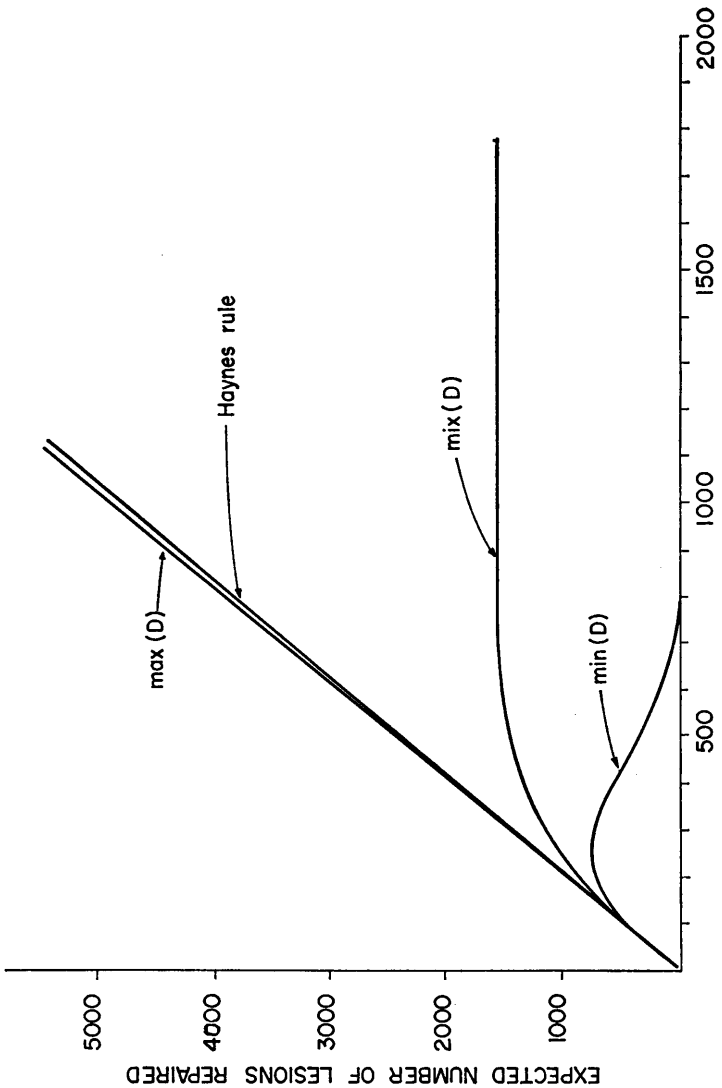

FIGURE 2

Repair functions for the survival function $\exp(-d^2/\sigma^2)$, $\mu = 5.0$, $\sigma = 357$.

5.1. *General assumptions.* Three general assumptions are made. The first is that the irradiated cells are homogeneous in their response to radiation. The second is that the principal effect of ultraviolet light for considerations of survival is the formation of lesions on the chromosome of the cell. The chromosome of *E. coli* consists of a long double strand of DNA. Each strand contains approximately 4.5 million nucleotides of four different types A, C, G, and T. The information coded by the whole sequence of nucleotides is vital to the survival of a cell. If only a section of the DNA is damaged there is some probability that the cell will lose its reproductive ability. Fortunately, the two strands of DNA are complementary to each other, so that damage to one strand may not result in a loss of information. The third basic assumption is that the cell can repair damaged sections of the DNA molecule by copying from the complementary strand.

5.2. *Specific assumptions.* (i) It is assumed that an ultraviolet dose d produces a Poisson distribution of lesions with mean d. These lesions are assumed to be formed randomly along the length of both strands of DNA. The term lesion is used to describe any kind of abnormal product of radiation. There is evidence [15] that these lesions may be the formation of dimers between adjacent T nucleotides in the DNA molecule. If all lesions were of this type, we would be led into an occupancy problem. Preliminary calculations show that in this case the Poisson assumption and the assumption that lesions are formed at random along the DNA would still be approximately valid.

(ii) The chromosome is assumed to consist of a large number N of repairable sections. For a particular section, repair is accomplished by removing the damaged strand within that section and copying from the complement. If only one strand is damaged in a particular section, it is assumed that the section will be successfully repaired. If both strands are damaged, then when one of the damaged strips is removed there is a loss of information and it will only be by chance that the correct information is recovered from the remaining damaged strip. There is also the possibility that faulty repair may physically damage the chromosome. It has been suggested by Harm [6] that breaks in the chromosome may occur. We will assume that if a faulty repair occurs in any section of the chromosome, then no matter what the subsequent history of the cell is, it will not reproduce. The probability of such a faulty repair will in general depend on the medium in which the bacteria are held. Let the probability of faulty repair for a section with both strands damaged be π for plating medium and ν for nonnutrient medium. It is assumed that this probability is independent of the success of repair of any other section.

If the bacteria are irradiated at a high dose rate, repair will not be possible in the irradiation period. The preceding assumptions enable the theoretical probability of survival $S(d)$ to be obtained. Let $s(d)$ be the probability that a particular section successfully repairs whatever lesions are formed after dose d, then

$$S(d) = s(d)^N. \tag{44}$$

If the number of sections N is large, then for reasonable dose ranges $1 - s(d)$ will be small. Taking logarithms in (44), we have

$$\log S(d) = N \log s(d) \cong -N(1 - s(d)). \tag{45}$$

If the bacteria are immediately transferred to a plating medium, we have

$$1 - s(d) = \pi\left(1 - \exp\left\{-\frac{\lambda d}{2N}\right\}\right)^2, \qquad d > 0, \tag{46}$$

where $\lambda d/2N$ is the mean number of lesions formed on a single strand in each section. Thus, provided N is large, from (45), we have

$$\log S(d) \cong -N\pi\left(1 - \exp\left\{-\frac{\lambda d}{2N}\right\}\right)^2 \cong -\frac{\pi\lambda^2 d^2}{4N}. \tag{47}$$

Harm [6] was led to a function of this form by similar reasoning. This function is fitted to empirical data for the survival of *E. coli* B/*r* exposed to ultraviolet light. The value of $\pi\lambda^2/N$ is estimated to be $(2.44 \pm 0.10) \times 10^{-5}$, where the dose d is measured in ergs/mm^2.

6. The repair function $M(d)$

For the mechanism described above, it is possible to obtain the repair function or the expected number of nucleotides which are replaced as a function of dose. For each section, we have the following events and probabilities

no damage:	$\exp\{-\lambda d/N\}$,
1 strip repaired:	$2(\exp\{-\lambda d/2N\} - \exp\{-\lambda d/N\})$,
2 strips repaired:	$(1 - \pi)(1 - \exp\{-\lambda/2N\})^2$.

If it is assumed that no nucleotides are replaced if repair is unsuccessful, then for the cell

$$M(d) = 2Nn_0\left[\left(\exp\left\{-\frac{\lambda d}{2N}\right\} - \exp\left\{-\frac{\lambda d}{N}\right\}\right) + (1 - \pi)\left(1 - \exp\left\{-\frac{\lambda d}{2N}\right\}\right)^2\right], \tag{48}$$

where $2n_0$ is the number of nucleotides per section. Assuming the same number of nucleotides are replaced even if repair is unsuccessful, then $M(d)$ is given by (48) with $\pi = 0$. In Figure 3, empirical data for the function $M(d)$ are plotted against dose. The bacteria *E. coli* $\bar{\tau}$ differs from the bacteria used to obtain the estimate of $\pi\lambda^2/N$. It has been suggested that the apparent drop in $M(d)$ as d increases may be an experimental artifact. A theoretical curve with parameters $\lambda/N = 0.0032$ and $\pi = 0.3$ is drawn to illustrate that equation (48) can represent the observed type of function. However, using these parameters and the estimate for $\pi\lambda^2/N$ obtained previously, we have $\lambda = 0.011$, $N = 3.4$, and $\pi = 0.3$. These values are not consistent with values available elsewhere and this experiment will be ignored in what follows.

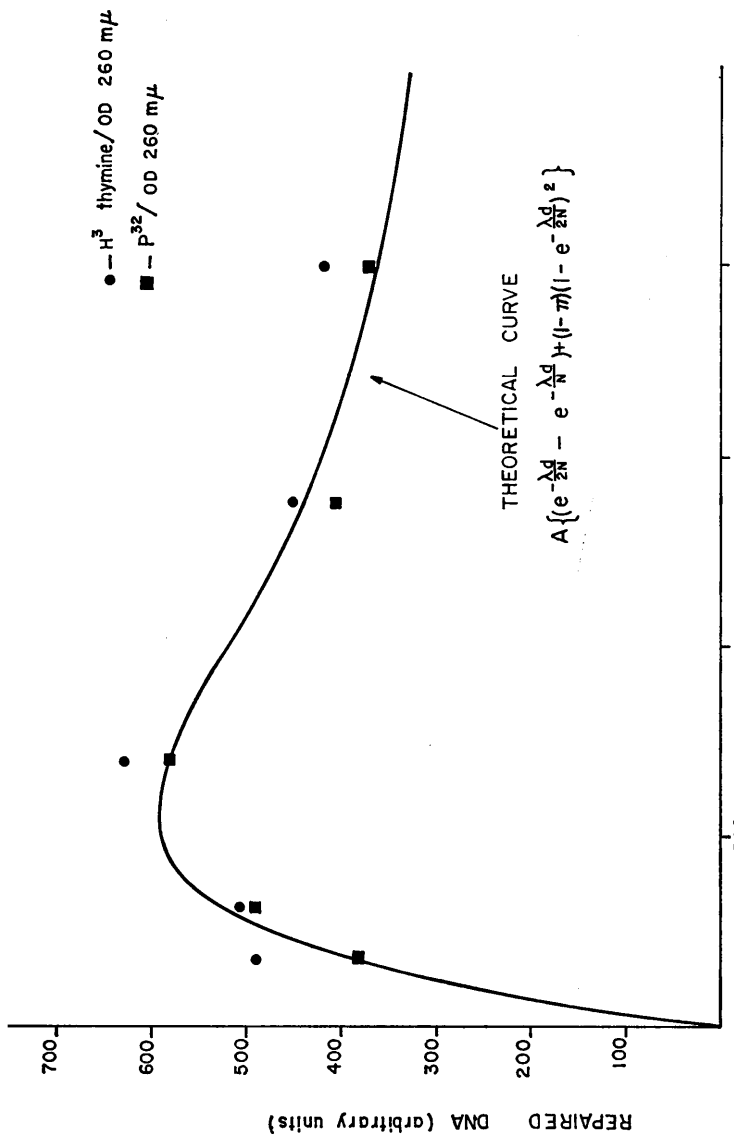

FIGURE 3

Repair function for *E. coli* τ. Data from Haynes [8].

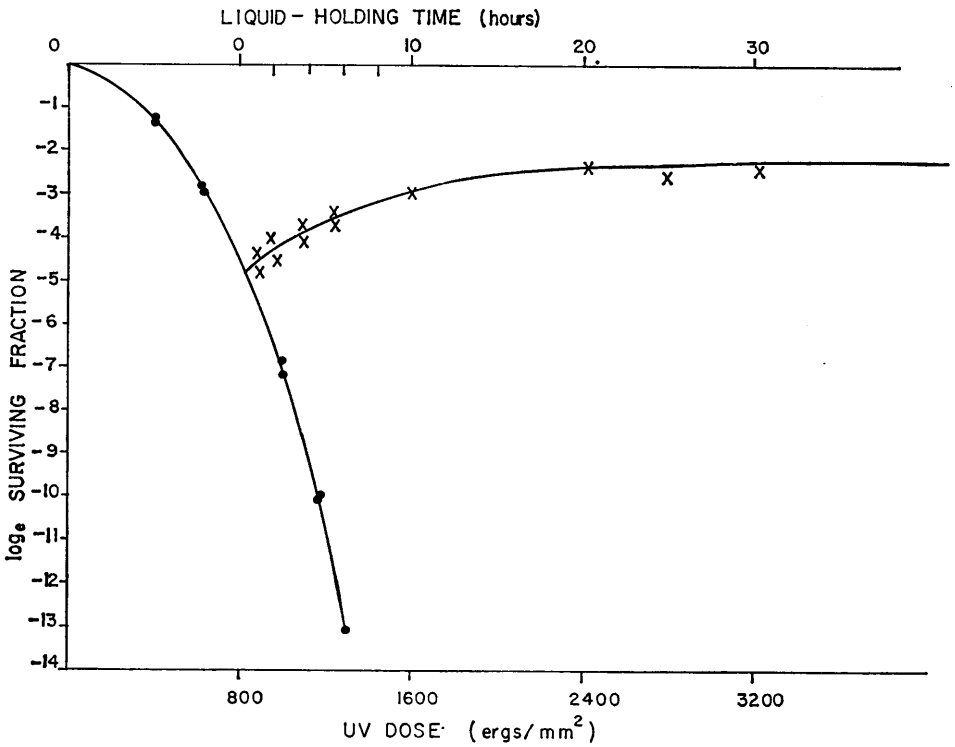

FIGURE 4

Liquid-holding recovery. Upper scale on the abscissa is the time of liquid-holding following irradiation. The fitted curve was obtained from equation (52).

At this point, it is necessary to consider how the mechanism of repair operates as a function of time. Previously, it has been assumed that the dose was instantaneous and that a sufficient time was available to enable repair, faulty or otherwise, to take place. Two phenomena described by Harm [6] are relevant. The first is the phenomenon of "liquid-holding" recovery. Bacteria are irradiated at a high dose rate, but before plating are held in a nonnutrient solution for various periods of time. It is observed that for a given dose the proportion of surviving bacteria increases as a function of holding time (Figure 4).

The second phenomenon is observed when bacteria are irradiated at a low dose rate for extensive periods in a nonnutrient medium. For the same total dose the proportion of survivors is markedly higher for low dose rate exposure than for high dose rate exposure (Figure 5).

The preceding model is readily modified to predict these observations. It is assumed that lesions are formed on the chromosome at a Poisson rate $\lambda\rho$ per hour. The dose rate parameter ρ is in units of ergs/mm^2/hr. For each section, the waiting time before a damaged strand is detected is assumed to be an exponential random variable with mean $1/\mu$. It is assumed that repair is instanta-

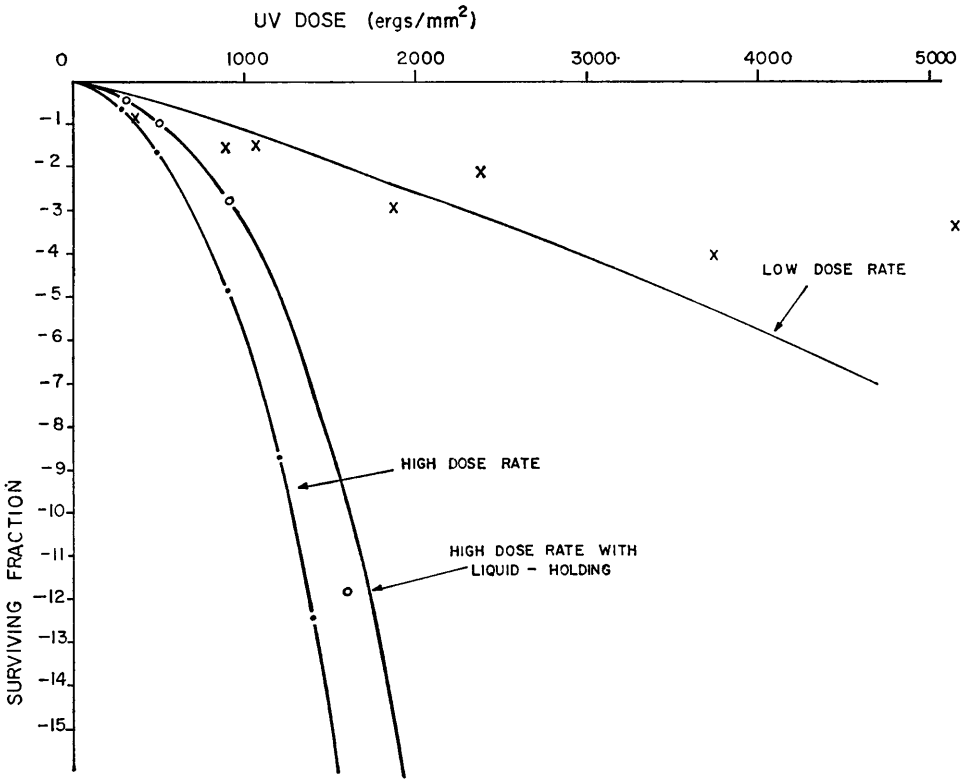

FIGURE 5

Comparison of survival for low dose rate and high dose rate exposure. The fitted curves were obtained from equations (47), (51), and (52).

neous once the damage is detected. The probabilities of faulty repair of sections in which both strands are damaged remain π in plating medium, ν in nonnutrient medium. At some time t in the low dose rate experiment each section will be in one of four states:

(0) no damage,
(1) damage on one strand,
(2) damage on both strands,
(3) faulty repair has taken place.

Let $P_n(t)$ be the probability of being in state n at time t. Since irradiation takes place in a nonnutrient medium, we have

$$
\begin{aligned}
P_0'(t) &= -P_0(t)\lambda\rho/N + P_1(t)\mu, \\
P_1'(t) &= +P_0(t)\lambda\rho/N - P_1(t)(\mu + (\lambda\rho/2N)) + P_2(t)2\mu(1-\pi), \\
P_2'(t) &= + P_1(t)\lambda\rho/2N - P_2(t)2\mu, \\
P_3'(t) &= + P_2(t)2\mu\pi.
\end{aligned} \tag{49}
$$

Suppose that the cells are irradiated for a time t_0 and then plated. It is assumed that in the plating medium, replication is delayed until all possible repair has

occurred. Thus, the probability that a particular section has a faulty repair when replication begins is $P_3(t_0) + \pi P_2(t_0)$. In terms of dose $d = \rho t_0$, we have

$$1 - s(d) = P_3(d/\rho) + \pi P_2(d/\rho). \tag{50}$$

Using relationship (45), $S_\rho(d)$ the probability that a cell survives a dose d at the dose rate ρ is given by

$$\log S_\rho(d) \cong N\{P_3(d/\rho) + \pi P_2(d/\rho)\}. \tag{51}$$

Similarly, let $H(d, t)$ be the probability of surviving a dose d at high dose rate exposure followed by liquid-holding for time t. Then it can be shown that

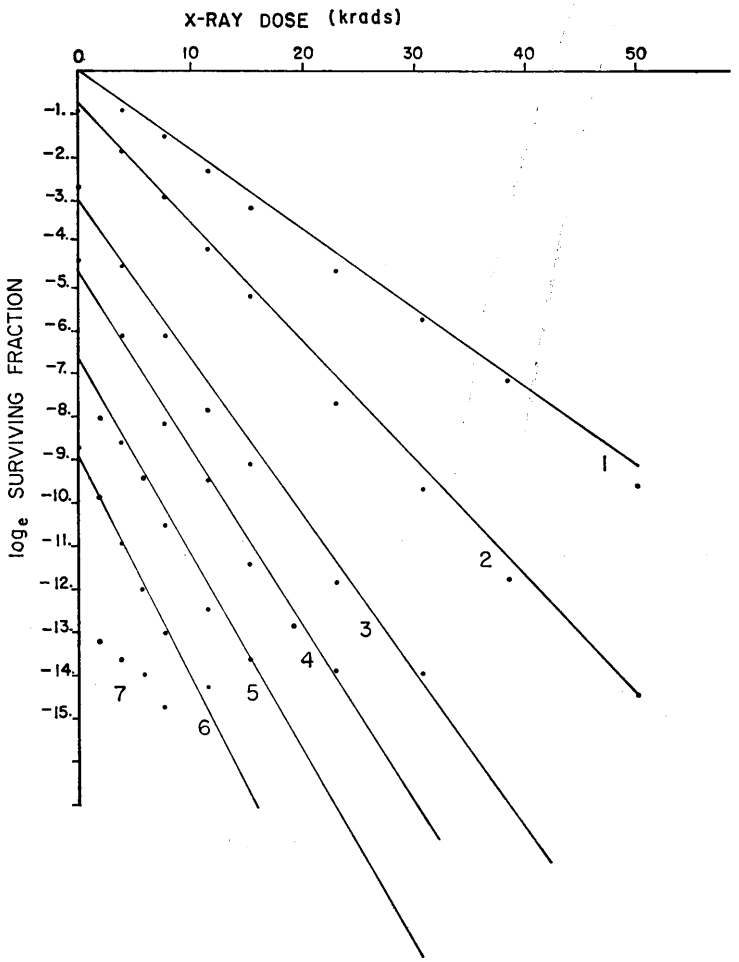

FIGURE 6

Effect of X-ray dose following ultraviolet exposure
(fitted curves are obtained from equation (54)).
Pre-U.V. exposure: 1: 0; 2: 400 ergs/mm^2; 3: 800 ergs/mm^2;
4: 1,000 ergs/mm^2; 5: 1,200 ergs/mm^2; 6: 1,400 ergs/mm^2; 7: 1,600 ergs/mm^2.

$$\log H(d, t) \cong -\frac{\lambda^2 d^2}{4N}\{\pi e^{-\mu\rho t} + \nu(1 - e^{-\mu\rho t})\}. \tag{52}$$

In the particular case $t = 0$, we have the case of immediate plating. To demonstrate the effect of low dose rate exposure as distinct from liquid-holding recovery, Harm also considers $H(d, d/\rho)$, that is, the effect of liquid-holding for the same time as low dose rate exposure. Three empirical sets of survival data corresponding to instantaneous dose, low dose rate exposure, and instantaneous dose followed by liquid-holding for the same time as the low dose rate exposure are given in Figure 5. Theoretical curves with the parameters $\pi = 0.25$, $p = 0.15$, $N = 2 \times 10^5$, $\lambda = 5.4$, and $\mu = 0.173$ are drawn for comparison. For larger values of total dose with low dose rate the model is inadequate since $\log S_\rho(d)$ must decrease steadily in this dose range whereas the empirical data suggest that the proportion surviving has reached a minimum. This effect could possibly be due to a process of damage reversal in which radiation is involved.

The data for liquid-holding recovery as a function of time should be fitted by the function $H(d, t)$. In Figure 4, the theoretical curve with the same parameters as above is superimposed upon the empirical data points.

In a series of experiments Haynes [7] irradiated the bacteria *E. coli* B/*r* at a relatively high dose rate with one dose of ultraviolet light and one dose of X-ray, alternating the order of exposure. Although there are indications that the order of exposure does affect the probability of survival, it is possible that this is an experiment artifact. With this possibility in mind, an extension of the previous mechanism is proposed. In this model there is no effect of the order of exposure. It is assumed that X-ray ionizations produce a Poisson distribution of X-ray lesions which are uniformly distributed along the chromosome. The X-ray lesions are considered to be large compared with ultraviolet lesions. They are assumed to damage both strands and may be extreme enough to cause chromosome breaks. Let $\eta\theta$ be the mean number of X-ray lesions on the chromosome after a dose θ of X-ray. Let p be the probability that a section containing an X-ray lesion and no other damage has a faulty repair. Let π be the probability that a section with either X-ray damage or ultraviolet damage on both strands will have a faulty repair. In all other cases it is assumed that repair is successful. Then the probability a section has a faulty repair after a dose d of ultraviolet and a dose θ of X-ray is given by

$$\begin{aligned} 1 - s(d, \theta) &= \left(1 - \exp\left\{-\frac{\eta\theta}{N}\right\}\right)\left(\pi - (\pi - p)\exp\left\{-\frac{\lambda d}{N}\right\}\right) \\ &\quad + \pi \exp\left\{-\frac{\eta\theta}{N}\right\}\left(1 - \exp\left\{-\frac{\lambda d}{2N}\right\}\right)^2 \\ &\cong \frac{\pi p\theta}{N} + \frac{(\pi - p)\eta\lambda\theta d}{N^2} + \frac{\lambda^2\pi d^2}{4N^2}. \end{aligned} \tag{53}$$

The probability $S(d, \theta)$ that a cell will survive a dose d of ultraviolet and a dose θ of X-ray is given by

$$\log S(d, \theta) \cong -\left\{\eta p\theta + \frac{(\pi - p)\eta\lambda\theta d}{N} + \frac{\lambda^2\pi d^2}{4N}\right\}. \tag{54}$$

This function can be readily fitted to the empirical data of Haynes [7]. With parameters $\eta = 49.3$, $p = 0.0037$, $N = 2 \times 10^5$, $\lambda = 3.84$, and $\pi = 0.25$; the fitted curves are superimposed upon the empirical data in Figure 6. The fitted curves compare favorably with the empirical data.

Dr. R. H. Haynes sparked my interest in this subject in the course of several discussions I had with him. In the preparation of the paper I have received encouragement and many helpful suggestions from Professors J. Neyman and L. LeCam.

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