June 6, 1949.

Dear Kim:

Since our very provocative discussion on the multiple-target theory, I have had a chance to look up some of the literature, and am surprised to have to confess that there has been surprisingly little treatment. However, I still think that something might be found e.g., as a treatment of the sigmoid survival curves when bacteria are allowed to form micro-colonies on agar before being irradiated. Luria and Dulbecco's approach is substantially the same, although they have to use certain slightly different terms, and appear to have depended on an arithmetic summation of their series in evaluating the numbers of units. Luria and Latarjet's J. Bact. paper on irradiation of infected bacteria was the only clear statement that I could find along the lines of the theorythat you are developing, and they seem to have used empirical methods of fitting to the untrans-formed curves. While on the train, I tried to see what I could do, but didn't come out with very much. Assuming a constant number of nuclei,n, we have, of course:

(1) $\quad p = 1 - (1-e^{-ad})^n$, or $\quad q = (1- e^{-ad})^n$.

I don't see any good way of simplifying this to facilitate the estimation of a and n from the p/d data, except possibly to approximate, for ad large with respect to n:

(2) $\quad p = ne^{-ad}$. This just means, what we know already, that the log p/ d curves will become asymptotic, for large doses to lines with slope -a which will extrapolate to the p = 0 line with an intercept dose equivalent to logn/a.

Luria and Latarjet refer to Delbrück's derivation of the expression:

(3) $\quad p = e^{-ne^{-ad}}$, which refers to the "apparent survival" using the full Poisson distribution (untruncated). I assume that this is the function which transforms so nicely with loglogs:

(4) $\quad$ loglog $1/p = \log n - ad$. There is one major difficulty with this expression that I can't see the solution for, and wonder how you may have handled it. Because of the derivation from a fictitious Poisson, the p in (4) does not refer to p_r/p_o where these refer to the observed values with and without radiation, but to $p_r/p_{oc} = p_r/p_o + e^{-n}$. It is fairly obvious in (4) that p does not become unity when no d is delivered. The full expression should read, then,

(5) $\quad$ loglog $(1 + e^{-n})/p_r = \log n - ad$, which would not give precise straight lines when loglog p_r is plotted against d.

The correction for p will become negligible when e^{-a} is small (e.g. will be less than 1% for n more than 5), and for values of a which allow low survival may be unimportant even for small n. But in the first couple of decades of killing, with values of n ca. 2 or 3, I think that this theory demands a rather appreciable deviation from linearity. However, the expression should lend itself to solution by successive approximation, by estimating an uncorrected n from (4), and then substituting this value of n in (5) and so on,.

I haven't been able to find that reference to Yule's paper, as we don't have a file of the Proc. Roy Stat. Soc London here, but I have a rather distinct recollection that it was about 1916, and that it covered a good approximate function instead of (1), using tables of the gamma-functions. It doesn't really have much bearing on the problem of (4). I'll be very much interested to hear how your analysis compares with this one, and am looking forward to seeing your manuscript. If you can't find the Yule reference, Dr. Rob't Boche, Institute of Radiobiology & Biophysics, U. Chicago, Chi. 37, is whom I heard about it from in the first place.

I'm not sending the "analysis" of the N. tetrasperma data, as I found an error in it: I neglected to include the 3-bit class. You'll be interested to look up Uber and Goddard, JGenPhysiol 17, 587, and recalculate their data on the basis that the 4-target-killed are dead, and all of the 3-, and half of the 2- class are self-sterile.

That stuff of yours on induced balanced heterokaryons in Neurospora sounds very exciting, and I am going to help myself to the ideas it provoked concerning some parallel expts. in diploid K-12.

Sincerely,

Joshua Lederberg

P.S. I didn't mind my p's and q's too carefully on the first page. But I think that you can get what I mean without revising it any further than I did in ink.

Notice that (2) gives you $\log p = \log n - ad$, while (4) gives you

$\log\log (1/1-p) = \log n - ad$. That is, inthe limiting case, p should approximate $\log (1/1-p)$., i.e., $e^{-p} = 1 - p\ (+ p^2/2 - p^3/3! \ldots..)$ which is of course true for small values of p.

$$q = (1-e^{-r})^n .$$

$$\doteq 1 - ne^{-r}$$

For $e^{-r} < .01$ $(r > 5)$

$$n < 10$$

e.g. for $e^{-r} = .01$ $n = 10$.

$(1-e^{-r})^n = .99^{10} = .903$

$1 - ne^{-r} = 1 - 10 \cdot .01 = .900$ OK.

$$q = 1 - ne^{-r}$$

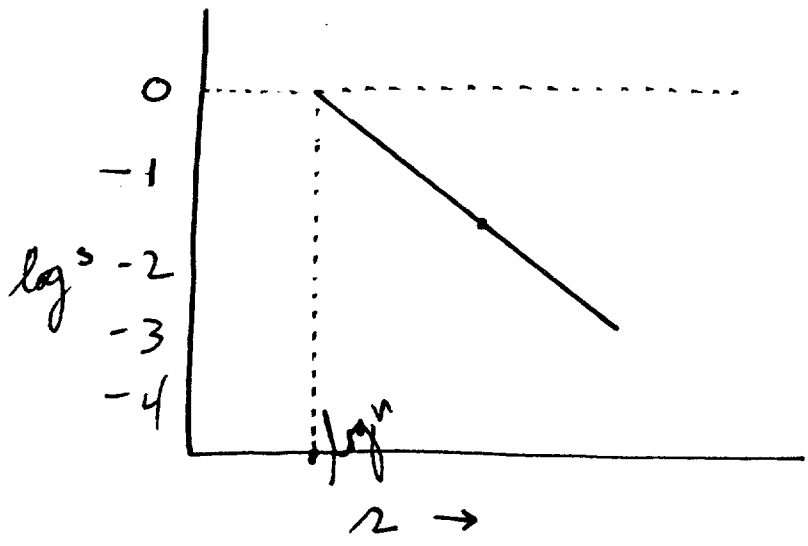
$$1 - q = ne^{-r}$$

f. surv.

$$\log s = \log n - r$$

while has an intercept for $\log s = 0$ of $\log n = r$.

$$\frac{d \log s}{dr} = -1$$



r can be evaluated by measuring the slope of the limiting line, and n from the intercept.

If we have a truncated Poisson:

KCA (10) $1-S = \sum_1 c_n q^n$ $\qquad q = 1-e^{-ad}$

$$= \frac{1}{e^r - 1} \sum_1 \frac{r^n}{n!} q^n$$

$$1 - S = \frac{1}{e^r - 1} \left[\sum_0 \frac{r q^n}{n!} - 1 \right]$$

$$S = 1 - \frac{e^{rq} - 1}{e^r - 1}$$

Defining $S' = 1 - e^{rq}/e^r$

we find $s' = S(1 - e^{-r})$.

and $\log\log \frac{1}{1-S} = \log r - ad.$