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THE INDEPENDENT ACTION THEORY OF MORTALITY
AS TESTED AT FORT DETRICK

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The independent action theory is sometimes used as an approach to all-or none dosage-effect problems instead of the more usual dosage-effect methods such as probit analysis. With the probit and similar analyses, the basic assumption is of varying susceptibility among the subjects. With the independent action theory in its simplest form the assumption is that any toxic unit reaching the site of action will be effective. Each unit is believed to have a small but definite chance of hitting its mark; a higher percentage response to larger doses is produced by multiplication of this chance. This theory obviously does not assume varying susceptibility among subjects, and will logically lead to the same slope for all trials. If a is the chance of hitting the mark, the chance of escape is $(1-a)$ for one toxic unit; for 2 units, it is $(1-a)^2$; for n units $(1-a)^n$. Danger from bullets on a battlefield has been used as one illustration.

The independent action theory was apparently first developed by Neyman and associates, according to K. L. Calder of Fort Detrick. It has been used by Watson (Phil. Trans. Roy. Soc. London, 1936) in studying transmission of plant viruses by insect migrants. It is also used by some workers in dosage-effect studies where the dose is of biological agents (S. Peto, Biometrics 1953; L. J. Goldberg and associates, 5th, 8th and other reports, Navy Biol. Lab., 1951-52). A. W. Kimball (1953 lectures, Fort Detrick) has applied the theory to radioactive particles. Peto presents detailed procedure for calculation, and mathematical methods are also presented by Andrews and Chernoff (Tech. Rept. 17, Applied Math Lab, Stanford, 1952), and by W. G. Cochran (1946 lectures, N. C. State). Goldberg (l. c.) has worked out special plotting paper for quick graphic estimation of LD-50 and its error. The extensive work on dosage theory assuming varying susceptibility is conveniently summarized by Finney. ("Probit Analysis", Cambridge U. Press, 1952).

Where such agents as bullets and radioactive particles are considered, there can be no question that the idea of independent action will apply better than the concept of dosage and varying susceptibility. With chemical toxicants which can be measured out accurately, the

idea of dosage and varying susceptibility undoubtedly applies better than the independent action concept. Susceptibility is know to vary. With biological agents such as pathogenic bacteria, we are on a middle ground where either procedure may have its advocates. The basic question appears to be whether susceptibility really varies substantially among subjects. If some individuals can use their provisions for combating invading agents to throw off effects of a moderate dose of organisms, while weaker subjects will succomb; the ordinary dosage treatment should apply.

The exponential approach obviously simplifies mathematical treatment of data, and in its simpler forms will allow calculation of an LD-50 from only one concentration giving partial mortality. Allowance can be made for varying susceptibility, but in so doing, simplicity if forfeited and advantages over probit analysis seem dubious.

With data of Fort Detrick, Goldberg's approach has given LD-50 estimates very similar to those from probit analysis. The graphic error estimates of his early publications seem inadequate. Where several concentrations give partial mortality, Goldberg's graphic method will yield several LD-50 estimates for the same experiment. These sometimes very incongruously for agents with characteristically low slope.

Critical test comparing the two approaches are very difficult since for ordinary experiments with small numbers results are apt to be quite similar. One possible test involves the form of the untransformed dosage-percentage curve. With the typical probit curve we have an asymetric sigmoid with a weakly defined but real lowe bend. With the exponential we have a single-bend curve of decreasing steepness. Demonstration of a lower bend in the zone of low mortality would be evidence for the probit approach, but would require hundreds of animals. In general, critical test would be expensive and would impede the progress of needed practical tests. We are at present limited largely to gleaning evidence from practical tests.

A preliminary test was afforded in 1953 by Fort Detrick data originated by A. N. Gorelick, of a number of toxic bacterial injections into mice. (See S. B. Job No. 433, Fort Detrick). Some 43 points based on 435 animals were available. If proportion of survival (q) with dosage n is estimated as $(1-a)^n$, then

$$\log q = n \log (1-a)$$

and dosage should be linear in relation to log survival. Significant departure from linearity should suggest that the logical basis of the independent action theory is weak in this material.

On plotting log survival against dose, a gentle curve was suggested by the chart. On fitting, a simple parabola gave a significant gain over a straight line. Statistics are as follows:

Source of Variation	Degree of Freedom	Mean Square
Linear	1	2.44
Quadratic (Additional)	1	0.33
Residual	40	0.03

Another test, not of a definite dosage affect study, but of some assumptions related to those of the independent action theory, was afforded by some of W. C. Patrick's data at Fort Detrick. It involved an encephalomyelitis virus injected intra-cerabrally into mice. A large number of test, made routinely in development work, were available. The agent is very toxic to mice, when injected intra-cerebrally at 0.03 ml of high dilutions. The regularity of results has led to some thought that any single infective particle reaching the site of action may be fatal.

Following this theory, in the high dioutions allowing survival, the survival is thought to be due simply to the fact that the small sample taken for injection contains no particles. This would imply a Poisson distribution of particles among such samples, with a rather small mean. This would throw us back on the independent action or "one-shot" theory of toxicity.

Patrick's numerous records offered a chance to test this theory. If infective particles have a Poisson distribution among injection samples, and if survival indicates a blank sample, the average number $\underline{M}$ of units per sample could be estiamted from the proportion of survivors $\underline{q}$:

$$q = e^{-m}; \quad M = -\ln q.$$

These estimates are quite easily made. Then with two successive concentrations, giving partial mortality; the ratio of two estimates

of m in one test should approximate the dilution ratio (in these cases
0. 5 log). This would not be realized exactly in any one comaprison,
but with a long series the relation should appear. Filure of the $\underline{M}$
ratios to agree with the dilution ratios is regarded as evidence against
the theory.

For illustration a firaly typical assay of an encephalomyelitis
preparation by intra-cerebral injection in mice is taken. Unlike
Patrick's series, dilutions were a log apart rather than half a log.

Log dilution	Response	o/o	p	q	Estimated m
7.0	16/16	100.0	1.000	0.000	--
8.0	16/16	100.0	1.000	0.000	--
9.0	9/15	60.0	0.600	0.400	0.92
10.0	3/16	18.8	0.188	0.812	0.21

From the first dilution (log is 9.0) showing partial mortality, the
value of q is 0.0400. The theory being tested would say that 0.4
proportion of the injection samples contained zero particles. Solv-
ing the equation $q = e^{-m}$ with q taken as 0.40, m comes out as
-ln(q) or 0.92. The second dilution similarly treated gives as an
estimate of m, 0.21. The ratio is 0.92/0.21 or about 4.4. This
is far from the dilution ratio of 10, to be expected if the theory holds.

With the aid of Pvt. Isen a large number of such ratios from
Patrick's 1955 and 1956 test were assembled. Logs of computed
ratios, from tests where 2 estimates from partial mortality were
possible, were assembled and compared with the theoretical 0.50.

Year	No. Tests Used	Mean Log Ratio Of Estimates of M	95 o/o Confidence Limits
1955	104	0.33	0.27 - 0.39
1956	166	0.40	0.33 - 0.47

Results do not bear out the theory that a Poisson distribution of
infective particles will explain mortality or survival.

To sum up, experience with the independent action model in all-or-
none tests at Fort Detrick, has not been very encouraging. Limited
tests of the theoretical basis have not sustained the basic theory.