



STANFORD UNIVERSITY MEDICAL CENTER

STANFORD, CALIFORNIA 94305

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STANFORD UNIVERSITY SCHOOL OF MEDICINE
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Dear Dr. Schatz,

I am not sure how many first-order examples I can recall of paradoxical effects but the following considerations may be relevant.

1. Most mutagenic (carcinogenic) substances both kill and alter cells, at different rates. If the mutation rate \ll killing rate there will obviously be an optimum dose qua absolute number of surviving mutated cells, namely that dose giving e^{-1} survivors. (Lederberg 1948 - Heredity 2:145-198, at p. 165).
2. I believe there are optimum rates of coding and of level of residual moisture for survival of organisms (cryobiology; lyophil.)
3. Water, indeed most nutrients qualify formally - unless one has ancillary knowledge that classifies the "toxicity of low doses" as a specific deficiency effect. I do not think the distinction is logically rigorous.
4. From the standpoint of behavior of the whole organism, most narcotics and anesthetics show paradoxical effect. cf the half-drunk who tries to drive vs the sleepy drunk who cannot. There are many other dose-dependent reversals of narcotic effects you should investigate.
5. In immunology, there are optimum doses of antigens for immunization - notoriously pn. polysaccharides, and of course for precipitation with antibody.
6. Excess phage multiplicity inhibits phage growth (lysis from without and related phenomena).
Viruses can do the same thing to animal cells via induction of interferon. (Isaacs early observations; his papers may also have given examples involving experiments with whole animals).
7. The most startling example in my own experience was penicillin/E. coli for survival of L colonies. (J. Bact. 75:151 ff). Recent findings of several receptors for penicillin may rationalize those observations.

You may find other examples of paradoxical inhibition by antibiotics and of the related (?) phenomenon of therapeutic interference

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in the books on antibiotic action, approximately 1950 by Work and Work and Albert.

8. There are of course many examples of substrate inhibition of enzymes that offer a kinetic model of paradoxical effects. Goldstein made a detailed analysis some years ago which is still worth reading and I recommend you do a citation search on this reference (Goldstein, A. 1944, J. Gen. Physiol. 27:529; see also his book - Principles of drug action; and P. Wilson's chapter in Lardy H.A. - Respiratory Enzymes, 1949).

Sincerely yours,

Joshua Lederberg
Professor of Genetics

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