

This Week's Citation Classic

Skipper H E, Schabel F M, Jr. & Wilcox W S. Experimental evaluation of potential anticancer agents. **XIII.** On the criteria and kinetics associated with "curability" of experimental leukemia. *Cancer Chemother. Rep.* 35:1-111, 1964. [Kettering-Meyer Lab. (Affiliated with Sloan-Kettering Inst.), Southern Res. Inst., Birmingham, AL]

This paper represents a theoretical interpretation of chemotherapeutic trial results obtained in animals bearing widely different burdens of leukemia cells, and ancillary experiments showing (a) the lethality of a single viable leukemia cell, and (b) the exponential growth rate of murine leukemia cells over the range of one to almost the lethal number (ca. 10^9 in the mouse). [The **SCJ**[®] indicates that this paper has been cited over **365** times since 1964.]

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"The authors of this report were a diversely trained but compatible trio: a biochemist, a virologist, and a physical chemist.

"From the available data we (not I) formulated this theory: a given dose of a given drug will kill approximately the same fraction, not the same number, of widely different-sized tumor cell populations—so long as they are similarly exposed and both the growth fraction and the proportion of drug-resistant phenotypes are the same. All neoplastic cells must be eradicated to achieve cure.

"This theory is somewhat akin to one proposed around the turn of the century by Arrhenius regarding the rate of *in vitro* killing of bacterial cells by certain toxic chemicals.¹ To put it mildly, the theory of Arrhenius was not welcomed or accepted by early biologists.² The principal reason was lack of knowledge concerning phenomena which limit its applicability.³

"We first sent the subject manuscript to another journal. The editor (still a close friend) sent it back saying his reviewers thought it was an important paper and that they would be pleased to publish it *if* we would (a) delete the detailed data, (b) delete most of the charts, (c) refrain from speculation, and (d) reduce the text by

about 90 percent. We declined, not out of pique, but because we thought the paper would be almost useless without documentation and charts illustrating what we thought the data implied. Parenthetically, the deletion of speculations in a theoretical paper seemed a bit much to Frank, Bill, and me!

"For some years after offering the above theory we were hard put to deduce which of several possible limitations to cure of disseminated cancers was the primary limitation in different circumstances, i.e., a low growth fraction, the presence of singly, doubly, or multidrug-resistant neoplastic cells, pharmacologic sanctuary problems, or others. Much additional experimental and clinical data, the early work of Luria and Delbrück,⁴ and the mathematical model of Goldie and Coldman⁵ now seem to make such deductions easier; e.g., (a) The presence or absence of drug-resistant phenotypes (tumor cells) is most often responsible for the inverse relationship between tumor cell burden and 'curability' by a drug or combination of drugs, (b) The same phenomenon (a wide variation in the proportion and absolute number of drug-resistant phenotypes) seems largely responsible for the wide variation in the degree and duration of response to chemotherapy observed in comparably staged and treated *individuals* bearing a drug-responsive neo-plastic disease. Failure due to CNS disease usually is easy to determine, (c) Growth fraction differences are more apt to account for the marked differences in the initial response or lack of response to chemo-therapy of different types of cancer; e.g., between different animal cancers, between different human cancers, and across species.

"It should be apparent that in some instances both of the types of tumor cell heterogeneity mentioned above may contribute to treatment failure. Local surgery or radiotherapy, when possible, will reduce the limitations to chemotherapy that result from both types of tumor cell heterogeneity."

1. Arrhenius S. *Quantitative laws in biological chemistry*. London: G. Bell & Sons, 1915. 164 p.
2. Clark A J. *The mode of action of drugs on cells*. London: Edward Arnold, 1933. 298 p.
3. Skipper H E. Some thoughts regarding the modes of action of drugs on cells and on application of available pharmacokinetic data (anticancer drugs). (Skipper H E, ed.) *Cancer chemotherapy*. Ann Arbor, MI: University Microfilms International, 1980. Vol. 10. (Published for the American Society of Clinical Oncology.)
4. Luria S E & Delbrück M. Mutation of bacteria from virus sensitivity to virus resistance. *Genetics* 28:491-511, 1943.
5. Goldie J H & Coldman A J. A mat hematic model for relating the drug sensitivity of tumors to their spontaneous mutation rate. *Cancer Treat. Rep.* 63:1727-31, 1979.