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This Week's Citation Classic®

Freireich E J, Gehan E A, Rall D P, Schmidt L H & Skipper H E. Quantitative comparison of toxicity of anticancer agents in mouse, rat, hamster, dog, monkey, and man. *Cancer Chemother. Rep.* **50**:219-44, 1966.
[M.D. Anderson Hosp., Houston, TX; Biometry Branch and Lab. Chemical Pharmacol., Natl. Cancer Inst., Bethesda, MD; Natl. Ctr. for Primate Biol., Univ. California, Davis, CA; and Kettering-Meyer Lab., Southern Res. Inst., Birmingham, AL]

Comparison of toxicity data acquired during clinical studies of 18 anticancer agents with those obtained in mice, rats, dogs, and rhesus monkeys uncovered close interspecies correlations when doses were related to body surface, much closer than when doses were related to mass. This finding has guided numerous trials of anticancer and other agents. [The *SCI*® indicates that this paper has been cited in over 390 publications.]

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In the early 1960s, developments in combination chemotherapy led a number of investigators to suggest that childhood leukemia could be controlled by fuller and more appropriate use of existing knowledge. Toward this end, C. Gordon Zubrod, then scientific director of the National Cancer Institute (NCI), organized the Acute Leukemia Task Force, which brought clinical scientists together with basic scientists, chemists, pharmacologists, tumor biologists, and statisticians. The purpose was to improve communication among disciplines and to accelerate progress. At the early meetings, it was noted that correlation of the results of studies in animals and humans was difficult.

As a clinical scientist, I was concerned about the variation between children and adults in their ability to tolerate anticancer drugs. The use of body weight for determining drug dosage did not allow reliable dosage choices. A number of other physiological variables had been shown to have a better correlation with surface area than with weight. In clinical studies, it became clear that using surface area as a unit for dosage administration, or the use of ideal weight, led to effective dosage levels for humans of widely divergent size.[1] In animals ranging from the mouse to dog in size, toxic doses correlated better with units of body surface than with units of mass. Therefore, the existing toxicity data were reviewed to determine whether there was a systematic relationship among species.

A "Subhuman Subcommittee" was formed. As the clinical scientist, I gathered data on maximum tolerated dosages in humans. David P. Rall, chief of the Pharmacology Section at NCI, collected data on larger mammals. Leon H. Schmidt provided data for mice, rats, dogs, and rhesus monkeys, and Howard Skipper collected data in mice. The subcommittee met and chose those agents for which adequate data in a number of species had either been published or were available from investigators' laboratories and clinics.

After the data were arranged in tabular form, it was clear that there was a systematic relationship between the toxic doses in animals and in humans. Skipper prepared the first draft of a manuscript that was revised by members of the committee and submitted for publication; however, it was rejected. (Some readers may benefit from the knowledge that a paper that is at first rejected for publication may ultimately become a *Citation Classic*.) We consulted a biostatistician at NCI, Ed Gehan, who clarified the nature of the relationship of dosage in humans to dosage in animal species and developed appropriate statistical models characterizing the relationship. The revised manuscript was accepted for publication.

When the authors considered senior authorship, each thought that the others had made the major contributions. Since this was truly a committee effort, and each author contributed in a major way to the contents of the publication, we decided on an alphabetical arrangement of authorship. I had the good fortune to emerge as the first author.

This paper is frequently cited because it was the first systematic effort to correlate preclinical and clinical toxicity data for anticancer drugs. The correlation was sufficiently strong so that a general strategy could be recommended for guiding the initial clinical testing of drugs using preclinical toxicology data. This has proven useful and has been widely applied. Secondly, this paper demonstrated that this correlation was simpler to understand and relate among species when data were expressed on a surface area basis. This property has proved to be valuable to laboratory and clinical scientists.

There has been confirmation of the usefulness of preclinical toxicology data and the strong correlation among species independent of size;[2] also there has been further work on estimating surface area in humans.[3]

1. **Pinkel D.** The use of body surface area as a criterion of drug dosage in cancer chemotherapy. *Cancer Res.* **18**:853-6, 1963.
2. **Rozencweig M, Von Hoff D D, Staquet M J, Schein P S, Penta J S, Goldin A, Muggia F M, Freireich E J & DeVita V T.** Animal toxicity for early clinical trials with anticancer agents. *Cancer Clin. Trials* 4:21-8, 1981.
3. **Gehan E A & George S L.** Estimation of human body surface area from height and weight. *Cancer Chemother. Rep.* **54**:225-35, 1970.

