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Dr. LEPPER. As one can see, I, too, have wrestled with the problem of the balance of good and harm which we always do in therapy. The problems of the use of chloramphenicol is one of the best examples of the many ramifications and difficulties inherent in establishing a clinical therapeutic index. I would emphasize there "clinical," because that is what we are talking about.

The concept of a therapeutic index, was originally stated by the father of chemotherapy, Ehrlich, early in this century, his concept was that the higher the ratio of therapeutic effective dose to toxic dose, the better the compound. This, however, was thought of primarily in terms of the experimental animal, and in them relatively easily handled on a statistical basis. Thus, it has become a routine to find the protective dose in an experimental infection and the lethal dose for toxicity in other animals of the same species.

The most common statistic used is the dose that is 50-percent effective on the one hand, and 50-percent lethal on the other. Thus, a drug that cures 50 percent of a group of animals at a dose level of 10 milligrams per kilogram and is lethal at a dose level of 500 milligrams per kilogram, in 50 percent of a group of similar, but uninfected, animals would have an index of 1/100. That is a very favorable therapeutic ratio, I might add.

If these doses were 10 and 20, respectively, however, the index would be one-half. That is not a very favorable ratio.

Certainly, this relatively simple laboratory guide has been quite a useful guide, but because of the many difficulties of going from a species, such as mice, with an artificially induced infection, to man with a naturally occurring infection, assures us that it is just a guide. The clinical investigator, therefore, is faced with the problem of developing a somewhat similar ratio for naturally occurring infections in a rather heterogeneous population from the toxicity point of view, as has been emphasized by the previous speaker.

Needless to say, the estimates of these ratios are much less precise and involve more than an arbitrary endpoint because we want 100-percent survival if we can get it, and obviously not a 50-percent lethal dose. However, there is a hierarchy of not necessarily mutually ex-