tion at which its effects become manifest [in the two classes of organisms] is, however, many times greater . . . with Gram-negative organisms than . . . with Gram-positive organisms" [Pratt and Dufrenoy, *Antibiotics* (Lippincott, Philadelphia, 1949), p. 214]. This view is not incompatible with the "unified hypothesis of penicillin action" cited by Ciak and Hahn as proposed by Park and Stromiger [*Science* **125**, 99 (1957)] nearly a decade later. The latter authors did, however, present precise quantitative data to support their view, whereas the earlier proposal was based on less refined data and did not pinpoint the effects on cell-wall formation.

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Therapeutic Dosage in Small and Large Mammals

The research report "Lysergic acid diethylamide: Its effects on a male Asiatic elephant" [*Science* **138**, 1100 (1962)] on the therapy of the Proboscidea contains an elephantine fallacy. In these days when certain highly organized groups are striving earnestly to legislate against animal experimentation, it is unfortunate that quite so gross an error should appear in print. The basic problem seems to be extrapolation from limited data acquired in therapy of small mammals in determining the first therapeutic dose to be used on a larger form. To my knowledge no very precise set of rules exist, but some general principles are of value.

Rule 1. If we wish to determine, from toxicity data based upon findings in the cat, a therapeutic dose safe for an elephant, our first rule is to consult a veterinarian or, if possible, an animal husbandman with experience in handling elephants. Probably the best individual is a veterinarian with experience in dosing animals in a zoological garden. Individuals experienced in human therapeutics are too much limited by their training. Their thinking is confined essentially to one species of animal, and they have no proper experience upon which to draw in trying to transfer data obtained from one species to a second species.

Rule 2. The metabolic rates, including the rates of metabolism of drugs, of two animals are related not as the weights of the animals but as their sur-

face areas. If the two animals are very similar in body proportions, and if their weights are not very different (a ratio of not more than 1 : 10) one may arrive at a fairly reasonable therapeutic deduction by extracting the cube root of the weights of the two animals, then squaring the two figures and obtaining a therapeutic ratio from the square. This calculation may be simplified by obtaining the ratio of the two weights, extracting the cube of the ratio, and squaring the root. For example, the ratio of the weight of a cat to the weight of a man is approximately 1 : 30; that of the weight of a man to the weight of an elephant, approximately 1 : 50. The cube root of 50 is approximately 3.7, and the square of 3.7 is 13.7. Accordingly, the dose of lysergic acid for an elephant, as extrapolated from the oral dose for man, should have been 2½ to 3 milligrams rather than 297 milligrams.

Rule 3. Extrapolation on the basis of a simple comparison of weights is not valid in the case of man and elephant because the two weights are not similar (the ratio is greater than 1 : 10). It is a useful rule in extrapolating from a relatively small species of mammal to a large species, especially if it is important to be on the safe side because the animal is of great value, to point off one additional decimal place in making the calculation and to use this low dose as a start. A dose of 300 micrograms is all that could be recommended as the initial dosage in experimental administration of lysergic acid to an elephant. Admittedly this dosage is not much above that found necessary in the oral treatment of humans. However, we are by-passing the liver when we administer the drug by injection, and we may expect a somewhat sharper reaction when the method of administration is that employed in the experiment described. I might point out that the effective dose for a cat bears much the same relationship to the effective dose for a man that the effective dose for a man bears to the suggested dose for an elephant.

Rule 4. In extrapolating from one species of animal to a very different species one should be extremely conservative in deciding upon the first dose to be administered because unexpected reactions are likely to occur. Generally, closely related species show similar responses to therapy, but many exceptions to the phylogenic rule are known. Caution is required.

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