To us, a more far-reaching danger is the FDA's subtle introduction of a requirement for evidence of "clinically meaningful" effectiveness results. The ramifications of this obviously transcend the direct concern and competence of the industry and regulatory personnel involved, as well as the concern of clinical investigators and bioscientists. This letter is to alert the scientific community to this development and thus, hopefully, to provide impetus for a broad discussion of the implications of the phrase "clinically meaningful." The following examples illustrate some of the issues involved:

1) On a conceptual level, "clinical meaningfulness" defies definition. It has significance only at the level of the individual physician and his particular patient.

2) The definition of a "clinically meaningful" response, even if conceptually feasible, presents many problems —not the least of which is coping in a "satisfactory" way with the inherently multivariate criteria that must be required for even the least complicated disease or condition.

3) There is much yet to be learned about clinical drug trials. For example, we have observed marked differences among investigators as therapists, even in a carefully controlled clinical setting (*1*). Without fundamental improvement in methodology, the evidence for "clinically meaningful" effectiveness must be obtained largely at the expense of an increasing likelihood of rejecting potentially useful drugs.

4) Without specific definitions of "clinical meaningfulness," the results of clinical investigations, even though conducted in rigid accordance with the pertinent guideline, will be evaluated on a very individual and unpredictable basis by the FDA's medical "expert" assigned to that drug class at that particular time. In one instance, there was a candid explanation that the FDA was not prepared to define a "clinically meaningful" result for the drug class in question, nor did it know when such a definition might be forthcoming.

5) The FDA is legally required to insure that there is "substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling thereof. . . ." We believe this statute is desirable, but in no way does it constitute a license for the FDA to enforce its judgment about the desirability of a particular drug treatment. FDA personnel have suggested, for example, that a drug sponsor must provide evidence that a hypotensive agent actually "causes" decreased morbidity in addition to lowering a patient's elevated blood pressure per se. This philosophy ignores the literature (*2–5*) which documents the danger of not treating hypertension. It is both unnecessary and dangerous to subject a control group with moderate and severe hypertension to placebo therapy.

We hope the scientific community will become aware of the FDA's use of the phrase "clinically meaningful" and respond in a positive fashion to this imminent regulatory development.

JACK FREUND
LESTER W. PRESTON
A. H. Robins Company, Inc.,
1407 Cummings Drive,
Richmond, Virginia 23220

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What Substitute for Cars?

H.R. Lahr (Letters, 6 Nov.) presents a good condensation of what I take to be the prevailing opinion of residents of the Los Angeles area—that the convenience of automotive transit outweighs its disadvantages. Thus, the paving of an appreciable portion of the area and substitution of an irritating yellow substance for air are acceptable.

This represents a value judgment and should not be criticized by us outsiders, but by the same token we should not be asked to help provide the best of two worlds to the Angelenos.

D. S. KYSER
1803-B Young Circle,
China Lake, California 93555

Lahr typifies the attitude of many affluent suburbanites who "wouldn't use a streetcar if it ran right past my house." His sense of what is economical, however, might change if he had to pay his true share of the cost of constructing and maintaining the superhighways which enable him to reach his destination so rapidly and conveniently. Most superhighways come into being because of the pressure exerted on our elected representatives by powerful, special interest lobbies. A large portion of the tax revenue required for their construction and maintenance, however, comes from the urban community whose residents rarely want and often actively oppose such construction. Lahr's letter might have been more pertinent if it represented the viewpoint of a resident of the Watts district of Los Angeles. . . .

MANFORD J. ROBINSON
37 South Main Street,
Yardley, Pennsylvania 19067

Lahr is quite correct in claiming that the automobile is the best mass transportatiion system for Los Angeles. The two grew together and influenced each other. He is also perfectly correct in saying that we cannot sell the public something unless it is better than what it already has. Nineteenth-century streetcars, buses, and subways will not work in Los Angeles. They are not very attractive in older cities, which have not grown up to cater to the horrifying extravagance the automobile brings about in cities.

However, there are a great variety of new transportation systems being developed which promise to combine all the advantages of the automobile and public transportation without most of the disadvantages. These are so-called "dual-mode" systems. Privately owned vehicles and public-operated transit vehicles alike will be able to join high-speed guideways that use a small fraction of the width of an expressway and that will handle 5,000 to 10,000 vehicles per hour in a continuous flow. When the labor component of public transportation is reduced, the incentives are toward the use of small vehicles rather than ever-larger units, so that more personalized public transportation is possible. Even the family automobile will probably become low-powered with short range, probably using battery power. When there are guideways within 3 miles of every part of a city, and going between cities, 300-horsepower automobiles will no longer be necessary and may even be banned in cities.

DAVID GORDON WILSON
Department of Mechanical Engineering,
Massachusetts Institute of
Technology, Cambridge 02139