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COMMENTS ON PRESENTATION BY PAUL COX

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It is always a pleasure (and enlightening) to attend a statistical session in which Professor Greenberg and Professor Hartley participate. They usually make important remarks, succintly, and thus save one from the responsibility of adding much more than "amen." Since they've spoken before me, I wish now to add my "not much more", (as well as "amen").

Mr. Cox has presented us with a very interesting problem in engineering which has a direct counterpart in medical and biological research. I have in mind among other measures the interpretation of electrocardiogram tracings, electro-encephalogram tracings, and the flood of apparently continuous measures that the physiologists are now capable of making. From this analogy, I am led to take slight issue, however with one of Professor Hartley's remarks.

A single response measure, such as the LD_{50} may well be inappropriate. Of course, Mr. Cox's engineer has been rather vague about what he really wants to know, and I suspect that more extended discussion with the statisticians might lead the engineer to specify his problem more. I am guessing that an LD_{50} would be inappropriate. Assume that the statistician finds, though, that he is interested in the shape of the curve, in some sense. That is, the specific shape of the curve, or the presence or absence of some specific wiggle tells him something about the physics underlying the system. For example, in the biological counterpart, a straight line inactivation curve (log response vs. time, for example) as was first postulated for the Salk vaccine for polio implies a simple one-step chemical process, or a single manner of excretion. A concave upward curve may imply a two-step process, or two (or more) modes of excretion, (i.e. a sum of exponentials) or some other functional arrangement. The investigation of the kinetics of such systems are a whole sub-field. Professor Hartley has some good advice to offer in the fitting of these sums of exponentials. Thus, the curves themselves may be the items of most importance to the experimenter. This should not be lost.

On the specific suggestions made by Mr. Cox for the analysis of the data, the physical meanings of the various points on the curve, A, B, C, D, E, F, might help guide the statistician into more fruitful lines--perhaps even into a solution of the problem the engineer wants solved. As Professor Hartley pointed out, the points on the curve are correlated, making the analysis of variance inappropriate because of the non-independence. One earlier reference on the non-independent regression problem then the Bailey-Hammersley reference that may be helpful is one by John Mandel, in the Journal of the American Statistical Association "Fitting a straight line to certain types of cumulative data," Vol. 52, p. 552 (1957). My recollection is that Mandel shows that a least squares approach gives an unbiased estimate of the parameters, but gives the wrong (too small) variance. He gives other references to this problem, too.

On the "shape" problem, there is a paper by G.E.P. Box and W.A. Hay which may be of interest. It appeared in Biometrics, Vol. 9, p. 304 (1953) "A statistical design for the efficient removal of trends occurring in a comparative experiment, with an application in biological assay." A recent doctoral dissertation by Francis J. Wall, from the University of Minnesota considers an aspect of the nearly continuous data problem in biology and medicine. The title is "Biostatistical linear models in longitudinal medical research problems." The title shouldn't mislead engineers. It's much the same problem as we had here.