be doubt of biological equivalence (eg, calcium added to tetracycline), biological tests should be required.

The exploration of possible chemical, physical, and animal tests that might satisfactorily be substituted for biological tests in man has already begun, and this should most certainly be encouraged. Particular attention is being paid to relatively insoluble drugs dispensed in solid forms as tablets or capsules. A Joint Panel of the United States Pharmacopeia and the National Formulary has been at work for some months on the development of standards and test procedures in vitro that will permit better definition of physiological availability. Biological data on the lack of therapeutic equivalence of various preparations of chloramphenicol recently dramatized this problem. Critical investigation of the chemical and physical properties of these preparations is currently in progress, and such investigations should certainly be encouraged.

The whole subject will require extensive scrutiny as well as close attention to process control of the uniformity of the chemical and physical properties of both generic and trademarked preparations. Appraisal of problems concerned with particular drugs will represent various degrees of medical, as well as technical, difficulty. For example, are high blood concentrations of short duration medically more desirable than lower, more prolonged, concentrations? The decision would be quite different in the case of an antibiotic in contrast with an antiepileptic preparation. What if such criteria a generic formulation turns out to be biologically superior to the original proprietary? What if blood concentrations cannot be measured?

With some drugs, there are reasonably good analytical methods for biological assays, whereas for others a meaningful test is virtually impossible at this time. Consequently, the problem of the biological equivalence of drugs should be approached expectantly and progressively. Critical evidence of chemical and physical equivalence is the first order of business. Obviously, new drugs and accepted drugs of greatest pharmacodynamic action or therapeutic importance may additionally require careful biological scrutiny.

It would seem reasonable for the FDA to require that the generic manufacturer submit, in addition to evidence of chemical equivalence and purity, data on dissolution rate and data from other in vitro tests demonstrating equivalency. However, if there is evidence that in vitro evaluation or animal tests do not correlate well with pharmacodynamic effects in man, there may be need to resort to clinical tests. In this way, the principle of generic prescribing based on therapeutic equivalence may become acceptable to the medical profession and be supported by the pharmaceutical industry.

W. B. CASTLE, M.D., *Chairman.*
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UNIVERSITY OF VIRGINIA,
SCHOOL OF MEDICINE,
Charlottesville, Va., May 12, 1969.

Dr. JOHN H. TALBOTT,
Editor, Journal of the American Medical Association,
Chicago, Ill.

DEAR DR. TALBOTT: I am disturbed by the publicity given to the decisions of the J.A.M.A. not to publish the paper prepared by Anti-infective Panels II and IV of the NAS–NRC drug efficacy study. I hope that you will have the opportunity to read the testimony I presented before the Nelson Committee on May 7. A copy of my formal testimony is enclosed for your interest.

In my verbal answers to questions, I acknowledged that the J.A.M.A. had rejected the paper as submitted by Mr. Trexler of the NAS–NRC. I also indicated that I have always been treated well by AMA publications and did not consider this action to be in any way directed against me personally. Indeed, you did recently publish a paper of mine on closed catheter drainage in the J.A.M.A. and on oral contraceptives and blood pressure in the Archives of Internal Medicine.