

tween physics teaching for future physicists and for nonphysicists is in the degree of difficulty of the problems. And, because the future nonphysicist never gets to the more sophisticated areas of the science, it all remains a vaguely disturbing, unpleasant memory. Broad-based science teaching does work, as I can attest from personal experience with an experimental endeavor called "Physics for Non-Physicists."

In the British Museum is displayed an ancient Egyptian papyrus entitled "Directions for Knowing All Dark Things." This document, written by the priestly scribe Ahmes before 1700 B.C., deals with fractions. It may not seem very mysterious today, but in a time when only the priests could perform these calculations, fractions may indeed have been "dark things." Today, the dark things are immeasurably more complex, and the technologists are the priests.

So long as technology is a dark thing; so long as those who make decisions do not understand its limitations; so long as the technologists are treated as priests with a direct line to God—the danger exists that the God of today will become the Devil of tomorrow, and the priests of today will be burned at the stake for witchcraft.

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May I take my place in the queue of persons waiting to point out to David that a perpetual motion machine is considered impossible because it violates the second law of thermodynamics. It need not, in principle, violate the first law, which is merely a statement of the conservation of energy.

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Fixed Combination Drugs


In his report (News and Comment, 4 June, p. 1013) on the Food and Drug Administration and combination drugs, Bazell's primary contention seems to be that the FDA intends to capitulate to commercial pressures by permitting combination drug products which may benefit a few but not most patients.


We suggest that the recognition of the true value of combinations is not an act of capitulation, but of medical and regulatory prudence. It is clearly not in the

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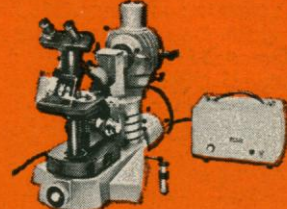
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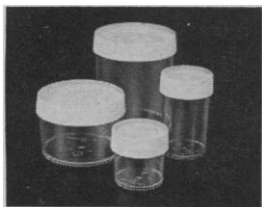
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patients' interest for the FDA to require that any medication benefit the majority of patients. On the contrary, the requirement in the law that there be "substantial evidence" of a new drug's safety and efficacy recognizes that medicine is not practiced on the average but on individual patients. Surely, the medicine which helps even one patient in ten should not be denied its role. Naturally, we agree that a combination product which contains ineffective ingredients should not be marketed, and we also agree that a combination should not be used when the desired therapy can be achieved just as readily through the use of a single ingredient.

The trouble is that physicians find it necessary to use more than one drug much of the time, because sick people are not always in the habit of presenting just one symptom needing treatment. For that reason combination products offering rational amounts of needed medicines are found useful. If these products were barred, physicians would not stop prescribing drugs in combination; they would often write multiple prescriptions requiring the patients to pay for needless extra pharmaceutical services.

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I believe I can speak for many of the physicians who served on the National Academy of Sciences-National Research Council panels that evaluated claims made for drugs based on the 1962 Kefauver-Harris amendments to the Food, Drug, and Cosmetics Act. The five antimicrobial drug panels, one of which I chaired, took the lead in condemning irrational fixed combinations of antimicrobial drugs. Our reasoning was presented in detail in the *New England Journal of Medicine* (1). No new facts have emerged that would change this point of view. Nevertheless, we are eager to evaluate any claims of enhanced efficacy of drug combinations that offer major patient convenience, lower cost, or important synergistic or additive effects.

Lasagna's position in his article in the *Wall Street Journal* (2) does a major disservice to the NAS-NRC study and to the FDA. Panel members were fully aware that their recommendations would strongly influence FDA policy. The proliferation of gimmicks used by the pharmaceutical industry to promote unwarranted fixed combination drugs must be subject to some system of

checks and balances. New drugs or combinations do not belong on the market unless substantial evidence of efficacy is presented based on sound, scientifically conducted clinical trials. This cannot be accomplished by a vote of physicians harassed by eager pharmaceutical representatives.

There are so many fixed combination drugs available for so many diverse indications that it is impossible to handle them all with the same arbitrary standard. Accordingly, they should be reviewed in relation to their "therapeutic index" or to their "cost-benefit" ratio. Ingredients that pose major toxic hazards (such as amphetamines) should be given the closest scrutiny, whereas combinations containing relatively harmless ingredients should be judged less critically. Patient convenience, not manufacturer's profits, should be the major consideration.

It is my hope that other panel members will speak out in support of the FDA. This agency has an extremely important mission in guarding the nation's health. Unfortunately, it must conduct its work on a very limited budget, under constant bombardment from industry, Congress, and consumer advocates. It is time for the medical profession to recognize the legal constraints under which the FDA must act and to help it arrive at decisions that will provide our people with safe and effective drugs.

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References

1. C. M. Kunin and W. Hewitt, *New Engl. J. Med.* **280**, 1149 (1969).
2. L. Lasagna, *Wall Street Journal*, 8 April 1971, p. 12.

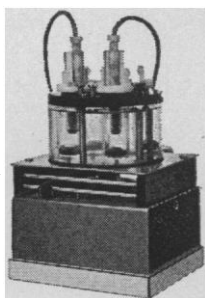
That the pharmaceutical industry should combat many of the FDA decisions based on the NAS-NRC study is readily understood, and the mechanics of implementing the FDA decisions do need improving. What is less understandable is the attitude being fostered in some physicians that the decisions of the NAS-NRC study threaten the status of the physician and that, as quoted in Bazell's report, "Old Doc knows best." What "Old Doc" often forgets is that he may have very little knowledge of how to evaluate the effectiveness of the drugs he prescribes and that his use of and confidence in certain drugs and drug combinations are based on the careful indoctrination he has received from the pharmaceutical industry. "Old

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Doc" should really welcome the opinions and judgment of the drug efficacy panels, which, despite contrary statements, did include physicians thoroughly familiar with the clinical problems in the areas reviewed by each panel.

I am also concerned by Lasagna's statement in his *Wall Street Journal* article that the NAS-NRC study might result in a decrease in drug company profits which would threaten support of pharmacological research. Isn't it paradoxical that support for advanced studies in pharmacology should be sought in the sales of drugs that, very frequently, have not been subjected to critical scrutiny? I doubt that the drug companies will reduce their research efforts, whatever the outcome of the FDA implementation of the NAS-NRC study. Drug research has proved very profitable to the companies that support it, and all their hopes for future growth and profits depend on the results of research programs they will undoubtedly continue to support. Those programs should also include sound and critical evaluation of drug products before they are offered for general use.

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None of us who were asked by the NAS-NRC to survey therapeutic agents were aware of any *specific* plans of the FDA to act on our judgments. Of course, it was assumed that some sort of regulatory action would follow, since it would have been insulting indeed to ask scientists to spend a great deal of time reviewing old drugs and then have their evaluations go for naught. Nothing, however, in the plans for the review spelled out specific regulatory actions or mandated demands for further data. For instance, the guidelines indicated that if a drug were judged "probably effective" in regard to a given claim, the rating might suggest a need for further clinical trials, or simply a change in labeling, or both. Since the review, the actions that have been taken on such claims have been largely in the direction of requiring further controlled trials, with a minimum of effort directed at correcting unjustifiable claims by simple labeling changes. I am happy to say that this situation seems to be correcting itself at the moment.

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