Letters

New Drugs: The Tortuous Road to Approval

It is time that a public dialogue should begin again with regard to the control of investigation into the usefulness of potential new drugs. These controls are administered by the Food and Drug Administration under a new law and under regulations which are not always interpreted so that the public interest is advanced. If these regulations are legally correct, it is clear that the law should be changed in some respects to prevent harm to the public welfare. Specifically, there should be clear recognition of the difference between giving clearance for scientific studies on a small number of subjects who voluntarily elect to participate in the study of an experimental drug, and giving sanction to the general sale and use of a new drug. The latter deserves great caution and exhaustive study of all possible ill effects because of the much wider range of subjects and conditions of use. But when excessively elaborate toxicity studies are required prior to approval of limited clinical studies of a new drug, four results follow. First, there is unfortunately an incomplete correspondence in some cases between the toxicity predicted from animal tests and that encountered under use conditions. Second, there is unjustified delay in obtaining a useful product if the drug proves to be valuable. Many more lives may be lost by such delay than might be saved by excessive caution. Third, there is a serious diversion and therefore a waste of investigative effort in making many unnecessarily complete toxicity studies, if it turns out, as it most frequently does during pilot studies, that the new drugs are not actually clinically useful. Fourth, many competent medical scientists have found that their efforts to test new drugs are hampered by the FDA's elaborate restrictions.

Unfortunately, Commissioner Goddard has not been able to recruit a full complement of scientifically competent and experienced personnel. For example, two persons in immediate charge of decisions affecting the clinical testing of cardiovascular drugs are not members of the relevant scientific society dealing with pharmacological matters. The society in question is not an honor society. Any modest scientific qualifications would meet the requirements for membership. If they have not sought to join, they betray lack of interest in their science.

Dedication is not enough to satisfy the real public interest. Furthermore, the stultifying effect of subconscious preference for inaction rather than action in politically sensitive decisions frequently paralyzes public employees. Errors of omission are easily glossed over as compared with errors of commission. An example of the politically generated paralysis was described by John C. Pollard of the University of Michigan (Letters, 18 Nov., p. 844) who indicated that he found it impossible to continue scientific studies of LSD. An example of general bureaucratic preference for negative rather than positive action is the case of a colleague who was for more than 3 months refused permission to test for a new purpose a potentially life-saving drug which had already been used, without evidence of toxicity, on half a million humans in other countries for a different purpose. He had submitted a great deal of toxicity data but still more was demanded. It happens that a million or more persons a year die of ventricular fibrillation, which this drug might prevent in many instances.

My points are that: (i) The public interest demands that risks of inaction as well as of action be taken into consideration in decision-making regarding the clinical testing of drugs. (ii) The FDA should use more outside civilian consultant committees of highly qualified experts rather than its own staff to make crucial decisions concerning testing of important new drugs. These experts, while not full-time employees of regulatory agencies, would be willing to serve their turns as decision-making consultants. The responsibility should not rest entirely upon hapless civil servants whose careers could be wrecked by an unfortunate positive decision, but will never be injured by even worse negative decisions. The use of such civilian panels of experts has many precedents in this country and elsewhere. (iii) The FDA should exhaust the opportunities for conference with parties at issue to attempt to resolve gray areas of scientific interpretation before resorting to heavy-handed and precipitate legal action. It should abandon the practice of issuing administrative orders without prior offering of opportunity for constructive criticism. The order of 30 August 1966 on experimental drugs is a case in point. (iv) Congress should reinvestigate through appropriate committees the actual operation of the new drug aspects of present laws and act to correct any defects it finds which are adverse to the public welfare. Congress did not intend to write laws that would improperly inhibit research on new drugs or on new uses of old drugs. But it has written laws which, in their effect, do exactly that.

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Definitions, Distinctions, and Dichotomies

I would like to answer with an emphatic "yes" the question posed by Reagan in "Basic and applied research: a meaningful distinction?" (17 Mar., p. 1383). The distinction is difficult to make in a one-sentence definition, but clear operational criteria do exist. To take physics as an example, you have only to compare, say, *The Physical Review* with *The Journal of Applied Physics* to see how these criteria operate.

There are two points worth making: (i) The distinction is not absolute; the criteria are not perfect. The editorial files of research journals are full of argumentative correspondence on this point. You can always find the occasional article in a "basic" journal, which should have been in an "applied" journal. More than an occasional article could have been in either. This reflects the basic ambiguities discussed by Reagan. (ii) The important point is who applies these criteria. It is the editors and, especially, their referees.