The Role of Industry in the Development of New Biologicals

MAURICE R. HILLEMAN.

Preventive medicine, and little else with the possible exception of antibiotics, has brought about the lengthening of the average human lifespan to the Biblical threescore and ten years. Among the most potent and effective weapons in accomplishing this longevity have been the vaccines.

The ever-increasing world population and the ever-decreasing world resources make it an increasing economic necessity that people be kept productively healthy. It is fortunate indeed that vaccines capable of controlling so many diseases already do exist and that they can be applied in such a highly favorable cost-to-benefit ratio. The Twenty-Seventh World Health Assembly, in its resolutions of 1973 (*1*) and 1974 (*2*) gave recognition to this and clearly delineated vaccination on a worldwide basis as both an economic and social imperative.

The vaccines that are used routinely and taken for granted today are based on advances that required study in human subjects in years gone by. All future vaccines will depend to the same degree on human testing; without it, there just won't be any new vaccines. Few thoughtful and responsible persons, I believe, would question whether new vaccine development and, therefore, human testing should continue. Instead, they would accept this as a necessity and would focus on such questions as how the studies should be conducted, with what constraints, and in what study populations. Fortunately, vaccines offer so much potential benefit at so little risk of harm to the vaccinated individual that their investigation can be pursued with a high level of confidence.

This part of the symposium dealing with research and development of biologicals tends, in its agenda for discussion, to assume that there may be differences in the viewpoints of persons doing vaccine research depending upon whether their research derives its impetus from a public, a private, or an industrial source. I doubt that there is any basis for this assumption. By definition, the sources of funds used to support research can only be public or private. Responsibility for studies carried out with public or private funds, or a combination thereof, is with investigators who function in academic, governmental, or industrial contexts. It is my belief that there should be no difference in viewpoint of these individuals. The standards of quality and the parameters for testing vaccines must be very much the same in all settings, irrespective of their auspices. Whether vaccine research and development are done by academia, by government, or by industry, they must be done properly by competent and capable people of good intention who are working toward improving the lot of mankind through medical advances of economic and social importance.

If I were to try to identify any differences in the research and development activities of government, universities, and industry, I would only make one personal observation: that industry may tend more to position itself for success in the developmental phase by assembling the critical mass of technical skills and numbers of persons needed to carry a promising lead through to final demonstration of its utility. Industry is also impelled by financial realities to focus on that which is prudent and

From the Division of Virus and Cell Biology Research, Merck Institute for Therapeutic Research, West Point, Pennsylvania 19486, USA.

potentially useful and tends, I believe, to be held more rigidly accountable for its actions and accomplishments than its counterparts in academia or government.

The preparation of candidate vaccines for human experimental use rests upon a century of technology and precedent that permits the making of vaccines for which safety and efficacy can be assured with a high level of certainty. The important objective is that the vaccine induces immune response(s) in the host as measured first in the laboratory and then in tests for prevention of the disease in nature, and that clinical adverse reactions, if any, be well tolerated and acceptable as weighed against the dangers of the disease itself.

Clinical tests of new vaccines are initiated only after the chemical, physical, and biological attributes of the product have been exhaustively defined. For most vaccines, this includes tests in a wide variety of *in vitro* systems and in a variety of experimental animals to insure safety. First tests in human beings are always restricted to small numbers and their main purpose is to detect possible clinical reactions and to measure antibody responses. The number of individuals given the vaccine is gradually expanded consistent with demonstrated safety and immune responses in the previous tests. Finally, there is expansion to large numbers of persons to measure protective efficacy against the natural disease in properly controlled studies, and to guarantee its safety under conditions of large-scale routine use.

The key issue, in all considerations of testing of vaccines, is the question of who—i.e., what persons—can reasonably be asked to participate as study patients in pre-licensure investigations. Obviously, in the testing of most vaccines, it is necessary to select persons who have not had previous experience with the agent in nature and hence are not already immune to it. For many diseases, this means children of young age, while in others, adults may also be susceptible. All the peoples of the world are subject to disease and I can see no compelling moral, ethical or legal argument that would justify exclusion of any segment of the world population from consideration for inclusion in vaccine testing—whether it be based on race, sex, age, political boundary, geography or institutional status. One inviolable ethic I would adhere to, however, is that the vaccine being tested must be of potential benefit to the recipient of that vaccine. A second is that the investigator must never purposely introduce the disease to volunteer populations simply for the purpose of being able to measure protective efficacy.

In choosing subjects for study, it is necessary to include persons in institutions as well as those in open populations. Persons in institutions, such as prisons or schools for the mentally retarded, often provide the unique situation in which the needed large numbers of persons still susceptible to a particular disease may exist in a closed environment. The ready availability of care and supervision makes possible very close and continuing surveillance for any clinical reaction that might unexpectedly occur. Persons who are given the vaccine may receive its benefits far in advance of the time when the vaccine becomes generally available. Moreover, it may have special advantage for them since infectious diseases often are more severe in institutionalized persons and such illnesses may add to the problems from which these persons are already suffering.

The inclusion of prison volunteers in clinical studies of all sorts has been a subject of discussion and criticism in the U.S.A. in recent years. Obviously, and particularly with prisoner populations, direct or indirect coercion of an individual to participate in studies cannot be condoned. Prisoners should not, however, be excluded from the opportunity to choose to participate for, by such participation, they may derive the benefit of protection afforded by vaccines and they may achieve personal satisfaction and a sense of usefulness in having contributed to a most meaningful human endeavor.

The need to test vaccines in persons in different geographic areas requires little elaboration. It is well known that diseases are regionally distributed and there may be very

great differences in the epidemiological pattern and in the clinical picture for the same disease in different parts of the world.

In a perfect world, investigations of vaccines in human subjects, properly conducted by competent persons, should require little regulatory supervision. Unfortunately, competence, morality, and good sense cannot be taken for granted and close regulatory scrutiny is necessary. The Government of the United States, for example, through its laws governing the investigation of new drugs has developed a thorough basis for regulatory control of studies of vaccines originating from the U.S.A. Essentially, these laws require that (a) informed written consent for any investigational use of a vaccine be given by the recipient himself or by his guardian, as in the case of minors or those incompetent to make such judgments for themselves; (b) that all clinical studies be reviewed by a competent, independent group of persons of varying experience and background before they are initiated; (c) that review, concurrence, and monitoring be carried out by the U.S. Food and Drug Administration. For the most part, these laws and regulatory requirements function well. They are controlled by protocol and are not difficult to handle once the guidelines are laid down. Importantly, they serve to protect the rights of the individual and the quality of the studies, and they usually do not hamper the investigative process excessively. Imposition of these regulatory requirements also serves to maintain a flow of research information to a central organization. Such information, when it becomes substantial and worthwhile, finds its way into scientific publication much as does any other scientific work.

In closing, I should make special emphasis that the critical matter in vaccine tests in man is not that of how to control the tests, since mechanisms already exist or are easy to develop. The critical matter is that of who, i.e., what people, will be allowed to participate in the studies. The conduct of clinical trials is complex, to say the least. They need to be carried out under the most optimal conditions, matching the particular vaccine under test to the subjects chosen. No segment of the world population should be excluded without real and valid reason, whether it be children, adults, prisoners, other institutionalized persons, persons in open populations, persons in closed populations, the underprivileged or even the overprivileged, if such exist. Disadvantaged and institutionalized persons, by the very imposition of restraints by society, are especially subject to the ravages of disease, and for them vaccines can be particularly important. Tests in persons of all categories are scientifically essential. With proper consent by normal adults and parental or supervisory consent for others, there is no compelling reason I am aware of that would justify exclusion of the institutionalized, the disadvantaged or any others from the early advantages of vaccination. I say this without hesitation, since the potential benefits to the individual who is given vaccine, irrespective of his status, and to the future of society itself are so consequential and the risks and inconvenience to the individual are so small as to preclude any convincing argument to the contrary. Halting or seriously handicapping science as it seeks progress toward fulfillment of social and economic imperatives carries a serious burden of its own and may indeed be immoral itself.

That, too, it seems to me, is part of our task—not just to delineate standards for vaccine testing that should be the model the world over, no matter what the study's auspices or source of funds—but, and perhaps even more importantly, to send forth the message that to stifle vaccine research by making study populations essentially unobtainable is to deprive present and future generations of protection against disease. The future of preventive medicine will be written in the outcome of the conferences and deliberations on issues such as those to which this group addresses itself.

References

1. Official Records of the World Health Organization: #212, 142-146, 1973.
2. Official Records of the World Health Organization: #217, 28-29, 1974.