ETHICAL AND SOCIAL ISSUES IN THE DEVELOPMENT OF NEW DRUGS AND VACCINES*

DAVID J. ROTHMAN, PH.D.
Center for the Study of Society and Medicine
Columbia University College of Physicians and Surgeons
New York, New York

TWO UNRELATED EVENTS during the early 1960s came together to transform the methods by which new medical technologies were created, tested, and marketed. One involved the discovery in 1961-62 that thalidomide, released for use in Western Europe but not in the United States, caused birth defects; the other was the realization during 1962-1966 that medical researchers were not necessarily obtaining the consent of their subjects before conducting their research. The single most publicized case was Dr. Chester Southam's injection of cancer cells into aged and sometimes senile patients without their knowledge; the single most significant publication was Henry Beecher's 1966 article in *The New England Journal of Medicine* describing 22 examples of clinical research that he considered of dubious ethics. Noting that these protocols put the subjects to considerable risk and made no mention of consent, Beecher concluded: "Ordinarily patients will not knowingly risk their health or their life for the sake of 'science.' Every experienced clinician investigator knows this. When such risks are taken and a considerable number of patients are involved, it may be assumed that informed consent has not been obtained in all cases."[1]

Both the thalidomide and the human experimentation incidents illustrate the power of scandal to effect political and social change. As William Curran has written: "The Drug Law of 1962...probably would never have been enacted...without the vast public outcry for stronger drug control laws that resulted from the terrible outbreak of infantile deformity...by the drug Thalidomide."[2] By the same token, it is doubtful if the United States Public Health Service would have insisted upon greater formal review of the consent process in human experimentation without the publicity generated by the Southam case and the protocols described in Beecher's article. In-

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deed, both "scandals" pointed public policy to the same conclusions: neither drug companies nor individual researchers could be trusted to act in the public interest. The potential for abuse was so great that only a keen and persistent oversight would protect the welfare of human subjects and the society at large.

No organization better exemplifies the spirit of these changes than the institutional review boards. Federal regulations mandate that institutional review boards examine every protocol submitted for federal funding, making certain that investigators obtain informed consent and that risks of the research do not outweight its benefits. As would be expected with any such body, controversies abound about the degree of such boards' effectiveness, and there is no shortage of critics from all sides. To some it is a sloppily conceived and administered system in which researchers protect each other's interests; lay representation, although mandated, is meaningless for they receive no pay and have no status or protection against dismissal. To others, the only sensible approach is to trust to the integrity of the researcher, for most patients have neither the intellectual capacity nor the ability to refuse procedures, experimental or not, that physicians recommend. Moreover, several studies indicate serious weaknesses in institutional review board operations; there are significant variations in the diligence with which boards perform their assignments and in the substantive decisions that they make. And, as Dr. DeVries demonstrated with his experimental heart transplantation procedures, an investigator who is dissatisfied or impatient with board decisions at one institution can move his research to another.

All these difficulties notwithstanding, the presence of the institutional review board is of symbolic and real import. The anticipation of review may be a more powerful force affecting the researcher than the actuality of review. Knowing that risks and benefits and consent will be monitored, researchers would not consider submitting designs that approximate those in Beecher's roll of 22.

Indeed, no matter how favorable the current political climate toward deregulation, by all indications institutional review boards are likely to expand in authority over the next decade, and so is Food and Drug Administration oversight. For one thing, many board members and, more generally, the outsiders who have entered medical schools and medical centers in the persons of bioethicists, social scientists, humanists, lawyers, and lay observers have defined as one of their essential missions the protection of human subjects. For another, the climate of opinion has changed and ethical

discourse has become far more a part of medical discourse. A recent study, for example, by the Institute of Medicine on *Assessing Medical Technologies* insisted that "the social, ethical, and legal questions" in this area must be addressed. "Although these questions do not always lend themselves to quantitative measurement and analysis, they can be systematically identified and evaluated." Moreover, this study identified eight organizations and administrative bodies, ranging from free standing institutes of ethics and health policy to the Congressional Office of Technology Assessment, which already include among their concerns the ethical, legal, and social implications of drugs, medical devices, procedures, and systems.

For still another, the public continues to be wary and suspicious in matters affecting health, an attitude that is reinforced by recurring incidents that bear indirectly on these issues. The public shares an understandable impulse to generalize so that incidents involving Johns-Manville and A.H. Robbins serve as reminders that oversight is critical in matters of health.[3] Prescription of the Dalkon shield for fertile women and the lung damage to workers with asbestos differed substantially from the events surrounding thalidomide, but an identical social and political message emerged: companies will compromise safety, and consumers or workers bear the burden. Distinctions that seem significant to insiders are not always relevant to outsiders, and the public interprets these events as compelling reason to insist upon oversight and formal procedures even if they inhibit the development of new drugs and new technologies.

All this means that researchers over the next decade will operate in the glare of official and public light, closely scrutinized. Although these attitudes may retard innovation and even discourage qualified investigators from entering or continuing research careers, governmental and institutional procedures will become still more demanding and rigorous. The controversies in infectious diseases which have a social or ethical component will be fought out in the public arena with a predisposition to resolve them through formal mechanisms and detailed regulations, not by trusting to the good will or professional ethic of the researcher.

Recently two major challenges have been made to the regulatory system. They come from very different directions and have very different spokesmen and constituencies, but they are both impatient and dissatisfied with the current practices and predictions of future directions. To one group, the recent AIDS crisis requires a fundamental alteration in procedure, although it may not be aware of just how fundamental the change would be. The sec-

ond insists that the United States is lagging far behind Western Europe and Japan in drug development and unless fundamental changes are made, the health of the nation and the viability of the American pharmaceutical industry will suffer. Let us examine the AIDS issues first and then turn attention to the drug lag question.

At first appearance, the prominence of a disease such as AIDS on the research agenda would seem to buttress the need for Food and Drug Administration and institutional review board procedures. Since this deadly and contagious disease mostly affects stigmatized groups (homosexuals and drug abusers), one would have anticipated acute concern that the rights and welfare of these subjects be protected against overeager or disdainful researchers.* And this concern has certainly been manifested, particularly to protect patient privacy and confidentiality.

But the AIDS epidemic has also prompted a basic challenge to established procedures. First, since the disease is uniformly fatal, the ethics of following random clinical trials are being questioned. Dr. Mathilde Krim, associate research biologist at St. Luke's/Roosevelt Hospital Center and Columbia University's College of Physicians and Surgeons, insists (and she is by no means alone in this) that in the case of AIDS, "it's immoral to give people nothing when there is something that could do them good." The question of the propriety of placebos in random clinical trials once seemed settled. AIDS has made it openly controversial.

Some investigators have responded that if the drug proves effective, those who received the placebo in the trial will be the first to obtain it. But, given the fatal nature of the disease, might it be appropriate to rely instead upon historical controls? National Institute of Health administrators and a variety of researchers, including Drs. Anthony Fauci, Samuel Broder, and Jerome Groopman are reluctant to do this; given the many unknowns about AIDS, need for placebo controls seems all the greater.[4] Their position is not simple to defend in the sense that compassion for the victims pushes in the opposite direction and the number of non-randomized drug trials is great, amounting to as much as 70% of the clinical trials that are presented to the Food and Drug Administration when a drug is proposed for approval. Why then not give experimental drugs to all who enter a trial when a disease has

*To be sure, to the extent that homosexuals are the subjects, this population is not as vulnerable as inmates; nor is this a group, like the aged, who may not understand the procedure or be competent to give consent. Moreover, the research is distinctly therapeutic in intent, looking to benefit the subject group.

proved so uniformly fatal? And researchers, after all, in cases where patients have advanced metastatic disease and a very poor prognosis, do use one-armed studies with no controls and no placebos. Nevertheless, whatever the instinct, an insistence on random clinical trials seems the ethically and socially appropriate response.

Unlike metastatic diseases, little is known about the course and progression of AIDS, and in ignorance researchers might confuse temporary improvement with long-term improvement were a control group not available. Clearly, future victims of the disease stand to benefit from the more rigorous procedures. But what about present victims? Here one must remember that powerful and highly toxic drugs of unknown efficacy are truly of unknown efficacy, that is, that they are as likely to do harm as to do good. The group on placebo may benefit more from the trial than the group on the drug, at least to the extent of being less harmed. Researchers may well be enthusiastic about the prospects of a drug performing well, otherwise they would not be testing it, but often they are wrong and the random clinical trial proves it. In a society trained to think in terms of magic bullets, it is sometimes difficult to remember that drugs of unknown efficacy may be more dangerous than placebos, but this formula properly guides research design.

The far more controversial question is whether it is equitable to limit the new drugs only to trial groups. Do subjects have a right to receive an experimental drug without entering a protocol? Should the circumstance that the patient contracted the disease through a blood transfusion, or that the disease is deadly and the victim young, alter established practice? Dr. Krim so argues. "Patients with very little time to live. . . should be entitled to any experimental drug that offers hope—no matter how slim that hope." Not that Dr. Krim expects that they will be cured but rather "it should be done out of respect for the patient's right to fight for life with whatever tools we can offer." To this end she asks that drug trials be conducted with patients newly diagnosed with AIDS. For those at the end stage of the disease, there should be a government subsidy of drug manufacturers to make "the safest and most promising" experimental drugs widely available to them; so too, the requirement that experimental drugs be administered only by investigators should be dropped and, instead, experimental drugs should be made available for use by "qualified physicians" outside of academic medical centers.[5]

Not surprisingly, the ethical and social aspects of the issue have been relatively unexplored. The bulk of analysis has been devoted to the protection

of human subjects within research protocols, not to the consideration of the rights of patients to receive experimental drugs outside of protocols.* A few physicians, often drawn from pediatric oncology, have criticized what they consider to be an unfortunate confusion of research and treatment, to the detriment of both. As Dr. Jan van Eys has noted, "That research therapy is usually the only access to curative therapy in such fields as pediatric oncology. . . is an ethical absurdity that American medicine has acquired." It puts "the greatest possible degree of coercion on the patient to participate." Moreover, researchers do not make good "healers," depriving the patient of the supportive optimism that a practicing physician brings to the encounter. "When a randomized clinical trial is performed, that faith in the effectiveness of the treatment, by definition, is absent." But for all the strength of this critique, neither this author, nor others, spell out an alternative approach or analyze the consequences of making experimental therapies available outside of research settings.[6]

The qualifications that Dr. Krim makes to her position, at least as originally formulated and presented, reveal some of its problems. For example, she asks that only "qualified" physicians be allowed to prescribe experimental drugs but no mechanism exists to select such a group out of the thousands of physicians in office practice, and accomplishing such a screening in a relatively short time might well prove impossible. Moreover, to the degree that the screening was rigorous, physicians might not come forward; to the degree that it was simple, incompetent physicians might be prescribing experimental drugs. So too, Dr. Krim wants only the safest and most promising drugs subsidized and distributed, but how is that safety and promise to be established? What would be the mechanisms for testing and the appropriate criteria that would at once be more lenient than existing ones and yet strict enough to exclude toxic and ineffective drugs? Indeed, if her premise is that AIDS patients are not likely to be cured by these drugs but should be given all possible hope, why limit the distribution to drugs with some efficacy? Why not administer placebos and say that they are investigational drugs with some efficacy?

We also have an historical record available that enables us to glimpse some of the consequences of adopting Dr. Krim's first proposals. For one, dis-

*Some bioethicists have raised questions about the right to receive an experimental drug outside of protocols. Robert Veatch, for example, once suggested that patients be given the right to choose the active drug, and the results of their treatment could be added to (not substituted for) the results of the blinded and randomized trials.

tributing drugs to patients with end stage disease would create a rumor mill of extraordinary proportions, with premature celebrations for success and premature laments over failures. Word would circulate that patient A has thrived under regimen A (for the past two weeks) and immediately there would be a run on the experimental drug, a shortage, a black market, inflated price, and a war of some against others to obtain this magic bullet, which probably has no magic at all. The converse would be equally likely: patient A dies on regimen B and the regimen is shunned, the drug overproduced, and a warehouse is left full of substances that might well have efficacy. These scenarios, of course, assume that the rumors have begun innocently; consider the possibility of rumors begun for the sake of profit, obtaining a cache of an experimental drug and planting rumors of success.

Dr. Krim would have it seem that one can have open distribution and random clinical trials at one and the same time, as though these were two worlds apart. But suppose rumors proliferate about an early success—are researchers to dare ask patients newly diagnosed with AIDS to take a placebo or are they to heed the rumors? Still more important, if experimental drugs were available through private physicians, why would any AIDS victims join a random clinical trial? And to say that investigational drugs would only be available to those at a late stage in the disease runs up against the extraordinary difficulties of defining what is an early stage and a late stage in a new and uniformly fatal disease. Second, there are major ethical problems in trying to distinguish between the two categories; and, finally, there is the practical impossibility of maintaining the distinction, for surely private physicains cannot and should not be expected to refuse to prescribe for their AIDS patients on the grounds that their disease is not yet advanced enough.

We must also ask why the government should subsidize the production and distribution of experimental drugs for AIDS patients and not for victims of other no less fatal diseases. To be sure, in some instances, these patients can obtain experimental drugs through "compassionate approvals." But not everyone with a fatal disease has access to experimental drugs; compassionate approvals were designed to be, and are, exceptions. On what grounds, then, should AIDS patients be privileged? And if they are not, should hundreds of thousands of dollars go into the production and distribution of all types of experimental drugs against a variety of diseases? In fact, were there to be a return to the day when physicians were free to prescribe drugs of no known efficacy, the very group most in need of protection from ignorance and abuse would become the most vulnerable. In ef-

fect, making what is now an exception for qualified researchers the norm, for private practitioners would in effect end Food and Drug Administration-institutional review board hegemony and return us to the open market conditons of the 19th century.

The AIDS epidemic raises a third question: given the statistics on fatality, how quickly should field tests which show some promise be expanded to include greater numbers? Should a different and weaker standard be employed here than is customary in other protocols? By the principles discussed above, it is difficult to justify any change in criteria. Administrative inefficiencies should be overcome—and there is some evidence that they are—but efficiency and rush to judgment are not identical and should not be confused.

The FDA response to azidothymidine (AZT) has confronted all of these problems, managing to resolve some, but certainly not all of them. Preliminary findings from double blind random trials indicated that AIDS patients with *Pneumocystis carinii* pneumonia (PCP) experienced increased longevity: in the first trials, nine of 10 were alive 14 months after receiving the drug, whereas the average median survival is 35 weeks. On September 30, 1986 the Food and Drug Administration issued a waiver of institutional review board requirements for some clinical studies of azidothymidine.* It noted that "AIDS patients meeting the inclusion criteria in the Burroughs Wellcome protocol [patients 12 years and older who have recovered from one or more episodes of PCP] "can be expected to benefit from receiving the drug," and therefore it deemed uncontrolled clinical trials conducted by licensed physicians, not researchers, appropriate. In mid-January 1987 a panel of advisors to the Food and Drug Administration recommended that azidothymidine be licensed for sale. The committee, however, called its recommendation "extraordinary," both because the knowledge of azidothymidine's side effects and toxicity was far more limited than would normally be required prior to approval, and the committee wanted assurances from the manufacturer that azidothymidine use would be limited to selected categories of AIDS patients (most notably, those have had PCP).[7]

The decision seems too precipitous to some observers and too restrictive to others. A number of researchers, including Dr. Itzhac Brook, a member of the Food and Drug Administration committee, believe that azidothymidine is far too toxic a drug to be released at this point; the first trials revealed that nearly half of the patients taking azidothymidine suffered severe

*The description of azidothymidine includes the subsequent Food and Drug Administration action of January 1987.

anemia and depletion of white cells. Dr. Brook thought it all too possible that health officials might later regret "releasing the genie out of the bottle." On the other hand, homosexual activists have argued that the drug should be made available without restriction, letting the AIDS patients decide what risks he wanted to take. "The basic idea," insists one advocate, "should be to legalize the use of unapproved drugs so long as patients receive appropriate warnings to insure informed consent."[8] All the while, one must still confront the issues of precisely who will receive the drug, whether it will be possible to control its distribution, whether it will be possible to run clinical trials for other groups with azidothymidine. It is also possible that the prospect of receiving azidothymidine may keep some AIDS patients from enrolling in trials with other drugs (which might prove more effective than azidothymidine) because using them would render the subjects ineligible for receiving azidothymidine.

The only certainty is that these questions will persist. All of them are now resurfacing in light of preliminary findings about the efficacy of ribavirin. Dr. Krim is concerned that the evaluation process is moving too slowly; other scientists are uneasy about the initial claims for efficacy.[9] Indeed, as one watches the process repeating itself, it becomes all the more apparent that weakening normal procedures in one instance is likely to reinforce and strengthen the call for weakening them in a second instance, then a third and fourth, until the market becomes crowded with drugs of questionable efficacy and great toxicity. We may find ourselves back in a situation where the consumer is at once empowered and practically helpless to decide which drug, if any, to take.

Were these issues not compelling enough, the development of a vaccine raises ethical and social questions that may be without precedent. What types of subjects should be recruited for the first tests? If it is those at low risk of infection, then the test results that will be not only long in coming but of dubious relevance. If the vaccine is tested on those who engage in high risk behavior, the researcher would appear to have a stake in having his subjects not adopt risk-minimizing behavior patterns, especially in light of very long incubation periods. But obviously it would be ethically irresponsible of a researcher to obtain consent to the vaccine test from a subject without informing him, at length and with diligence, about his need to adopt a variety of precautionary measures. Each time the subject returned for follow-up and testing, it would again be incumbent on the researcher to urge safe behavior. And yet, to the degree that the researcher is an effective educator, to that degree has he reduced the value of the subject as a test case for

the vaccine. How this problem in data accumulation and analysis is to be resolved is not at all clear, but it is apparent that the answer cannot be to silence the researcher and keep the human subject ignorant of the steps he should be taking to minimize his exposure to the AIDS virus.[10]

Finally, AIDS is reviving the controversy about a "drug lag." Research here is raising the thorny issue of whether our regulatory apparatus is excessively stringent and ultimately responsible for a significant "drug lag." In the aftermath of Rock Hudson having to fly to Paris to obtain an experimental drug being tested against AIDS, the Food and Drug Administration came in for considerable criticism for not facilitating AIDS drug testing here. But those who have followed the claims and counterclaims over the past 15 years about the Food and Drug Administration's performance, more particularly, whether there is a drug lag, and if there is, whether the Administration is responsible in whole or in part, did not need Hudson's trip to alert them to the controversy.

The concept of a "drug lag" has been difficult to define and to measure. Is it to be expected that drugs developed in one country will make their way into other countries at different rates of speed. How does one document a drug lag—by examining the rates at which *all* investigational drugs are processed or the speed by which truly important drugs are introduced, and who defines "truly important?" If one discovers a slowdown in the introduction of new drugs in the United States, is this the fault of the Food and Drug Administration or the amount of money that drug companies are devoting to research, or because the 1950s, with the advent of antibiotics, saw an unusual explosion of new drugs and we are now returning to a more "normal" albeit slower pattern? Each position has its avid defenders, and if the preponderance of the literature makes a strong case that Food and Drug Administration regulations have been cumbersome and its administration inefficient, still the relative import and wisdom of the system remains open to debate.

In many ways, the controversy comes down to a question of trade-offs. No one will deny that the Food and Drug Administration could and should move its papers more quickly, but the key issue is whether it should relax or alter its requirements for testing and demonstrating safety and efficacy. Should policy opt for more rapid diffusion of new drugs even if that raises to some degree the level of risk? How much of a slowdown is one prepared to allow to prevent a drug such as thalidomide from entering into circulation?

Although the evidence must necessarily be impressionistic, it would ap-

pear that the public has been willing to trade off more rapid gains in drug therapy for greater safety. For more than fifteen years complaints about a drug lag have been made and yet, methodological points apart, they have not been able to provide a widespread response in public opinion or in political circles. The Food and Drug Administration may well be responding to a consensus that the harm associated with thalidomide or the Dalkon Shield are too heavy a price to pay for the rapid diffusion of new drugs. To be sure, its officials may find it safer to err to the side of safety than rapid diffusion—the onus of releasing a dangerous drug is far greater than the rewards for getting a new drug onto the market more quickly—but a compelling case can be made that the sum of the pressures on Food and Drug Administration through Congress and public opinion reinforce this choice.

Whether the AIDS epidemic will spark a change in this calculus is one more consideration that will have to be confronted. Given the relatively narrow delineation of who is struck by the disease and its uniform fatality, it is likely—and evidence already exists—that the Food and Drug Administration will speed up its procedures. It now boasts of approving investigational drugs for AIDS far more rapidly, and it may be setting for itself a standard that will hold in other instances. Whether the Food and Drug Administration will succumb to the pressures that the AIDS crisis is generating and trade off safety for rapid diffusion of drugs remains to be seen.

In sum, over the next decade Food and Drug Administration and institutional review board principles and procedures will be confronting a series of basic challenges to its underlying principles and procedures. Although the unpredictability of events associated with AIDS makes any forecasting hazardous, it seems most likely that these challenges, whether made in the name of compassion or technological progress, will not alter the system in fundamental fashion. The development of new drugs and vaccines will probably take place under highly formal procedures, with researchers and companies bound by rules that look to rigid adherence to scientific method, stiff requirements for the consent of subjects, and a willingness to reduce the likelihood of harm rather than maximize the prospect of benefits.

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