Biomedical Research: Its Side-effects and Challenges

by Joshua Lederberg, Ph.D.

Reprinted from *Stanford M.D., October 1967*, Series 6, Number 3.
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Biomedical Research: Its Side-effects and Challenges

We are approaching the ultimate scientific revolution– the precise control of human development. But the payoffs in terms of human betterment will depend on how wisely, boldly, and quickly we can act in the coming years.

by Joshua Lederberg, Ph.D.

RECOGNITION of basic scientific research as one of the major expressions of the aspirations of Western culture is a milestone in human intellectual history. It represents for American achievement a movement no less creative than the renaissance of the arts was for Europe after the Middle Ages. Starting with physics and chemistry, the wave of scientific insight has reached biology and medicine and is beginning to enrich our understanding of the most important aspects of human personality. Medical research is a major branch of this movement: specific applications to disease problems rest on man's fundamental understanding of his own nature and of his relation to the universe.

The scientist, however, is not necessarily the best judge of the social utility of his own work, or of that of science in general. His motives in doing research are irrelevant to the consequences of his work for the community. In fact, it is fair to say that society exploits the poetic fascination that motivates many academic scientists, eventually capitalizing on applications that no one could have foreseen. It may even be that research work loses rigor and sharpness of focus if the research worker himself is too sensitive to the unpredictable implications of what he is doing.

It is important that such utilities be discovered as soon as they can be useful. This discovery, though, is a function of a whole community of basic and applied scientific effort. To place the burden on individual projects would be the surest possible way of stifling the most creative and the least predictable advances in scientific understanding. From my own experience, I do not know any scientific or technical advance of importance that did not make utterly unexpected demands on knowledge from unpredictable sources.

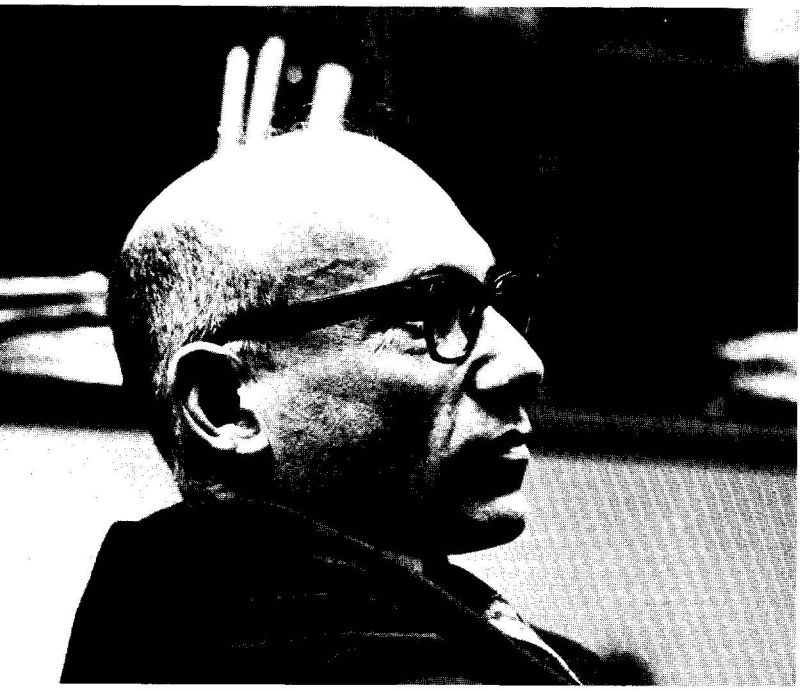
This is all a preface, and the statesman might reply: "I have heard all this before; I might almost be willing to believe it. Nevertheless, are we making the most effective allocation of our resources for the public good? Are we doing all we can to 'make sure that no life-saving discovery is locked up in the laboratory?', as President Lyndon B. Johnson has put it. How can we achieve the President's expressed wish for the most constructive 'payoffs in terms of healthy lives for our citizens?' "

These are questions of technological development, not of basic science. Many discoveries in physical science have resulted in practical utilities rather quickly. Only six years passed from the first observation of nuclear fission to the first demonstration of man's ability to make the earth uninhabitable, and a hardly longer time intervened between enunciation of the principle of the transistor and the actuality of portable TV. Can we not emulate such rapid progress in biomedical research? What are some of the difficulties and challenges? Can we also foresee some of the stressful and unwanted side-effects of some branches of biomedical technology?

May I first comment on some of the difficulties and obstacles. Some of them reach far beyond biomedical science; they are among our most pervasive social problems. We cannot consider the manipulation of human nature in a vacuum that ignores religious and political controversy over the proper bounds of what we propose to do; we cannot evade poignant ethical and moral concerns for life and death.

The homeliest examples may be the most instructive. It takes very little biological science to know that babies who do not get enough to eat are unlikely to develop into healthy, socially well-adjusted, and economically productive adults. Throughout the world—even in this country—there are at least a few children who are not getting the benefit of this scientific information, because their parents can't afford it. As important as I believe the furtherance of basic science to be, if I had to choose between it and the applied science of feeding hungry children, I would choose the latter. But I would also ask why that particular choice was obligatory; why is it not made over a wider range of priorities?

Only a question of scale distinguishes this question from many others of economic allocation. Some hundreds of patients with kidney disease are still dying each year essentially because they can't afford an artificial kidney. It is also true that we might be unwise to sink all of our resources into this year's technology, when the technology is advancing rapidly. But, meanwhile, there is a simple economic discrimination for the



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chance to live. Is this a problem chargeable to biological research? If we deal with it on the customary scale for basic research, the cost will inevitably be several hundred more lives than if we gambled a few hundred millions of incentive money to distract some mechanical engineering inventiveness away from washing machines into kidneys.

Can we provide economic incentive for such a new industry? If so, how? And how do we relate federal seed-money for technology affecting human life and health to a body of talent embedded in profit-oriented commerce?

In the long run, skilled manpower is the limiting factor in making the best of existing knowledge freely available, though better techniques could be developed to make more effective use of the scarcest kinds of people. The education of the patient population is also of utmost importance in evoking intelligent avoidance of quackery and encouraging use of preventive facilities when they are available—for example, prenatal care and survey screening for cervical cancer.

The discrepancy between existing scientific knowledge and public availability and acceptance of that knowledge is immediately visible in attitudes on narcotics. The medical case against alcohol and tobacco is overwhelming. Yet these agents are tolerated by the Establishment. This might seem to reflect a principle that the law hesitates to intervene against determined self-abuse by legally competent adults, despite the enormous social problems generated by easy availability of these commodities. In this context, the savage recriminations against marijuana are incomprehensible, except insofar as the pronunciation of any synonym of "hashish" amounts to spitting in the face of organized society. The failure of the law to follow pharmacological science and discriminate carefully among different drugs in some relationship to their actual hazards encourages defiance of the law in far more damaging ways, such as taking LSD and opiates. In general, the law on narcotics remains the despair of rational medical science, and is a testimony to the power of symbols of conformity.

The situation is even more complicated where conflicts of religious belief still enter into public policy. For a long time the importance of birth control for the health of the family has been universally conceded, but a militant religious minority nevertheless has opposed the spread of the appropriate knowledge and only grudgingly acquiesces in its availability now, even to members of other faiths. Since contraception has been practiced throughout this period by the whole middle class, the practical consequences of this perverse class discrimination have been to deepen the gulf between rich and poor, by class and by race.

The Johnson Administration has finally gathered the courage to insist on a rational policy in furnishing birth control information. Perhaps we need not resuscitate what may be a settled controversy. However, a similar conflict is following a similar course in the related field of therapeutic abortion. A scientific understanding of man is of the utmost importance for social policy here in several ways.

Most important is the discovery of a number of catastrophes where the continuance of a pregnancy can be predicted to result in a deformed child, or in serious physiological or psychiatric injury to the mother. Techniques for safe interruption of pregnancy are now well established. More to the point, biological science offers no support of the theological speculation that fertilization of the human egg immediately results in a "human being." On the one hand, the fertilized human egg differs from that of an ape in a finite number of DNA components; on the other hand, any tissue of the human body, including cells of the menstruum regularly discarded by every woman, has in it the same hypothetical potential to participate in a developmental process. The egg does eventually develop into a human being, but

only gradually does it become differentiated from the forms of other animals. By the time a viable infant *is* in being, we have no doubts about enfolding him into the species; but every scientific observation shows his development to be a gradual elaboration of the potentialities ultimately inherent in every cell.

If we are to ask honestly about impediments to utilization of scientific knowledge for human benefit, we must include these strictures despite their relationship to religious controversy. The consequence of a dogmatic position on therapeutic abortion has not been to prevent the practice. Instead, abortion has been forced underground. Perhaps a sixth of all pregnancies are now terminated illegally under conditions that are a serious medical and psychological hazard to a million women every year. Judging from trends around the world, we may hope for a gradual transition of authority in this area from the penal code to private morality, where it has a place I would not presume to intrude upon. Our political problem is how to respect the conflicting passions intensely held by different groups of constituents, giving the utmost latitude to individual liberty where it does not intrude on the welfare of the whole group.

THE QUESTIONS I have just discussed help to illustrate the complexities of applying merely scientific attitudes to human problems. Allocation of resources is likely to remain subject to the same complexities.

Medical *molecules* are even more valuable fruits of biomedical investigation than are elegant medical *machines* like the artificial kidney. It would be highly desirable to subject the whole process of drug research to an operational systems analysis and attempt to rationalize it once for all. Under the impact of federal support for research in medical schools, and an aggressively defensive patent policy connected to that support, fundamental biochemical research is becoming less and less effectively coupled to the actual development of useful drugs in the pharmaceutical industry. Indeed, with more effective regulation of drugs, and appropriate demands for more rigorous testing, and with legislative interest in drug pricing, there is serious danger that risk capital for drug development will be choked off, that a larger and larger proportion of capital investment in that industry will be devoted to the promotion of existing agents—the few that have passed the scrutiny of an agency pressed to assure impossible goals of absolute security and perfect efficacy. Attention to promotion versus research is also encouraged by the growing bewilderment of an over-busy medical profession unable to maintain its own ability to assess new drugs discriminately, and therefore increasingly reliant on the drug industry's slick ads and detail men for expertise.

Here the ultimate problem is the inability of the medical profession to keep faith with the demands of the times. By failing to maintain its own capacity to judge the merits of new agents, it has abdicated its responsibility to a federal agency that inevitably must follow the most cumbersome procedures towards monolithic judgments about drug safety and efficacy. In the process, a great deal of flexibility is lost; only those drugs can be allowed even on the ethical market which are safe for the average practitioner, who is assumed to be guided by the fine-print disclaimers and precautions in the manufacturer's literature. To the extent that only an enlightened minority of practicing physicians remains in contact with modern medicine through systematic postgraduate training, the profession as a whole will remain at the mercy of self-interested advertising, which does have to be policed by a regulatory bureaucracy. The profession itself must accept the responsibility of qualifying its membership; the government could, however, accelerate the process by recognizing a gradation of responsibility that can be assumed by practitioners with more sophisticated training—an end toward which the roster of qualified drug-experimenters is a useful step.

The expertise of the medical profession is, however, so vital to our national well-being that we should begin to consider more far-reaching measures. The most essential is the reinvigoration of our centers of medical education to encourage the training of many more physicians over a wider variety of skills and specialties. Some of these centers must also be dedicated to the continuing education of mature physicians. We have modern techniques of dissemination at our fingertips—wideband communications, computerized information-retrieval, videotape libraries, but we have not yet learned to apply them to this vital use, more out of perplexities of economic policy than because of technical limitations. One of the fundamental difficulties is that the time of the mature physician is so valuable he can hardly afford even his present efforts at continued self-education. The organized profession's tacit attitude that every physician is equally and identically perfect offers the most limited encouragement to his self-improvement.

It should be possible to devise tax incentives or even more direct subventions to encourage a more positive trend. Consider, for example, the career scholarship proposal. A meritorious fraction of medical students should be offered full scholarships covering their own living expenses and the cost of their education throughout their initial training period, which usually runs at least seven years after the college degree. These scholarships would, however, be loans rather than gifts: means of repayment would be not in cash but in credits earned through 1) later national or community-oriented service, 2) regular intervals of postgraduate education, the credits partly compensating for time taken from practice, or 3) time spent in clinical teaching, as is now generously volunteered by many of our finest specialists. If the prorated cost of education were included in the stipend, the system would already provide a big step to funding the needed expansion of medical education, and the students themselves would constitute a very broad selection committee for allocation of support to beneficiary institutions. Such a program is undoubtedly self-liquidating in terms of the tax yield from improved earnings, but even if it were not, the social interest even exceeds the personal interest of the physician in his own continued education.

Analogous approaches are worth considering to encourage the most creative deployment of the resources of the drug industry. In view of the restraints on profiteering on drugs, secondary incentives for risking capital in research are essential. The operations of FDA ought to be financed by a manufacturer's excise tax on drugs amounting to, say, 25 per cent of their wholesale value, or about 10 per cent of the consumer price. However, the company's research and testing costs (its investment in innovation) should be credits against that tax. Furthermore, companies that contribute matching funds to university research should be able to participate fairly in patents in which the government now would retain a preclusive interest, and even worse, a vaguely defined bureaucratic involvement. The lack of clear definition of the scope of government interest in patents that bear any relationship whatsoever to federal health research support is an intolerable barrier to industrial-academic cooperation. Perhaps we might altogether bar patents for the more fundamental aspects of drug innovations, and leave the patenting privilege open only to the fruits of the later, costlier development work for which industry is better suited. For example, a drug might be patentable only at the stage where it could qualify for FDA approval. The interested drug company might be allowed some period of time after preliminary registration during which to pursue the development work, for the registration itself entails a substantial commitment of effort.

Every possible measure should be considered to minimize the commercial value of a brand name on a drug in favor of the actual merit of the innovation in the drug itself. Another way to approach this problem might be to relax the law that requires a prescription to be filled by the brand-specified product, so as to encourage the use of generic names. Physicians must, however, be left the discretion to specify a particular formulation and manufacturer.

A new superstructure of precepts and institutions needs to be consolidated for the rapid and orderly extrapolation of fundamental biological research findings to human problems. This realm has seen most extraordinary advances within the last decade, especially in elucidation of the genetic material, DNA, and the chain of events that links DNA to the synthesis of the proteins from which cells are made.

Clinical research on human beings is incredibly slower and more expensive than comparable work on microbes and laboratory animals. It is also fraught with grave moral problems. Whenever any one of us gets effective medical treatment, he benefits from the risks, inconveniences, and sacrifices of others who have participated in the clinical trials to prove the efficacy of that treatment. Knowing consent must regulate the repayment of this moral debt to our predecessors. Moreover, risks to patients in clinical experimentation should be covered by a new form of insurance. It is enough that the subject volunteers his body. Financial redress for bad luck should be charged as an explicit cost of the research and not be confined to consequences of culpable negligence.

But the most stringent bottleneck at present is in trained people. The very clinicians who might be best able to do this kind of research are the busiest people in the community, working overtime in the care of patients. If we are to get good clinical research, these men need relief. Our medical schools must have financial support adequate to enable the hiring of two in place of one person to do the work of three. And we must take a new look at the manpower goals of, and recruitment for, medical education.

Besides the manpower shortage, clinical research suffers from serious difficulties in the collection of data on the life-histories of human beings. For example, in 1955, at least 4,000,000 children were inadvertently inoculated with a virus, SV-40, that contaminated some polio vaccines. Subsequent studies on the geographic incidence of various diseases have shown no relationship to the distribution of SV-40 exposure, and we can possibly breathe a sigh of relief that this was not the worst medical catastrophe of modern times. However, our health data management is so bad that it would be almost hopeless to correlate individual cases of future disease with past exposure to this virus. We are confined to rather general comparisons of time and geographic trends, which would be quite insufficient to detect risks which, while far short of catastrophic, would generate considerable alarm if attached to other drugs.

The same concern attaches to other drugs now in widespread use. For example, the oral contraceptives as a group have been exonerated from any acute, substantial risks—compared, for example, to the hazards attached to the normal pregnancies they are intended to avert. It is very difficult to evaluate very low-level, long-term hazards—or, for that matter, incidental benefits—with our existing techniques of population study. A number of different agents and dosage forms are already on the market, and after ten years are past it will be quite useless to get reliable information on exposure-history by retrospective interrogation of a woman who may turn up with some or other disease which might or might not be within the range of average expectation.

Situations like these cry out for definitive registration of patients and their treatments. But there would be a justifiable outcry of potential invasion of privacy if data like contraceptive prescriptions were centralized. The concept of the computerized data bank has already been introduced before Congress, and vigorously criticized. Within the existing legal context, I would have to support such criticism. Compulsory registration of personal information has already reached the margins of abuse, and it makes little difference whether the data are managed by a computer or not. However, so long as transactions within the Executive branch of the federal government are virtually insulated from judicial overview, the private citizen would have little recourse against political blackmail. I believe the dilemma may be soluble through legal definition of the rights of privacy—by making the divulgence of personal information from the data bank a crime that can be punished by the courts. Since the courts will not act against the President, the

data bank should be confided to a semi-public corporation, which would be vulnerable to judicial oversight according to the law established by Congress for privacy. It would not be difficult to construct computer-coding techniques to ensure the registration of every access to privileged information. The Bureau of the Census has in fact operated under a system of privileged information for many years, with no known example of abuse. Like the Census, a data bank would have a purely statistical function and should never be used without consent to impinge in any way, good or bad, on the life of an individual citizen.

WHEN WE COME to the problem of replacing natural body organs with mechanical substitutes, the gaps again are likely to be technological rather than scientific; that is, they depend on great investments in design and development, with a relatively small distance of untraversed knowledge to cover. The artificial kidney is the outstanding example of a device whose utility was proved long since, and for which cost factors have been the outstanding obstacle. No very fundamental obstacles stand in the way of similar developments for the heart or lung, and the payoff is that much larger in proportion to the incidence of serious diseases affecting the heart and lung. This kind of engineering is, however, extremely expensive, of the order of hundreds of millions of dollars—comparable to the investments we make in weapons systems, nuclear energy spacecraft, or supersonic aircraft. Our health statesmen have yet to learn that they can think in these terms and carry Congress' enthusiasm into support of the necessary gambles. Much the same can be said for extensions of the human limbs and senses: only a rather large amount of money stands in the way of very substantial improvements in artificial arms, legs, and fingers, or in surrogate eyes and ears.

These remarks take for granted the need for substantial federal participation in the research and development costs of medical machines. The arguments for this need are more compelling than those which have been put forward for the supersonic transport. There are inordinate discouragements for private capital; the investor would face the likelihood that even if his risk paid off, the social attitude against "profiteering" would keep him from making any really substantial return. Even after a successful device has been engineered, it must then undergo very costly certification, and after that may still be liable to civil litigation in the event of unforeseen shortcomings. More important, a new industry must be vitalized on a large scale to pool the diverse talents needed for real innovation in medical machines. The necessary combination of biomedical and engineering skills does not exist.

The highest overall social payoff of any of the applications of system engineering now visible clearly lies in modernization of the hospital. Following quickly behind that is analysis of the research process itself. There are many sophisticated instruments, or more broadly, services—for example, the sequence-analysis of proteins, or the calculated synthesis of known sequences—which now occupy an enormous amount of routine effort in academic laboratories and belong in just the same category. Once again, university scientists have been too accustomed to think very small, in terms of their individual project budgets, to specify the kind of development support that would ultimately magnify their efforts.

WITH THE leadership of the Department of Defense, other science-oriented agencies have begun to realize that large-scale facilities like computers, expensive though they are, have become indispensable for the full realization of the intellectual capabilities of scientific research workers at the universities. Why is it traditionally defense, rather than health, that commands such leadership?

Engineering support for development work is not in competition for the same manpower needed for the conduct of scientific and medical research. It has, however, been suggested that funds for target-oriented work in health be allocated in competition with those for basic research. The logic of this competition eludes me. As our civilization grows more complex and its problems more demanding, we should and do place an ever-higher premium on intellectual attainment and our institutions for education to it. The fastest possible growth of individual educational accomplishment remains the most plausible goal of our efforts in that area, a principle that could well furnish the backdrop to questions about where we should accept a plateau in supporting science.

When it comes to technological development, we have a much larger aggregate investment than we do in basic research at our educational institutions. That investment is, by necessity, spent very abundantly for national defense. We must learn how to allocate the resources we do have for technology—mostly contracted with industry—to meet our own priority decisions among defense, health, urban affairs, and all the other needs of our society.

Important as it is, the optimization of our economic resources to encompass biomedical science and technology is only part of a larger political and social problem. The application of science to biology has reached near the fundamental secrets of life, and whether it be twenty years or 200, we are still very close to the ultimate scientific revolution: the precise control of human development. Wise decisions about the uses of such power can be made only in a climate of effective communication between the political and scientific communities, in one of continuing mutual education about social purpose and scientific opportunity. If we demand narrow payoffs too quickly, we may indeed get them, as we already have—and then find ourselves with nuclear weapons but insufficient means of control and inspection—with splendid automobiles and unmitigated smog—with innumerable healthy babies and an inadequate base of population control. Our capacity to react quickly to the next generation of technological problems, the progeny of the first payoffs, depends on the broadest base of scientific knowledge and the techniques of new discovery.