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The Social Imperatives of Medical Research

Impeding medical research, no less than performing it, has ethical consequences. Not to act is to act.

Leon Eisenberg

Peculiar to this time (*1*) is the need to restate a proposition that, a decade ago, would have been regarded as self-evident, namely, that fostering excellence in medical research is in the public interest. Contemporary news accounts and learned journals alike have announced as exposé what always has been true: that doctors are fallible, that researchers are not all noble, and that what appeared to be true in the light of yesterday's evidence proves false by tomorrow's. The sins committed in the name of medical research are stressed in entire disproportion to the human gains that continue to flow from the enterprise. That a significant amount of funded research will inevitably fail to yield the expected answers is taken as a sign of boondoggling, because the nature of science is not understood. We are asked for guarantees of absolute safety as if this were an attainable goal.

Some of the specific criticism has been just and instructive, some of it merely misinformed, some of it completely irrelevant. A constructive response to the criticism of medical research would have been easier had not distrust been aroused at the same time by the misapplications of technical knowledge (the spread of weapons systems, wire tapping, computerization, nuclear wastes) and the use of technical devices by government against its own people. Those of us who argue for the necessity of scientific research in medicine are too often regarded as if we were indifferent to misuses of it and as though we were apologists for the Establishment. I know of no remedy other than to redouble our effort to explain the nature and the justification of well-designed medical research, the calculus of risk and benefit that is an integral part of it, and the design of methods to maximize its potential for gain. If we permit it to be circumscribed with a bureaucracy of regulation so cumbersome as to impede its progress, we incur a risk to society from the restriction of medical science that will far outweigh the aggregate risk to all the subjects in experimental studies.

Medical Practice and Medical Research

One source of misunderstanding is the confusion of what is usual and customary in medical practice with what is safe and useful. The critics of research are often exquisitely aware of the dangers in an experiment (indeed, the responsible investigator is at pains to spell them out as precisely as he or she can). At the same time, these critics, surprisingly naïve about the extent to which medical practice rests on custom rather than evidence, fail to appreciate the necessity for controlled trials to determine whether what is traditional does harm rather than good.

Consider, for example, the fact that about 1 million tonsillectomies and adenoidectomies are done each year in the United States; T and A's make up 30 percent of all surgery on children. Set aside budgetary considerations, even though the outlay—about $500 million—represents a significant "opportunity cost" in resources lost to more useful medical care (*2*). During the 1950's, T and A's resulted in some 200 to 300 deaths per year (*3*). Current mortality has been estimated at one death per 16,000 operations (*4*). Yet this procedure (whose origins are lost in antiquity) continues at epidemic rates though there is no evidence that it is effective (*5*) except for a few uncommon conditions (*6*). Doctors disagree so widely about the "indications" for T and A that within one state (Vermont) there is a fivefold variation by area of residence in the probability that a person will have his or her tonsils removed by age 20 (*7*). Thus, we have a procedure of dubious value employed at high frequency despite significant mortality and dollar costs. Why? It is done because doctors and parents believe in it; having become usual and customary, it is not subject to the systematic scrutiny of an experimental design.

Compare the human cost from this single routine and relatively minor procedure to the risk to human subjects in nontherapeutic and therapeutic research. Cardon and his colleagues (*8*) surveyed investigators conducting research on 133,000 human subjects over the past 3 years. In nontherapeutic research, which involved some 93,000 subjects, there was not one fatality, there was only one instance of permanent disability (0.001 percent), and there were 37 cases of temporary disability (0.04 percent). In therapeutic research (that is, clinical research carried out on sick people who stood to benefit directly from the knowledge gained), among 39,000 patients, 43 died (0.1 percent) and 13 suf-

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fered permanent disability (0.03 percent). (Most of the deaths were of patients on cancer chemotherapy.) The risk to experimental subjects in nontherapeutic research is comparable to the rates for accidental injury in the general population (when one makes appropriate calculation for days of risk per year). Tonsillectomy, a relatively minor surgical procedure, produces more deaths per 100,000 each year than the total from all nontherapeutic research! If we add into our calculation the deaths resulting from major surgical procedures that may be performed more often than is warranted—for example, the current rate of 647 hysterectomies per 100,000 females projects to loss of the uterus for half the female population by age 65 (*9*)—and from excessive and injudicious prescription of powerful drugs, it becomes clear that the gain in public safety from exacting scrutiny of medical practice by means of controlled trials would far outweigh any possible gain from the most restrictive approach to medical research. Let me not be misunderstood: I do not deny the necessity for surveillance of the ethics of the research community; the point I stress is that medical research, applied to medical practice, stands alone in its ability to avert unnecessary human suffering and death.

The Sources of Medical Error

Among the reasons given for the persistence of medical error are venality on the part of physicians, professional incompetence, and lack of commitment to the public weal. There are venal physicians; we need look no further than the exposure of Medicaid mills to find them. But that hardly accounts for the overprescription of surgery when we recognize that surgery is performed on physicians' families even more often than it is on the general public (*10*); physicians as consumers follow the advice they proffer as providers. There are incompetent doctors, and we still lack adequate methods for weeding them out; but anesthetic and surgical deaths occur in the best of hands because of the risks inherent in the procedures. Not all doctors are actuated by the public interest, but this hardly explains what concerns us about physician behavior. Although these factors contribute to wrongheadedness in medical practice, a far more important source is simply the doctor's conviction that what he or she does is for the patient's welfare. When good evidence is lacking, the best and most dedicated of us do wrong in the utter conviction of being right.

Bloodletting as Panacea

Let me offer a historical illustration from the career of a man with many admirable qualities, a leading U.S. physician of the late 18th century. Benjamin Rush was uncommon among his peers in having a university degree in medicine (from Edinburgh); he was appointed professor of chemistry at the College of Philadelphia (soon to become the Medical School of the University of Pennsylvania, the first medical school in America) and later professor of the institute and practices of medicine. He was among the most steadfast of patriots, a signer of the Declaration of Independence, a member of the Pennsylvania delegation that voted to adopt the Constitution of the United States, and a founder of the first antislavery society (*11*). His book *Medical Inquiries and Observations upon the Diseases of the Mind* was the first comprehensive American treatise on mental illness (*12*). Thus, we have a physician with as good an education as his time could provide, a leading member of the faculty of the premier school of medicine, and a man dedicated to the public interest.

In 1793, a severe epidemic of yellow fever fell upon the city of Philadelphia (*13*). It is estimated that more than one-third of its population of 50,000 fled the city and that more than 4000 lives were lost. Panic beset the medical community, and doctors were among those who took flight to escape the pestilence. From illness and defection at the height of the epidemic, only three physicians were available to treat more than 6000 patients. Rush dispatched his wife and children to the safety of the countryside and remained behind to fulfill his medical responsibility.

Rush was an adherent of the Brunonian system of medicine, according to which febrile illnesses resulted from an excess of stimulation and a corresponding excitement of the blood. In keeping with this theory, he ministered to his patients by vigorous bleeding and purging, the latter to "divert the force of the fever to [the bowels] and thereby save the liver and brains from a fatal and dangerous congestion." Rush went from patient to patient, letting blood copiously and purging with vigor. His desperate remedies, contemporary critics contended, were more dangerous than the disease, a criticism history has borne out.

His beliefs were not something he reserved for others. He himself was taken with a violent fever. He instructed his assistant to bleed him "plentifully" and give him "a dose of the mercurial medicine." From illness and treatment combined, he almost died; his convalescence was prolonged. That he did recover persuaded him that his methods were correct. Thus, when the epidemic subsided, he wrote: "Never before did I experience such sublime joy as I now felt on contemplating the success of my remedies. . . . The conquest of a formidable disease was through the triumph of a principle in medicine" (*13*, p. 442). Neither dedication so great that he risked his life to minister to others, nor willingness to treat himself as he treated others, nor yet the best education to be had in his day was sufficient to prevent Rush from committing grievous harm in the name of doing good. Convinced of the correctness of his theory of medicine and lacking a means for the systematic study of treatment outcome, he attributed each new instance of improvement to the efficacy of his treatment and each new death that occurred despite it to the severity of the disease.

Introduction of the Numerical Method

Bloodletting continued to be a widely used medical remedy until the middle of the 19th century. According to Osler (*14*), it was finally abandoned because of the introduction into American medicine of the "numerical method" of the French physician Pierre Charles Alexandre Louis. Louis had been disenchanted with his medical education and his experience as a practitioner. He withdrew from practice to devote himself to study. As one contemporary commented (*14*):

> He consecrated the whole of his time and talent to rigorous, impartial observation. All private practice was relinquished and he allowed no considerations of personal emolument to interfere with the resolution he had formed. For some time, his extreme minuteness in inquiry and accuracy of description were the subjects of sneering and ridicule, and "to what end?" was not infrequently and tauntingly asked.

One result of his study, an essay on bloodletting, appeared in Paris in 1835 (*15*). Within a year, it was translated into English by G. C. Putnam (*16*). In a preface to the volume James Jackson, physician to the Massachusetts General Hospital, wrote (*16*, pp. v–vi):

> If anything may be regarded as settled in the treatment of diseases, it is that bloodletting is useful in the class of diseases called inflammatory; and especially in inflammation of the thoracic viscera. To this general opinion or belief on this subject, M. Louis gives support by his observations; but the result of these

observations is that the benefits derived from bleeding in the diseases, which he has here examined, are not so great and striking as they had been represented by many teachers. If the same methods should be obtained by others, after making observations as rigorous as M. Louis, many of us will be forced to modify our former opinions. . . . The author does not pretend that the questions, here discussed, are decided forever. He makes a valuable contribution to the evidence, on which they must be decided; he points out the mode, in which this evidence should be collected, and in which its material should be analyzed; seeking truth only, he calls on others to adduce facts, which, being gathered from various quarters, may show us, with a good degree of exactness, the precise value of the remedy in question.

Louis himself began his monograph with the comment (*16*, p. 1):

The results of my researches on the effects of bloodletting in inflammation are so little in accord with the general opinion, that it is not without a degree of hesitation I have decided to publish them. After having analyzed the facts, which relate to them, for the first time, I thought myself deceived, and began my work anew; but having again from this new analysis, obtained the same results, I could no longer doubt their correctness.

He was led to conclude:

We infer that bloodletting has had very little influence on the progress of pneumonitis . . .; that its influence has not been more evident in the cases bled copiously and repeatedly, than in those bled only once and to a small amount; that we do not at once arrest inflammations, as is too often finally imagined; that, in cases where it appears to be otherwise, it is undoubtedly owing, either to an error in diagnosis, or to the fact that the bloodletting was practiced at an advanced period of the disease, when it had nearly run its course.

Yet, so strong was the power of authority, that he was moved to comment (*16*, p. 22):

I will add that bloodletting, notwithstanding its influence is limited, should not be neglected in inflammations which are severe and are seated in an important organ.

Louis's precise observations, his stress on the importance of studying series of cases, and his insistence on reexamining standard belief were to have an enormous influence. Many American physicians went to Paris to become his pupils and returned to these shores persuaded of the value of his method. Insofar as it can be said that any single contribution led to the abandonment on this continent of bloodletting as a panacea, it was Louis's numerical method. It had its roots in the earlier applications of elementary statistics to public health and became far more powerful as a method when the concepts of probability statistics were applied to its simple tabulations (*17*). From these beginnings stems much of the progress in medical science.

Importance of Clinical Description and Classification

I have thus far stressed the contributions of the controlled clinical trial (*18*) to the provision of more effective remedies and to the elimination of harmful ones. But before physicians can treat, they must be able to discriminate disorders one from another. Here, careful delineation of disease patterns, both immediate and longitudinal, and attention to ways in which patients resemble and differ from each other provide the necessary groundwork for identifying the underlying pathophysiology. The process begins with the report of a puzzling and hitherto undescribed group of cases. Initially attention is directed at differentiating the new syndrome from superficially similar conditions. Some decades pass during which doctors disagree on the diagnosis and include or exclude a penumbra of cases which markedly affect the reported outcome. Next a fundamental pathogenic lesion is discovered, and confirmed by other workers, to be present in "typical" cases. As the mechanism of the disease is clarified, the disease itself is redefined in terms of the underlying pathology. Now new and variant clinical forms can be identified, cases that would not have met the original criteria. Let me illustrate this by an example from hematology.

In 1925 Cooley and Lee separated out from the group of childhood anemias (known as von Jaksch's anemia) five cases with hepatosplenomegaly, skin pigmentation, thick bones, and oddly shaped red cells with decreased osmotic fragility. Cooley's anemia was renamed thalassemia in 1932 by Whipple and Bradford, who noted that the children came from families of Mediterranean origin. The genetic basis of thalassemia was established by Wintrobe in 1940 in a paper which distinguished thalassemia minor (the heterozygous state) from thalassemia major (the homozygous state). Fifteen years later Kunkel discovered the normal minor hemoglobin component hemoglobin A_2 and found it to be elevated in individuals with thalassemia minor (*19*). A subsequent explosion of research on the hemoglobin molecule has led to the recognition of some 50 combinations of genetic errors which can produce the clinical picture of thalassemia.

In the transition from clinical to laboratory criteria the definition of the disease had been radically altered. Thus in the first edition of Wintrobe's *Clinical Hematology* (*20*) we were taught that

Mediterranean anemia is characterized by chronic progressive anemia commencing early in life, well-marked erythroblastosis in the peripheral blood, a characteristic facies, splenomegaly, and a familial and racial incidence.

But in the current edition (*21*) we learn that

Thalassemia comprises a heterogeneous group of inherited disorders of hemoglobin synthesis. Indeed, it can no longer be said that the presence of hypochromic, microcytic red corpuscles, which are not the result of iron deficiency and whose osmotic fragility is decreased, is the sine qua non of thalassemia. The morphologic picture varies in the different thalassemia syndromes, even to the point of total absence of morphologic features or clinical manifestations in some heterozygotes.

Or, to turn to a current review by Weatherall (*22*):

The thalassemias are a group of disorders of hemoglobin synthesis resulting from the reduced rate of production of one or more of the globin chains of hemoglobin. The result of this unbalanced chain synthesis is the production of a relative excess of the partner chains which are synthesized at a normal rate. Most of the clinical features of thalassemia can be related to the deleterious effects on erythropoiesis caused by the precipitation of these unpaired globin chains. The disorders can be classified broadly into alpha and beta thalassemia and each of these can be further subdivided into several distinct subtypes.

The process that began with the abstraction of a Platonic "type" based on clinical features led to the isolation of a group of "classical" cases which provided the basis for laboratory research. In turn, the research enabled the disease to be redefined in terms of its pathogenesis. It became possible by laboratory methods to recognize cases lacking some of the typological clinical features. But the gain in precision also led to a recognition of the molecular heterogeneity of what appeared to be a clinical entity.

The undifferentiated psychiatric diagnosis of "depression" is analogous to von Jaksch's anemia, and studies in various academic centers are in the process of isolating the subtypes which are the analogs of Cooley's anemia and its variants. With the pace of progress in the study of brain amines, peptides, other neurohumors, and their receptors, it is not too wild a hope to anticipate the discovery of the equivalents of the "disorders of globin chain synthesis" in the near future.

Basic Research and Disease Prevention

Hand in hand with the controlled clinical trial and with the continuing search for diagnostic precision must go fundamental research in basic biology. Much of our armamentarium for the treatment

and prevention of disease is at the level of what Lewis Thomas (*23*) has called "halfway technology," measures which, though useful, only partly reverse the disease process, are costly, and are toxic. Consider the situation this nation faced not long ago in coping with poliomyelitis. Each year it took 2000 lives and left 3000 persons with severe paralysis. The hospital cost for acute and chronic care, the iron lung, the wet pack, and physiotherapy exceeded $1 billion a year. For an investment of $40 million in the basic research which led to Ender's method of cultivating the polio virus in the chick embryo, and not more than several hundred million dollars for applied technology and population trials, an enormous human and financial loss has been averted (*24*).

The psychiatrist today is in the position of the pediatrician a generation ago. Chemotherapy aborts acute psychotic episodes, but recurrence is common, permanent disability frequent, and drug toxicity considerable. We have strong evidence for familial predisposition but cannot specify modes of inheritance or what is inherited, or distinguish the potential patient before illness occurs. The hope of prevention must rest upon increased support for fundamental research in neurobiology, genetics, and epidemiology (*25*). The problem is not a gap in the application of knowledge but a gap in knowledge itself.

Basic research does not begin and end with molecular biology. Vaccination provides a model for infectious diseases and perhaps even for neoplasms; it is simply irrelevant to behavior-linked health problems: the consequences of smoking, overeating, drinking, drugging, and reckless driving. Belloc and Breslow have shown that seven personal health habits sum to a powerful prediction of morbidity (*26*) and mortality (*27*) for middle-aged adults. To recognize that cultural patterns, social forces, and idiosyncratic personal behaviors have major effects on health (*28*) is not equivalent to knowing how to alter them. It does, however, argue for the urgency of research in the social as well as the biological sciences if physicians are to learn how to intervene effectively (*29*).

The Restriction of Risk and the Risk of Restriction

Health will be held hazard to custom until the current preoccupation with the dangers of research is placed in the appropriate context: namely, weighing in the very same scales the dangers of not doing research. Surveillance of research ethics requires simultaneous assessment of the scientific and the ethical soundness of the protocols themselves. "A poorly or improperly designed study involving human subjects—one that could not possibly yield scientific facts (that is, reproducible observations) relevant to the question under study—is by definition unethical" (*30*). Commendation for a high rate of rejection of research proposals implies that the proper goal for a research review committee is blocking human studies. To the contrary, the systematic imposition of impediments to significant therapeutic research is itself unethical because an important benefit is being denied to the community.

This is not a call for unrestricted rights for medical researchers. If I do not accept the view that medical researchers are worse than lawyers or philosophers, I will not argue that they are better. They are simply human; that is to say, fallible. As in the case of all professional activity, social controls are necessary. But in establishing those controls, it is necessary to weigh fully the possible resultant losses. The decision not to do something poses as many ethical quandaries as the decision to do it. Not to act is to act (*31*).

Important ethical issues in medical research have been overlooked in the preoccupation with ethical absolutes. Consider, for example, the clear social class bias in the likelihood of being a subject in a medical experiment. For that there can be no justification. Even if risk in research be inevitable, inequity in exposure because of caste or class need not be. The patients on whom clinical research is most often done are clinic patients, those who by reason of economic circumstance and education are the least able to assert their rights against medical authority.

It was not long ago, to our shame, that this practice was explicitly justified on the ground that the poor paid society back for the "privilege" of receiving charitable care by being suitable clinical material for research and teaching. Few would defend that position in so callous a way today. Yet the practice continues, less by plan than by fallout from our two-track medical care system. Researchers are located in teaching hospitals. Teaching hospitals are a major medical resource for the poor. The poor become the patients on whom studies are done because of their convenience as a study population and our insensitivity to the injustice of the practice. It is not enough to say that we now offer explanation and choice and obtain informed consent. Indeed, we do. But the quality of consent is not the same when the social position of doctor and patient are disparate as it is when they are more nearly equals.

Enhancing the human quality of the community in which we live is the responsibility of every citizen; one way to meet that responsibility is by sharing in the risks of the search to diminish human suffering. Richard Titmuss (*32*) has pointed to the health benefits to the United Kingdom from a public policy based on a voluntary blood donor system [but see Sapolsky and Finkelstein for a contrary view (*33*)]. I suggest that there will be moral gain as well as health gain to the United States to the extent that we succeed in creating a community of shared responsibility for health research.

Informed Consent in the Absence of Information

What does "informed" consent mean in the real world of medical practice? When risks are specifiable so that it is possible to make a rational decision by weighing alternatives, it is clearly the physician's duty to inform the patient fully. That has long been a hallmark of good medical practice and sound clinical investigation; it is no contemporary discovery. But what does "informed" mean when what is available to the physician, let alone the patient, is not information but noise? In what sense is there a choice to be made between treatment A and treatment B if there is no proof that either works or that one is superior to the other? What right have I lost if, in a national health scheme, I am assigned to a randomized trial without being asked my preference, when that preference can only be capricious? The very justification for a randomized trial is that there is insufficient information to permit a rational, that is, informed, choice. In a free society we will reserve the right for any citizen to opt out. But when we respect the privilege to be guided by superstition, astrology, or simple orneriness, let us drop the adjective "informed" and speak only of "consent."

Do We Need Medical Research?

A major undercurrent in the criticism of medical research is a growing belief that it is basically irrelevant to contemporary human needs. The argument runs something like this: what doctors do has only marginal effects on health; anyway,

what researchers learn, when it does add to knowledge, doesn't get into practice; besides, from a higher moral view, what really matters is learning to live with the existential realities of pain and dying and not to permit technical iatrogenesis to alienate man from his nature (*34*). To what extent is this credible?

There is good evidence for the proposition that the increase in longevity over the past century in industrialized nations has been principally the result of social forces: better nutrition, better hygiene, and changed behavior (*35*). An instructive example is the striking decline in mortality from tuberculosis over the last 100 years, with only a small additional decrement visible after the introduction of streptomycin. But there is no assurance that further social change will eliminate the residual cases. Moreover, chemotherapy is decisive in the treatment of the tuberculosis that is still with us; the lack of a prominent effect on aggregate mortality statistics reflects the lesser prevalence of the disease as a public health problem, not the ineffectiveness of treatment. But the major defect of the proposition, as a general indictment of medical care, is at a more fundamental level. Doctors, at best, postpone death; death itself is inevitable. Most of what doctors do is to mitigate discomfort and pain and to enhance function in the presence of chronic disease, an effect that is not registered in mortality tables (*36*). Sole reliance on longevity and mortality leaves unmeasured the benefits most patients consult doctors for and the major benefits they have always derived from them (*37*). Morbidity rates, and the consequent demand for medical resources (*38*), cannot be predicted from mortality data (*39*).

The second theme, the failure to translate research into practice, what we might name the "Lyndon Johnson doctrine" in view of his 1966 speech at the National Institutes of Health, is grossly exaggerated. Lag undoubtedly occurs in the transfer of medical skills from highly specialized centers to rural areas; the much more troublesome problem is the indiscriminate introduction into practice of new drugs and surgical innovations well before their indications and limitations are clear, often in such ways as to compromise their usefulness. The major barriers to the treatment of life-threatening disease stem not from failing to use what we know but from not knowing what to use.

Eighty percent of the deaths in this country are caused by cardiovascular, neoplastic, cerebrovascular, and renal disease (*23*). For the very great majority of the specific disorders within these categories the treatments we have are only palliatives. Palliatives are important, and certainly they should be distributed fairly; but the most evenhanded and prompt distribution of all available remedies would have only a small effect on death rates. As to resource allocation, the percentage of the health dollar (well under 2 percent) devoted to applied and basic medical research in toto is so small a part of total health costs that complete diversion of those funds would have negligible effects on health care delivery. The one clear result would be to end all prospect for improving the quality of the care delivered.

The idea that pain and dying are integral parts of man's fate, though put forth as a truism, is in fact a theological view of the human condition (*34*). To comprehend its meaning, it is necessary to ask: How much pain? Death at what age? Whose pain and whose death? By what standards: today's or a century ago's, white American or black American, Indian or African? Perhaps, with a life expectancy exceeding the Biblical threescore and ten, affluent white Americans can afford the luxury of wondering whether medical research makes much sense in view of the risks and costs it entails. That is, we can if we mistake our fate for man's fate, ourselves for all of humankind.

A Third World Perspective on Research

The armchair view of medical research as fun and games undergoes radical transformation from the standpoint of the third world, where infant mortality may be as high as 20 percent and life expectancy no more than 30 years. "People are sick because they are poor, they become poorer because they are sick and they become sicker because they are poorer" (*40*). Six infectious diseases that are almost unknown on our shores plague Africa, Asia, and Latin America: Malaria afflicts an estimated quarter billion; the mosquito that spreads it is becoming resistant to the standard pesticides and the plasmodium to chloroquin. Trypanosomiasis afflicts perhaps 20 million; we lack effective weapons against either the vector or the parasite; the treatment in use can be more dangerous than the disease. Leishmaniasis claims some 12 million; there is no known treatment. Filariasis and onchocerciasis infect 300 million; treatment is ineffective. Schistosomiasis afflicts 250 million; as nations attempt to improve their agricultural productivity through irrigation, the snail vector multiplies. Finally, there are 12 to 15 million lepers in the world; the current treatment requires 7 years; drug-resistant lepra bacilli have begun to appear.

In the face of all this, there is a clear moral imperative in developed nations for medical research in tropical diseases, to seek to permit two-thirds of the world's population to share in the freedom from pain and untimely death we have achieved for ourselves. In the forceful words of Barry Bloom (*40*):

> Discourse about medicine and ethics has focused almost entirely on problems of a wealthy society, and relatively little attention has been given to those affecting the vast majority of people in the world. There is a preponderant concern with individualism and individual rights, most recently reflected in the enormous preoccupation with death and dying. Imagine the impact of the anguished disquisitions about the Karen Quinlan case on the reader in Bangladesh or Upper Volta. The public agitation over "pulling the plug" on a single machine seems almost perverse when juxtaposed against the unmet health needs, the desperate struggle for survival of millions of people around the globe. I do not deny that there are serious problems of individual liberty at stake or that the Quinlan case may serve as a model for delimiting the role of the family, physician, or state in authorizing medical treatment for those unable to speak for themselves. But when the model so fills the horizon as to obscure the reality, then all perspective is lost.

M. Pasteur's Dog Kennels

I began my exposition with a commentary on current concerns with the dangers of medical research. Let me conclude by placing these concerns in historical perspective, for they are in no sense novel.

In 1884 the following article (here translated in full) appeared in *Les Annales Politiques et Litteraires*, under the title "M. Pasteur's Dog Kennels" (*41*):

> M. Pasteur is not lucky. The city of Meudon has already vigorously protested against the creation (on the outskirts of the forest in which Parisians enjoy walking on Sundays) of the dog kennels of this eminent scientist. Now the surrounding communes also protest. Since the [National] Assembly has been presented with a proposed law dealing with the appropriation of the estate of Villeneuve-l'Etang, all the surrounding communes have protested. Saint-Cloud, Ville-d'Avray, Vaucresson, Garches, and Marnes-la-Coquette appeal to the Senate in order to stop the realization of this project.
>
> The municipal councillors who signed the petition written to this effect, observe that the introduction to the bill presented before the Assembly states that M. Pasteur's dog ken-

nels will be located far from any housing, in order to avoid causing any embarrassment to the neighbors and to keep them from possible contagious cattle diseases.

But if the dog kennels were to be located in the so-called La Ferme buildings, on the Villeneuve-l'Etang estate, they then would be in the close neighborhood of houses of Marnes, Vaucresson and Garches. The animals' cries would be troublesome; the excrements would be unhealthy. Since M. Pasteur's research will deal not only with rabies, but also with cattle pneumonia, anthrax, erysipelas, chicken cholera, etc., flies would become a terrible catastrophe (which nobody could handle) for visitors as well as for the inhabitants, in a word, for any living being. The stables which are now in the communes would be threatened; finally, the park of Saint-Cloud and the forest of Ville-d'Avray, where Parisians and young college students like to go for walks, would be deserted. We who sign this petition are so apprehensive that we predict that even artists, who like to work in the forests surrounding the aforesaid communes, will no more undertake such ventures.

Even worse, the buildings which will presumably be allocated for the creation of M. Pasteur's labs are precisely in the middle of the Villeneuve-l'Etang estate, just in front of the railway station of Garches-Marnes. These considerations determine us to ask the senators to stop the realization of a project which, if completed, would fatally disrupt the development of a very promising area.

M. Pasteur wrote M. Christen, municipal councillor of the city of Vaucresson, the following letter:

"Arbois (Jura), 6 October 1884

"Sir,

"I am very grateful for your letter, in which you inform me about the reactions to the plan to allocate a part of the Villeneuve-l'Etang estate for my studies on rabies and other diseases, in the communes of Saint-Cloud, Ville-d'Avray, Marnes, Vaucresson and Garches.

"I am equally grateful to you, for allowing me to make it clear to the inhabitants of those communes how exaggerated are the fears on which such protests are based.

"I shall be back in Paris on October 24: in the morning of the 25th and the following days, I shall be in my lab rue d'Ulm, ready to give to the authors of these protests all desired information, which, I hope, will diminish their fears.

"If my own words were not sufficient, we could decide on a date to go to Villeneuve-l'Etang. Then, I would show the impossibility of any danger whatsoever—for the inhabitants of these communes, as well as for Sunday visitors—from the experiments which I intend to perform.

"What you can already tell your fellow citizens and all those who are so deeply alarmed, is that there would be no rabid dog in Villeneuve-l'Etang. There would only be dogs immune to rabies. For lack of space in my lab, I am now obliged to give to various veterinaries those dogs which I myself would very much like to be kept in one large dog kennel, with a roof, and barriers.

"You are, Sir, perfectly right to characterize the dangers which I would provide as illusory and I am very grateful to you for trying to calm down all this turmoil.

Sincerely yours,
Pasteur"

That threat to his laboratories, reminiscent of today's municipal ordinances against work with recombinant DNA, took place just one year before Pasteur undertook for the first time to vaccinate a boy who had been bitten by a rabid dog. The story is a dramatic one because the work under attack was Pasteur's and Pasteur succeeded so magnificently. Most studies do not make such great leaps forward; they add only modest increments to knowledge. But that process provides the foundations for greater accomplishments.

Because science is incomplete, reason imperfect, and both can be put to damaging uses, some would abandon science and reason in favor of mysticism, hermeneutics, and transcendental rapture. It is not knowledge but ignorance that assures misery. It is not science but its employment for inhuman purposes that threatens our survival. The fundamental ethical questions of science are political questions (*42*): Who shall control its products? For what purposes shall they be employed?

Four years after the community protests against the dangers of his research, the citizens of France, by public subscriptions in gratitude for his contribution to human welfare, erected the Pasteur Institute. In the ceremony of dedication, Pasteur, overcome by his feelings, asked his son to read his remarks, which concluded (*43*):

Two opposing laws seem to be now in contest. The one, a law of blood and of death, ever imagining new means of destruction, forces nations always to be ready for battle. The other, a law of peace, work and health, ever evolving means of delivering man from the scourges which beset him. The one seeks violent conquests, the other the relief of humanity. The one places a single life above all victories, the other sacrifices hundreds of thousands of lives to the ambition of a single individual. The law of which we are the instruments strives even in the midst of carnage to cure the wounds due to the law of war. Treatment by our antiseptic methods may save the lives of thousands of soldiers. Which of these two laws will ultimately prevail, God alone knows. But this we may assert: that French science will have tried by obeying the law of Humanity, to extend the frontiers of life.

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