#VP271

THE SECOND CENTURY OF LOUIS PASTEUR:

A GLOBAL AGENDA FOR BIOMEDICAL RESEARCH

JOSHUA LEDERBERG

The Rockefeller University, New York, NY 10021

INTRODUCTION: Louis Pasteur and the Pasteur Institute

Nothing could have given me greater gratification than this invitation. For me, as for my entire generation of scientifically inclined youth, Louis Pasteur was a global culture hero. The Pasteur Institute was an exemplar that inspired the foundation of the Rockefeller Institute in 1901. In 20th Century America, Pasteur's work reached popular attention largely through the writings of Paul de Kruif - "Microbe Hunters". The author was a microbiologist who began his career at the Rockefeller. Rene Dubos, an important admirer and biographer of Pasteur, was my colleague at the Rockefeller -- and long before that one whose work and writings I looked up to. Starting in 1946, figures like Andre Lwoff, Elie Wollman, Jacques Monod and Francois Jacob have towered at the very top of those scientists who worked in fields closest to my own interests, who made important discoveries correcting and enlarging my own, and whose criticism and esteem counted the highest in extracting the fullest meaning from my own work. When there was occasion to plan spaceflight missions to Mars, the search for chiral molecules presented itself as the most universal of indicators of extra-terrestrial life. I was presumptuous enough to label that "The Pasteur Probe." Many of my closest friends and colleagues have had the good fortune to be able to spend a significant time working at the Pasteur Institute, to their lifelong advantage. Today, the Institute has continued in Louis Pasteur's tradition of providing new scientific knowledge in infectious disease that is our only hope of fending off a pandemic that is already a global catastrophe.

These images of Pasteur and his Institute complicate my task in seeking a worthy topic for such an occasion. He has been the subject of many biographies; yet there is much more to be learned about the history of his ideas and their reception, and how they related to his contemporary architects of scientific revolutions: epitomized by names like Gregor Mendel, Charles Darwin, and Friedrich Miescher. The Institute itself deserves a formal history in more detail than my own scholarship could encompass. You are fortunate to have many other celebrants who will look up from their exciting work at the laboratory bench, and by describing what they know so elegantly, give you a perspective of the contemporary science that proceeds throughout the world in these traditions.

As an introductory speaker, I claim a different canvas. My questions will include: What can we hope from the next century of research in the Pasteurian tradition? What old and new problems will we face? What do these tell us about our agenda for today? I will also comment on the social milieu in which science now functions, and some of our challenges in sustaining the utmost creativity and intellectual boldness of the young minds who are our most important hope for the future.

PROPHECY: as Cassandra told, is a perilous profession. Why do it?

The best justification I owe to Alex Keynan: that a vision of the possible motivates many social actions; and our policies are already permeated by much false prophecy, if only that tacit one that the future is static. I have committed a few lamentable, spasms of technological forecasting, starting some 25 years ago. They are lamentable not so much because they were wrong -- for the most part they were accurate -- but because it is hard for me to see any difference that it made to enunciate them. One can urge on any scientist that he will influence the future far more by what he puts into the permanent record of scientific experiment and discourse than by what he articulates to the public. Nevertheless, eloquent writers like Lewis Thomas, the late Peter Medawar, and your own Jacques Monod and Francois Jacob have had an important impact on the public mind.

A ceremonial occasion as formidable as this still invites some reflection. And I will have some excuse to mix in some prescription.

If we try to look ahead to foresee the development of science for the next century, we encounter first of all the overwhelming impact of compound interest, of the exponential acceleration that already impressed Henry Adams at the beginning of this century. As Derek Price pointed out we have experienced a 6% growth rate -- a 12-year doubling time -- in Western science throughout the modern era. We have indeed assimilated a 300-fold increase in the first Pasteurian century. Can we imagine a like multiple in the second? Probably not for Western Europe and America: even before we reach the physical limitations of a growth rate exceeding that of the GNP, we already experience painful constraints. On the other hand we must consider the potential development of science in China, India, Eastern Europe (as it throws off the shackles of Lysenko and his nepotic offshoots), Latin America, perhaps some of Africa. Recall where Japan was in 1887 (for that matter the U.S. in medical science) compared with today. The cultural space for science is in the process of a tenfold augmentation.

How does such a forecast inform us? To extrapolate for, say, 20 years may be a reasonable exercise. There will be surprises, but our baseline is numerically a third of the estimate; and most of the technology in use in 2007 will be based on scientific fundamentals now visible. To guess at the substantive content of science for another century is not forecasting but divination. Hardly just technology, the very fabric of global human affairs is subject to the most unpredictable of perturbations -- a truism that should temper the assertion of absolute categorical prescriptions about what should or should not be ethically permitted, based on a projection of contemporary circumstance. Geopolitics aside, will we take the same view of death and dying when it is no longer at the whim of "natural causes"? Leo Szilard would say that an optimist is one who believes the future is uncertain: I will proceed with that admonition.

Forecasts about the kinetics of science are more credible than about its substance. Apart from its impact on the social yield, the process of growth is part of the vitality of science: it has given us the luxury of trying new people, new projects without making painful choices about the relicts; it has been an important factor in the youthfulness and audacity of temperament of its practitioners. As growth slows down we face almost inevitably a graying of our culture -- a side-effect of the control of population growth and of the prolongation of lifespan

that we urge as a fundamental policy for Western society. We should also anticipate that 1) science will be far more broadly distributed among cultures and polities of the world, and 2) ever more attention will need to be given to the integrative measures needed for some coherence of the research enterprise - matters rarely attended to in the highly specialized training offered our young scientists today.

These integrative measures are both external and internal to science. At one extreme, they speak to a broadening of the educational base, at least for some professionals, towards understanding of the socio- cultural framework of vast technological expansion: how to stay abreast of accumulated information, and relate it to the needs both of the professional discipline and of humanity. These are not the same skills needed for bench research, though they overlap it as do the qualifications for teaching. We do not have an appropriate balance in our academic status and reward system today. At the other extreme, we urgently need innovations in mathematics and computer-science to cope with the complexity of scientific description itself.

LOOKING BACKWARDS INTO THE FUTURE (which is, so I am told, the Chinese perspective)

100 years ago, Jules Verne and other science-fictional utopians gave us fairly accurate premonitions about mechanical technology: space travel and submarine warfare. He had little to say about biology. For Pasteur, the microbe was the concept that revolutionized medicine. Today, the structure of DNA is the paradigm that informs every aspect of contemporary biomedical science. Working out the full detail of DNA structure, its diversification on the evolutionary landscape, in individual variation, in the development of the organism is already the undisputed agenda that may well occupy us for much of the next century, in the way that the microbe did for the first.

Such clarity of opportunity for exploitation is a rare good, and it will have enormous technological fruits. We have also to guard against being so dominated by the opportunity that we close off acts and thoughts that deviate from the mainstream: the very idols or paradigms that inspire rapid progress. Did this occur in 20th Century microbiology? I can think of a few possible examples that (needless to say) warrant further debate. The very success of the established paradigms in the early conquest of infectious disease gave little encouragement to challenge them. As Kluyver and Van Niel have pointed out, the view of bacteria as enemies of humankind helped to obscure the closer examination of their biology.

1. Skepticism about genetic variation in bacteria: this was too often discounted as contamination, the horror to be avoided in microbiological technique. Here, Pasteur was conceptually correct in the face of skepticism about his attenuated variants; though he resisted the pure culture methodology of his teutonic competitors. A further consequence was a long lasting muddle about adaptive phenomena, where bacteria were long regarded as refuges of Lamarckian biology.

2. The definition of bacteria as Schizomycetes, namely fission-fungi devoid of sexual processes, and therefore beyond the pale of Mendelian genetics. This idol stemmed in part from Leeuwenhoek's original description of bacteria, as the simplest organisms in the Scala Naturae, barely resolvable with the microscope. (Unfortunately, even the best microscopes are still of little help in understanding genetic exchange in bacteria.) The cleavage of bacteria from genetics persisted for a half-century after Pasteur.

3. The discouragement of anti-bacterial chemotherapy, despite sporadic observations of antibiosis long predating Fleming. Even Fleming was daunted from pursuing penicillin after 1928 by the expectation of failure. The toxicity of Ehrlich's arsenicals and dyestuffs did furnish empirical foundation for those negative beliefs; but they were prematurely canonized, in favor of the virtues of serotherapy.

4. In related fashion, the mystique attached to antibody globulins -- do but recall the jargon of "lysins, agglutinins, opsonins, ablastins, amboceptors, ..." -- supported the presumption that they were infinite in variety, and helped sustain the instructive theories of their specificity that dominated the field until 30 years ago. We could not have monoclonal antibodies, nor the conceptual framework of modern immunology, until those idols were superseded by contemporary insights based on cell selection. One must admit that English invention, Occam's razor, the precept of minimizing new suppositions, has been a poor guide to discovery of the divers cell types involved in the immune response.

5. The concept of a "toxin" as a lethal weapon -- the military jargon itself accents the idol -- long obscured the recognition of cholera exotoxin as a substance that "merely" promotes the intestinal secretion of water. It took the clinical acumen of a far-from-mainstream Indian pathologist, S. N. De to overturn the Kochian ikon, no longer ago than 1951.

These iconoclasms are no mere academic exercise. Tens of millions of human lives have been hostage to the intellectual confusion of the prior mythology. Is there a common thread to them? Dimly I see some vestiges of vitalism, a refusal to recognize mechanistic explanations of living cells' behavior, and a resistance to Darwinian theory. Pasteur himself, in his quarrel with von Liebig, denying cell-free fermentation, exemplified that tendency. Even when they repudiate vitalism in principle, some biologists still act as if life is so complex as to be beyond the scope of the human intellect. There is also the idol of the "Dragons of Eden", that the tree of life is guarded by sacred guardians that humanity dare not challenge. Do not smile: in Washington, suits have been filed against the US Department of Agriculture for infringements on the "Telos" of barnyard animal species. In some quarters, "Evolution" has been deified. (Not that we dare disregard the delicacy of evolved ecological webs.) If that god prevail, we should not rely on the human species having any privileged place in its purposes for the future of the planet.

Other fields, most notably genetics and neurobiology, have been impeded in similar fashion.

6. It is an extraordinary anomaly in the history of biology that the human chromosome number was erroneously recorded, as 48, until 1956. The human cell was simply not a place one probed. Until that number could be accurately rectified, 22 pairs of autosomes and one pair of sex chromosomes, the field of human cytogenetics could hardly be initiated. Promptly after 46 was understood came the reports that illuminated Downs syndrome as a redundant 21' chromosome, and we could begin the map the entire

set.

7. When Johannsen introduced the term "gene" in 1909, he promptly cautioned against assuming it had a material basis. Further, he insisted that many genes might influence a given character and vice versa. At a time when "protoplasm" was widely assumed to have vital properties (rather scantily veiled vitalism), he was perhaps defending against the expected criticisms of others rather than exposing his own convictions. Those cautions were justified for many characters that are manifest as the end results of a long epigenetic chain of cellular events. They were nevertheless an unwonted source of resistance to the ideas finally enunciated by Beadle and Tatum in 1941, that all enzymes are primary products of chromosomal genes. Data to support that view had been tabled long since by Garrod, but he barely hinted at a like theory of gene action. I believe that as a physician he felt intimidated by the world-view of the genetic profession.

Mechanism is now firmly in the saddle in contemporary biochemical research. This is no guarantee against mythical errors. I confine myself to biological studies.

8. The presumption that only proteins could have enzymatic activity has made even more exciting the recent findings of ribozymes -- RNA molecules that mediate their own chemical transformations.

9. Who would have doubted the dependence of terrestrial life on energy inputs from the sun -- until the recent discovery of the thermal vents on the ocean floor, and a rich biota that is fueled by chemical seepage from primordial sources beneath the crust. These findings may give additional credit to Tom Gold's geological iconoclasm that some natural gas and petroleum may not be of paleobiologic origin.

10. Have we discovered all the major taxons on earth? We thought so until Carl Woese's increasingly persuasive arguments for elevating the archebacteria to major phyletic status. Should we believe that is the end of natural historic discovery?

SOME SPECULATIONS ABOUT CURRENT RESEARCH DIRECTIONS

Keeping in mind these historical repudiations of common wisdom, I offer some unconventional and speculative challenges to how we think about some large problems in contemporary biology. Most of them are not new thoughts, but to my knowledge have not been refuted. I know they are mostly wrong; but I am not sure all are. They will surely be addressed, and most of them solved, during the next century. If I could foretell exactly how, I would be wasting no time getting to work on them in the laboratory.

Eobiology (origin of life): Conventional theory makes this a photochemical process of the early atmosphere of our own earth. But the cosmic condensation necessarily involves preeminently light elements, including H, C, N, O. The aggregation of stars and planets is already an exercise in organic chemistry. Many large molecules have now been observed in space. Should we not look there for early chemical evolution, perhaps even of the rudiments of nucleic acids and proteins or their predecessors?

Exobiology ("are we alone in universe"). The cost of radio receivers and of computation may finally be reaching an asymptote that would justify some modest investment -- if not now, in the next decade or two -- in acquiring and processing potentially intelligent signals. We have no way to assess the probability of their occurrence. As to the solar system, the 1975 Viking mission gave a discouraging report on Mars; but it is wrong to foreclose the possibility of microhabitat refuges -- especially at modest subsurface depth -- perhaps from a more hospitable epoch in that planet's history. The thermal vents on our ocean floors offer an interesting analogue of such habitats.

The Epigenetic Dilemma.

The central model of cellular differentiation must reconcile:
a) the orderly delimitation of gene expression in embryonic cell lineages.
b) the clonal inheritance of these self-sustaining differences,
c) the apparent reversibility of these effects in some stages.

On account of (c), we usually assume the genetic uniformity of all somatic cells, and therefore that epigenetic cell changes are epinucleic, i,.e., they do not alter the primary informational sequence of the DNA, but involve secondary structures or lateral attachments like methylation, histones, etc. However, the dogma of genetic uniformity of somatic cells was overthrown with modern concepts of antibody formation. This is unlikely to be the only exploitation of nucleic diversification of somatic cells. Many mechanisms of reversible nucleic differentiations are now known in prokaryotes. Should we abandon the search for epinucleic explanations? I favor an eclectic perspective; but we have still to find a robust example and rationale of epinucleic transmission. We seek a consensually accepted experimental model, not just of modulation of gene expression, but also of its quasi-stable inheritance without nucleic alteration. The field might look for a Max Delbruck who would establish some discipline about the models to be pursued, as he did in plying phage T2 forty years ago.

More attention should be given to grossly obvious histological differentiation of nuclear and chromosomal structures -- the bands in polymorphs, the dimples in monocytes must be epiphenomena of underlying chemical differentiation; and I will be rather surprised if they are not associated with fairly specific segments of DNA information and their current expression. The recent explorations of human fragile-X chromosomes show the value of correlating morphological and molecular-biological observations.

Aging

Here too, we have yet to establish a consensus on what phenomenon we are investigating, what would constitute an explanation. I suggest we use as a standard the difference in lifespan between human and mouse: are there any cellular attributes that can be correlated with that outcome?

Cancer

The paradigm of the oncogene is properly taking hold, and I do not dispute it. My remarks are on another tack: to ask whether chemotherapy or radiotherapy can really be explained as eradication of all tumor cells. This seems very doubtful, and the collaboration of endogenous biological defenses must be involved. If so, it has been mischievous to focus on modifiers

like interferons or interleukins as sole therapeutic agents to be tested as single agents. They must be examined as adjuvants to cytocidal agents.

Heart Disease

The HDL/LDL (lipoprotein) ratio has been established as the best predictor of atherosclerosis. Almost no therapeutic research is founded on efforts to modify this ratio, which is certainly a question of differential gene expression under metabolic regulation in the liver.

Psychiatric disease

Our ONLY leads are a) psychotropic drugs' mode of action, and b)genetic influences in disease. We are beginning to see important studies on DNA probes for polymorphisms linked to disease susceptibility. However, almost noone is looking at polymorphism in drug metabolism, although there are many clinical hints of it. This would reflect the handling of endogenous metabolites.

On Human Intelligence

Are we too wedded to the prewired switchboard model? There is abundant evidence for extensive cell migration, during development. Could this continue throughout adult life, be part of learning? There is recent evidence of cell turnover, at least in song nuclei in birds. Is human cerebral function merely a numerical extrapolation of the neurobiology of lower mammals, or are there higher orders of differentiation of neuronal types in the human brain? Else, Why is so much nucleic information uniquely expressed in the brain?

Physiology, Anatomy -- Some orphans.

That exercise influences muscle hypertrophy is an everyday observation. To understand it and other banalities at a molecular level could have great practical application: not just for Olympic competition, but for maintenance and rehabilitation of the heart and of that organ so uniquely vulnerable in the human, the intervertebral disk. To refer to "compensatory hypertrophy" of muscle or any other organ as a response to functional demand is hardly to explain its mechanism.

Toxicology

Toxic "side effects" are no longer incidental in the process of adoption of new drugs, pesticides and other chemicals: they are the central issue. Toxicology must be elevated from a stepchild of pharmacology to a central position in the health sciences, as one of the most important applications of fundamental molecular biological insight. Most of our expenditure on empirical toxicology is wasted, would better be devoted to mechanistic analysis of toxic effects, especially the interaction of exogenous chemicals with oncogene mutation and expression.

The paradigm of comparative toxicology would seek a fundamental understanding of the similarities and differences of human responses to chemicals compared to other species. We can protect human health only by well founded extrapolation from simpler models. Historically, toxic substances (metabolic inhibitors) had been central to the unravelling of pathways. The study of colchicine helped uncover tubulin; neurotoxins did the same for synaptic mechanisms. However, metabolic inhibitors have been displaced by more sophisticated tools of microanalysis, tracer methodology, genetic lesions for pathway analysis, and the direct isolation of enzymes. These have left a generation only dimly aware of that history.

Public Health and Epidemiology:

We have no good alternative to the blind clinical trial: but this is devoid of mechanistic content. Therefore it tests only the narrowest of hypotheses: the efficacy of the specific treatment, conducted precisely according to the protocol. Its conclusions could be quite misleading about the most minute variations, unless a sensitivity criterion can be established. But blind trials are prescribed today as the essential criterion of adoption of therapeutic regimes.

Parasitology:

When I started compiling this list a decade ago, I felt it important to press not only the humanistic importance but the scientific excitement that would attach to intensified research on protozoan and helminthic parasites. That lesson is one I would hardly have needed to bring to the Pasteur Institute. It was a privilege to work with Jacques Monod and many others on the advisory committees to the WHO that helped support the Tropical Disease Research initiative, and with financial support from many foundations there is now a global scientific network devoted to these problems. The effort still needs much more support and especially from governments. There is no doubt that the field will be one of the most challenging and effective for the application of the modern tools of molecular biology.

The bio-political myth of aggression versus altruism.

It is commonplace to hear how human evolution has not kept pace with and therefore cannot properly control the technologies of destruction in modern warfare. The "ghost in the machine" is purportedly the aggressive instinct, insufficiently tempered by altruism. I can scarcely challenge the problematics of today's human condition; but I challenge the biopolitical model so presented. The root problem may be too much altruism, too little individual aggressiveness, as deepseated human instincts. The main technologies of warfare entail mass mobilization in response to threats to the defined group. Some of the most altruistic self-sacrifices in historical record are those of combatants on behalf of their fellows. It is beyond imagination that organized warfare could be conducted if each recruit aggressively pursued his own narrow self-interest. I offer, further, the gloomy speculation that emergence of altruism, intelligence and mythopoiesis -- the signatures of humanity -- had, as its primary selective driver in human evolution, the pressures of intra-specific conflict, viz., warfare with other human groups. This is not a cheerful contemplation; but if we are to seek remedies for the psychic roots of global problems, better that they be correctly diagnosed. One answer is of course the global cultivation of human intelligence, and the accumulation of a culture of socializing traditions, to harness aggression and transcend misplaced altruism. The prescriptions are futile, however, until they can be symmetrically applied to competing groups.

Partly on account of the anxieties raised by international economic competitiveness we are experiencing a new debate about the optimal styles of organization of science. This is a reflection of old controversies about needs for relevance or early application, which have caused much grief in many countries, perhaps most of all in the U.K. Biomedical science has been stressed by such demands, but far less than, say pure chemistry or mathematics. The debate now has a new wrinkle: the availability of intricate but costly technology -- like the supercomputer -- has raised questions about the need to restructure even basic research. It is said that existing academic departments interfere with cooperative work across disciplines, and that regroupings are necessary to share in the justification of costly equipment. This is not controversial for "Big Science" instruments like particle accelerators or large telescopes. But there is an itch to invoke similar principles to establish new "centers" devoted to particularized objectives for science on a smaller scale than the national laboratories.

This is not the place to prolong a parochial discussion of one country's science policies; but I do wish to register my concern that today's solutions may be tomorrow's larger problems. Some of the root difficulties of inter-disciplinary effort and other innovations are that, in the US, support for science is too much tied to specific, pre-approved projects. If we could just identify the most creative people and give them the freedom to make their own affiliations, they will do a better job than imposing fixed structures on them. There are mega-projects looming that will, nevertheless, impinge directly on how we go about the pursuit of molecular biology during the next century: in particular the proposed sequencing of the human genome.

This is a structure of formidable complexity: 3 billion nucleotide pairs of DNA, a full ~~three~~ meters of double-helix if unravelled from a single cell. If, as is widely assumed, about one percent of that total length is transcriptionally active, about 100,000 gene products will have to be accounted for. The ultimate reductionism would be to build an analytical factory that could complete the reading of all 3 billion units as one technical exercise. A price tag of a few billion dollars is cited, perhaps less if there is prior investment in new technology to automate the task.

Is it worth the cost? Undoubtedly. Is it the wisest use of that level of expenditure? I have very grave doubts. Part of my reservations have to do with the style of research it encourages, part with a misunderstanding about what we need to learn in "mapping the genome".

We have by now profound information concerning a score or so human proteins; each of them is at least a life's work. At a modest $10 MM each, that would amount to a trillion dollars for the full set; and obviously we must make discriminating selections of targets before committing to the task. About a hundred human proteins are now discernable as agents of important biological activity; that number will soon grow to perhaps a thousand, these should be the priority list for further inquiry. It will be far more important and more feasible to learn in depth about that percentile of the human genome than to have an exhaustive listing of a sequence of 3 billion nucleotides. For these, we will look in detail into regulation, three-dimensional structure, genetic variability within and between species, physiological interrelationships and therapeutic applications.

To pursue such enquiries will take much more than the engineering mentality that would apply a single methodology for a single sweep. It will need a sense of the organism, and a focussed expertise on, even fascination for the parts under scrutiny.

This mega-proposal is, however, a plausible extension of the "project mentality" I mentioned before. It is most appropriate to what I call the exploitative phase of discovery. Exploratory research engenders revolutionary breakthroughs with new perspectives; the agenda for exploitative science then becomes fairly obvious. Exquisite technical skills are to be recruited, but not too much imagination. Such projects can then be fairly readily judged by objective reviewers. There is little likelihood of plans being disrupted by totally unexpected discoveries -- though this may happen even in the best regulated laboratory. Precisely because the DNA-sequence paradigm is so central to modern biology, it does set the agenda for almost all of the foreseeable, the plannable research at least of the next couple of decades. My fear is that it may also submerge new revolutions, not unlike the ones that initiated us into this phase of the history of biology.

DNA-sequencing is, however, so central to biotechnology that I have little concern whether it will be adequately supported over the next few decades. I heartily agree that desperate exigencies like AIDS and the need for vaccines for third world disease require a large public investment as well.

My recipe is that we not overlook exploratory research, often best done in the context of natural historical observation -- the field of view may be under the microscope, or at the hospital bedside, as well as the open countryside or the oceans. Such research is often not informed by a prior theory (or one not much more than a hunch, like my own 40 years ago that bacteria might in fact be crossable). It must of course be supported by much the same conceptual intricacies and instrumental methods as is exploitative work; but it takes the past less for granted; it waits for Nature to show new tricks.

For many years we have taught that advances in medical practice would be the fruit of prior scientific progress. This was surely the Pasteurian lesson, and it had much truth in dealing with infectious disease through its culmination in vaccines and antibiotics. Sometimes forgotten was the historical fact that much scientific advance, much of the foundations of the germ theory for example, eventuated from feedback from clinical observation raising scientific questions and offering some clues to their solution. The epic instance is the discovery of the genetic function of DNA by Avery, MacLeod and McCarty in 1944. This was a product of a research program that had its roots in seeking serotherapy of pneumonia. That in turn required looking at antigenic variation in the pneumococcus, and an inspired stroke by Griffith to trying transforming one variety with extracts of another. Only the medical significance of the pneumococcus could have justified so much attention to its natural history. But if Avery had been obliged to defend his group's quest for the transforming factor, it is doubtful any group of experts, reviewing such a research proposal, could have forecast its significance.

Constitutional disease (heart disease, cancer, psychiatric disorder) surpassed infection as a public health problem around mid-century. At that point, the teaching "science first" was no longer an accurate portrayal of therapeutic advance. In fact the

science of the human constitution was hardly up to the task. The most important advances in practice were semi- empirical, e.g. the drugs used in cancer chemotherapy. To this day, we have no insight into their organ specificity or their therapeutic index; and I have grave doubts whether their cytocidal effects are more than the beginning of their mode of action. From 1950-1980 most pharmaceutical innovations were substantially empirical, the result of vast screening programs. The quest for antibiotics was rationalized by the perception that they could be found as secondary metabolites of soil microbes. We still argue what their ecological function may be; and we learn a good deal of cytophysiology by exploring their mode of action after the fact. Subsequently, structures (like beta-lactams) found to be bactericidal may be the subject of random synthetic chemical variation in a quest for further activities.

The same applies a fortiori in the development of psychopharmaceuticals. Without exception these were empirically discovered; in some cases they prompted further studies of mode of action that have contributed importantly to neurobiochemistry.

A similar story can be told of one of our most important drugs: aspirin. The elucidation of willow bark as an inhibitor of the prostaglandin synthetase system was a most worthy citation for a recent Nobel prize.

In this decade, we are seeing a turn-around. Just when there has been accumulated skepticism about so much investment in basic research, it has begun to bear abundant fruit. Most recent pharmaceuticals have been the product of calculated search for compounds that would bind to targetted receptors, like angiotensin-converting-enzyme or beta-receptors or calcium-channels, or enzymes in the biosynthesis of cholesterol. And biotechnology has offered the means of production, increasingly often even discovery, of polypeptides and proteins important in functional regulation.

I have already offered a recipe, to sustain an eclectic balance between deductive and inductive approaches to scientific discovery, in some sense between the Appollonian and Dionysian styles. This is not accomplished very well in our current educational regimes. The Ph. D. degree is all too specialized: students in a biochemistry department even in a medical school are unlikely ever to see a patient; the M.D. students rarely visit a research laboratory. To wait for both degrees is to be a perpetual student. In the U.S. there are almost insurmountable financial incentives for M.D.s to enter the high-earning specialties, and pay their educational debts, and against going into a research career, whose material compensation is in inverse proportion to its fundamental significance. Undergraduate education is an ever narrowing strait between remedial makeup for the failings of the secondary schools and premature enrollment in a graduate specialty.

The Ph.D. graduate must look forward to a lifelong career of seeking project grants. His most promising years may be those in graduate school and as a postdoctoral fellow when he at least has the administrative and financial shelter of an established laboratory. We should not lose sight of the often contradictory demands on the scientific personality: antitheses such as imagination vs. critical rigor; iconoclasm vs. respect for established truth; humility and generosity to colleagues vs. arrogant audacity to nature; efficient specialization vs. broad interest; doing experiments vs. reflection; ambition vs. sharing of ideas and tools -- all these and more must be reconciled within the professional persona. They are intrinsic to the nature of science. We should work hard to avoid piling on gratuitous stresses that discourage, perhaps even deter, some of the worthiest young people seeking scientific careers today.

The M.D. contemplating research today faces the added complication of widespread confusion about the nature and future of clinical investigation. Research ON patients is indispensable for answers to many urgent medical problems; it is also very difficult to conduct with the rigor and efficiency of laboratory studies. No wonder that the majority of papers in the Journal of Clinical Investigation concern animal, tissue-culture, or cell-free models! Lamentably, many M.D.s who remain in research have fled clinical problems altogether, with an obvious wastage of individual and social investment in their clinical education. The ideal example is clinically informed investigation, conducted with the most efficient tools on the part of medical scientists who remain involved in clinical practice, are inspired by their observation of disease, and may return to experiments on patients at the appropriate stage of elaboration of principles worked out on more amenable models.

In our role as mentors, there is one universal: we can set a good example of not fearing to display our ignorance: in the way we present our seminars, and how we ask even "dumb" questions. Some may feel that is no voluntary calculation on my part. Too many presentations are self-congratulation about what we have accomplished rather than a sharing of perplexity about what remains to be learned.

My final remark about scientific process: we don't understand it very well; and we have not been much helped so far by those few Olympian philosophers who have attempted to analyze it. There is little authentic descriptive data on how discovery was actually accomplished. Even when there has been a singular "Eureka!", there is usually a more complex process of confirmation, refinement, reconstruction of context, social dialectic of acceptance, resistance, and remolding. In a tradition solidified by Claude Bernard, our publications are recipes and rationalizations after the fact; rarely do they describe the stumblings and false starts: so Medawar called them lies. They do little to teach how science is done; and they give too much inappropriate support to those who think that scientific discovery can be planned and written up in advance in project proposals.

SOCIAL MILIEU

The sporadic campaigns for a return to primitive nature and against technology notwithstanding, there is no sign of a diminished appetite of the world's people for the fruits of scientific and technological advance. People are worried that they may have to make ethically difficult choices which probe their innermost values -- and these are often bitterly argued. They also worry (appropriately) about the shadow of nuclear destruction. We have to tell them it is the unrepealable laws of physics that make bombs possible -- and that would be at least half right. The most irrational demands are for perfect environmental safety, for zero pollution (in the face of the immensity of Avogadro's number). All of these issues are amenable to public education about the substance of science -- much has been written about the disgraceful state of that, at least in American schools.

More deepseated are cultural changes that challenge authority: the secular priesthood of scientific expertise no less than that of abandoned beliefs in traditional religion. Personal privacy is jealously guarded even in the face of overwhelming threats to public health. Animals are being invested with ethical and legal rights in an extension of democratic principles. Many people expect to get all the benefits of medical innovation while encumbering the process with an ever-increasing bureaucracy; and of course many livings are to be made by the officers and lawyers who police science and medicine. I do not expect much amelioration in these tensions: they are almost inevitable byproducts of the disestablishment of given authority. Science will be slowed down, but it can accomodate to these challenges.

I am more morally troubled by the individualists' selfish preoccupation with micro-ethical issues. There is enormous publicity given to the fate of one frozen embryo; the avertable death of 3 million children per year, from disease that can be prevented with known vaccines, is all but ignored.

Fears about the hazards of recombinant DNA are recurrently incited, and they take ready root in a public that has an almost theological (or diabolical) preoccupation with DNA, and one which especially has no competence in the assessment of risk under uncertainty. It should be understood that work with recombinant DNA is not an idle game: without it, for example, we would be virtually helpless in dissecting the AIDS virus.

We can argue that our HIV predicament has followed almost syllogistically from our neglect of the health problems of the third world. It was predictable that those populations would be ideal foci for the evolution and seeding of novel infectious agents. HIV has an insidious quality that transcends what anyone could have imagined for an emergent virus. I am certain that it will not be the last.

The hazards of monoculture of our main food crops, their consequent vulnerability to devastating plant diseases, have had much comment (but little responsive action). The global conditions of modern life : the combination of crowding, an underclass of neglected people exposed to zoonotic infections, primitive health facilities, rapid jet transport and selfish individual behavior are almost designed for similar evolutionary outbreaks of human disease. Our enormous advances in chemotherapy for bacterial infection are so far not matched for viruses; we are barely beginning to learn the specializations of viral metabolism that would provide targets, and there is no assurance they will work.

That the apocalyptic challenges to humanity are hunger, overpopulation, pestilence, and war is so truistic that one may be shy about repeating the reminder. We have all dedicated our scientific endeavors to do all possible to meet them -- we do not often get requisite political and social attention. I am all the more grateful that President Mitterand and M. Elie Wiesel will be holding a convocation here in Paris in January for a serious mobilization of intellectual and moral concern about humanity's needs.

Their program would be in wonderful harmony with Louis Pasteur's remarks on his 70th birthday:

'...Do not let yourselves be tainted by a deprecating and barren skepticism, do not let yourselves be discouraged by the sadness of certain hours which pass over nations. Live in the serene peace of laboratories and libraries. Say to yourselves first: "What have I done for my instruction?" and, as you gradually advance, "What have I done for my country?" until the time comes when you may have the immense happiness of thinking that you have contributed in some way to the progress and good of humanity. But, whether or not your efforts are smiled upon by fate, what really matters in the end is to be able to say: "I did what I was able." '