# "the war of time against the soul of man..."

—Alfred, Lord Tennyson

## An Interview with Mark W. Bitensky

by Judith M. Lathrop

**A scientist cannot be asked to do research in an adverse milieu just as a pianist cannot be expected to perform a sonata while wearing mittens.**

*In January 1981 Dr. Mark Wolfe Bitensky became leader of the Life Sciences Division at Los Alamos. Behind him he left a professorship in Yale University's Department of Pathology; with him he brought ongoing research in biochemistry and extensive training in pathology, clinical medicine, and molecular biology. Here at the Laboratory he seeks those interactions with the physical sciences that will fashion the powerful tools of tomorrow's molecular biology—tools that address, he says, the human term in the equations of energy and defense.*

*Mark Bitensky is a man who approaches science with driving energy and conviction. As the provocative title he chose for this interview indicates, he is intensely concerned whether the nation at this time fully understands the prudence of basic research. He is well qualified to speak on the subject because of his own life- long dedication to it. He is currently engaged in a three-year study of "Glycosylation of Membrane Proteins in Diabetes ''for the National Institutes of Health and in a twelve-year study of "Light Regulated Retinal Enzymes and Cyclic Nucleotides" for the National Institute of Arthritis, Metabolism, and Digestive Diseases. He stresses the importance of "staying with" a piece of fundamental research for the long term. "Only when you know a field as well as you know your own hand do you have the proficiency to break through established dogma. "*

*Bitensky's enthusiasm for science carries the imprint of the ancient Greek "entheos," and those who share in his research soon share his excitement as well. They collect fond anecdotes of his talent for "relating any and every experience to molecular biology. " There was, for example, the occasion on which he spotted a potent regulator of the brain enzyme andenylate cyclase in the snack he was having for lunch. Subsequent research verified his brown-bag hypothesis. Indeed, a warm smile lights his eyes each time he exclaims, "Today we talked science!"*

*Dr. Bitensky is an acknowledged pioneer in the areas of cyclic nucleotide metabolism and light activated enzymes in the retina. He is a Fellow of the New York Academy of Sciences and has become a perennial lecturer at the Gordon Conferences on cyclic nucleotides and sensory transduction. When he speaks of the creative force of excellence in science, he is not just indulging in rhetoric: he is very much involved.*

**SCIENCE:** *Dr. Bitensky, the title you have selected for this interview suggests a serious conflict with time. Do you feel we do battle with time in attempting to shape our research goals?*

**BITENSKY:** I wish to tell you a parable that is attributed to an ancient Buddhist monk. He was examining a newly completed building in a previously unused portion of the temple grounds. The structure, without trees or shrubbery, seemed naked, This revered elder asked, "How long will it take to grow such great temple trees as grace the older buildings?" "At least a hundred years," he was told. "Then," he said, "we must plant the seeds at once. "

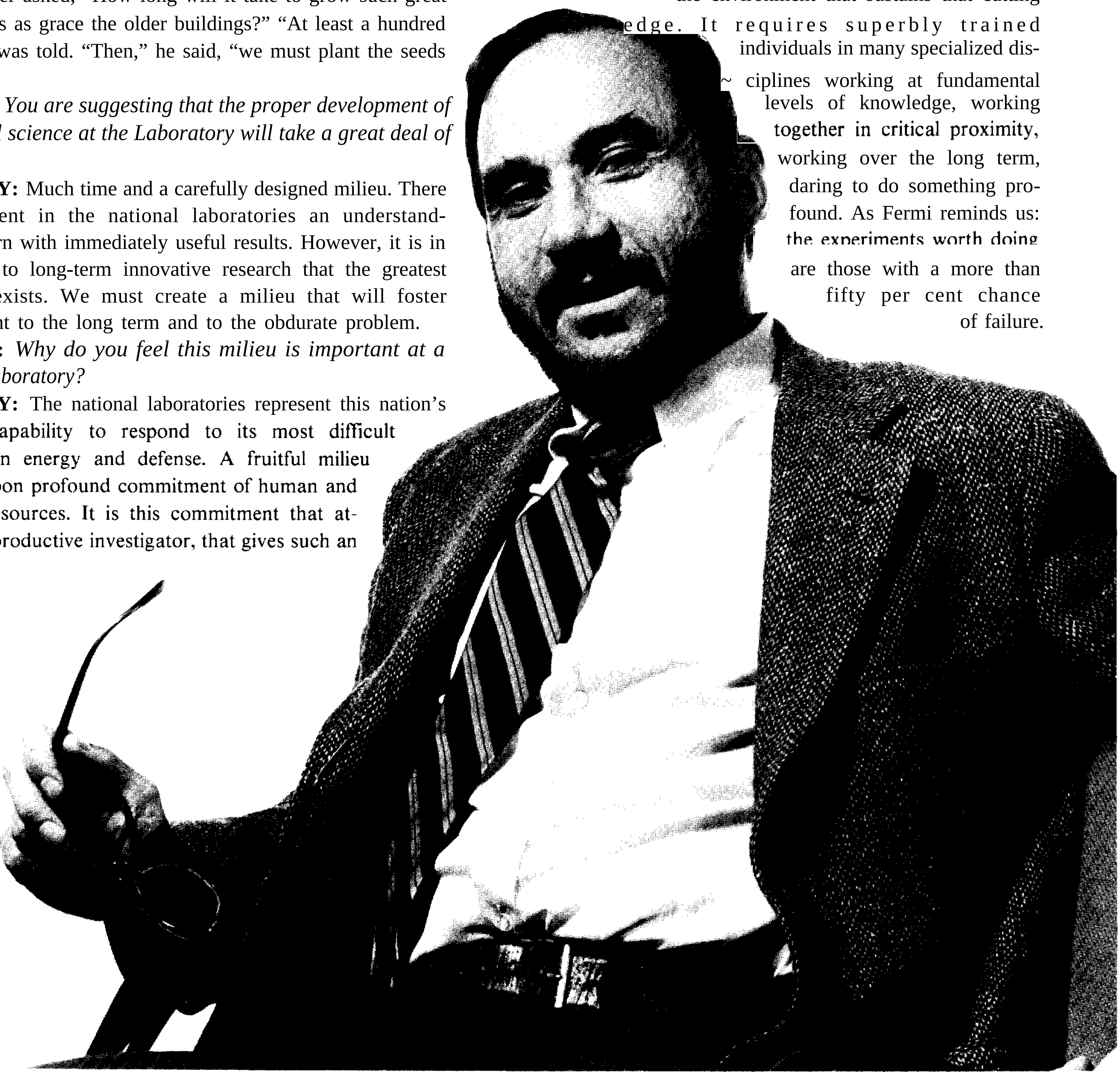
**SCIENCE:** *You are suggesting that the proper development of biomedical science at the Laboratory will take a great deal of time?*

**BITENSKY:** Much time and a carefully designed milieu. There is at present in the national laboratories an understandable concern with immediately useful results. However, it is in dedication to long-term innovative research that the greatest potential exists. We must create a milieu that will foster commitment to the long term and to the obdurate problem.

**SCIENCE:** *Why do you feel this milieu is important at a national laboratory?*

**BITENSKY:** The national laboratories represent this nation's ultimate capability to respond to its most difficult problems in energy and defense. A fruitful milieu depends upon profound commitment of human and material resources. It is this commitment that attracts the productive investigator, that gives such an investigator the conviction that he can commit his life and talents to a particular line of research. A scientist cannot be asked to do research in an adverse milieu just as a pianist cannot be expected to perform a sonata while wearing mittens.

Only science at the very cutting edge has the analytical and technical power to wrestle with the central problems in physics and biology. A national resource like Los Alamos can provide the environment that sustains that cutting edge. It requires superbly trained individuals in many specialized disciplines working at fundamental levels of knowledge, working together in critical proximity, working over the long term, daring to do something profound. As Fermi reminds us: the experiments worth doing are those with a more than fifty per cent chance of failure.



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**INTERVIEW**

**SCIENCE:** *How do you resolve the perennial dichotomy between basic and applied research?*

**BITENSKY:** There ought not to be such a dichotomy. Both applied and basic research can be excellent research—relevant, well conceived, carefully executed research. Of course, there is inevitably work of lesser quality in both categories.

Now, you cannot do superb, meaningful "basic" research without eventually having a wonderful, practical result; and, what is just as important, effective and meaningful "applied" research derives from findings and techniques that emerge from the basic laboratory. At the present moment in the Life Sciences Division, our research emphasizes toxicity testing. We do superb inhalation toxicology, Ames testing, carcinogen testing, mutagen testing. But quality testing can't be done in a vacuum; we can't go much beyond the near term without continuing excellence in basic research, We very much need to invest in more of the high-risk research that takes us into the unknown. This is our window of opportunity.

**SCIENCE:** *You feel that Los Alamos cannot adequately serve the nation unless the Laboratory is engaged and supported in long-term basic research?*

**BITENSKY:** The vitality of all our programs in energy and defense is inextricably bound to present efforts in long-term, high-risk research. Breakthroughs in fundamental research often depend upon serendipitous and interdisciplinary interactions that are the hallmark of the right milieu. The nation must invest in those studies that will define the boundaries of tomorrow's reality,

**SCIENCE:** *Can you show us how scientific interaction and serendipity define the boundaries of reality?*

**BITENSKY:** I can cite the well-known, classic example. Polio vaccine emerged from initially unrelated basic research in virology, epidemiology, cell culture, and immunology. Those were the disciplines that finally interacted in the development of the vaccine. Critical work on the polio vaccine was made possible because people had learned how to grow Green monkey kidney cells in culture. It was this cell type that proved invaluable for subsequent studies of polio virus. No one could

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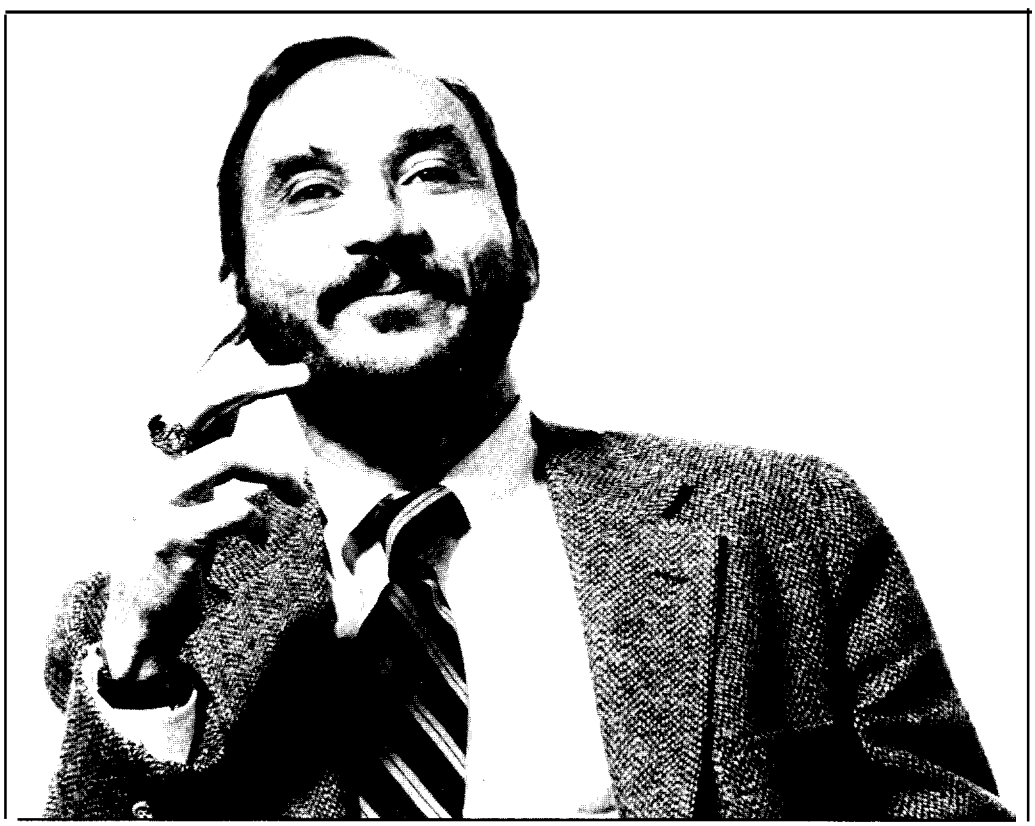

have guessed, when scientists first began growing such cells in culture, that we were a hair's breadth away from solving a major problem. In contrast to the thousands of 1940 dollars needed for daily care of a patient with bulbar polio, we can now administer the vaccine to children for a few pennies per dose.

**SCIENCE:** *Has there been this kind of interactive basic research in Life Sciences at Los Alamos?*

**BITENSKY:** Yes, flow cytometry is a prototypic example. It's multidisciplinary; it uses advanced technology indigenous to the Laboratory; it provides a capacity that didn't exist before; its development depended heavily on both basic and applied research. With it we can rapidly measure cell size, DNA content, cell surface receptors, a variety of cell functions such as phagocytosis, and the shapes and sizes of chromosomes. It's a marvelous and powerful tool, but it wasn't created in a short time. The program began about 1965 under the Atomic Energy Commission and over the years has drawn on the expertise of many Laboratory disciplines: organic chemistry, DNA staining techniques, computer science, electronics, fluid dynamics, laser science, and theoretical modeling. The work brought apparently unrelated technologies together in profound synergy.

Flow cytometry is now used worldwide in research and medicine. At least three U.S. manufacturers offer advanced instruments for sale; the Laboratory has been awarded a five-year grant from the National Institutes of Health to function as a national resource in flow cytometry; physicians from Tokyo to Manhattan to Albuquerque rely upon it to rapidly classify malignancies of blood, brain, and breast tissues.

Another example is the program in stable isotopes that has developed in the Chemistry-Nuclear Chemistry and Life Sciences divisions. The program is making an innovative effort in the study of metabolism. Stable isotopes of carbon are being used to study the metabolic function of cells. These living cells need not be disrupted to be analyzed. Using topical nuclear magnetic resonance spectroscopy, one can follow the flow of sugars, amino acids, and lipids into and out of larger molecules. One can actually observe a hormonal influence spread through a living cell. This technique may be available for totally noninvasive clinical metabolic studies within the next decade.

Offhand, this basic program may not seem critical for either defense or energy. But stable isotopes have already been used to produce tracer molecules that provide precise information about wind flow patterns, information important to defense. Stable isotope studies in cellular metabolism may also help us anticipate and avoid potential health hazards associated with the development of oil shale or other fossil fuels. They could also provide useful tools in our studies of the movement of toxic chemicals through the environment.

**SCIENCE:** *Can you indicate how energy-related studies in the Life Sciences Division evolve into long-term fundamental research?*

**BITENSKY:** An illustrative example has emerged from studies of the metal cadmium, which is a significant contaminant of coal and shale. Cadmium is known to be extremely toxic to living cells, and most known living forms have developed a protective program consisting of sulfur-containing proteins. These proteins are quickly synthesized (>20,000 copies per cell) in response to heavy metals. Each protective protein can bind seven molecules of cadmium and thereby prevent cellular toxicity. Genes for these protective proteins have been cloned and sequenced by our genetics group and are now being studied. Studies of the regulation of gene expression are of central importance to our programs in cancer cell biology.

**SCIENCE:** *You spoke a moment ago of the window of opportunity and of the need to invest in high-risk studies, What are some of the investments you think Life Sciences should be making for the future?*

**BITENSKY:** We should have the courage to invest in areas of biomedical research where we could exploit the scientific strengths that have been assembled in the national laboratories. We have made virtually no commitment to the sciences of neurochemistry and neurobiology, burgeoning areas which will come to depend more heavily upon sophisticated electronics and computer science.

We must learn enough about the brain and spinal cord to be able to replace damaged parts of the nervous system with prostheses, to be able to reconnect isolated neuronal components, to be able effectively to replace sense receptors. We must attempt to learn enough about data processing by the brain to use such knowledge for computer science.

Now, to some extent that is already happening here at the Laboratory. In the Theoretical Division George Zweig is making a unique effort to discover the algorithms of sensory transduction in hearing: all the events that proceed from the initial sound oscillations in air to the corresponding events

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within hair cells in the organ of hearing, to our final full preception of meaning. Through painstaking data analysis of electrical recordings from the acoustical nerve and its associate neurological centers, possibilities emerge for understanding the brain's translation of spoken sound into meaning.

**SCIENCE:** *You've been describing revolutionary discoveries. Can you tell us one or two of the practical developments that can be expected?*

**BITENSKY:** There are countless practical and productive applications. A laboratory-scale, or "bench," retort is now operational in Life Sciences Division. With this practical research tool we are carrying out a research program to learn more about economic and safe ways to recover valuable hydrocarbons from our vast deposits of oil shale. We are attempting to study how the extraction itself influences the toxic effects of the product; we are attempting to modify the process so that the extraction of energy is maximized and the toxic hazards understood and carefully controlled. Advances in this critical area can have enormous ramifications for energy independence.

Work with photosynthetic microorganisms provides another example. Instead of having perpetually to depend on the dinosaur era for our fuels, we could relax energy needs somewhat by innovative combinations of living organisms and biochemical reactions. Suppose we begin with a photosynthetic organism that efficiently utilizes solar energy. And suppose that organism releases amino acids or other nutrients. A second organism, perhaps a genetically engineered one, might take the metabolizes made by the first and convert them into something we need. Imagine combining microorganisms and sunlight with sewage effluent, as a nitrogen source, and obtaining starting materials for the synthesis of plastics and fertilizers or amino acids for cattle feed.

Japanese scientists are working effectively with microorganisms to produce amino acids by fermentation technology. At Los Alamos we combine expertise in recombinant DNA technology, genetic engineering, bacterial fermentation, solar ponds, and waste management in a fledgling effort to explore these possibilities.

**SCIENCE:** *We can't possibly do it all, can we?*

**BITENSKY:** There is always a danger in trying to do too much. But there is a built-in safeguard in the compelling requirement for excellence. We must also avoid duplication and, whenever appropriate, promote synergistic interaction with our colleagues in academia, the private sector, and other national laboratories. Above all we must also be careful to retain a healthy balance in our portfolio of scientific investments: it must include not only mature and productive programs but also a suitable admixture of high-risk, long-term investments for the future.

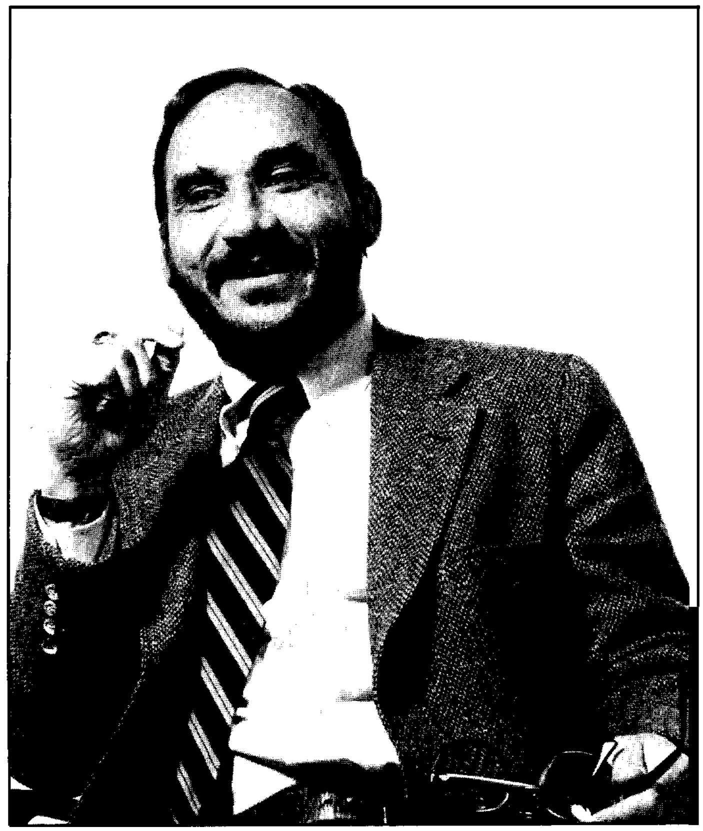
**SCIENCE:** *How can this work for the future best be undertaken?*

**BITENSKY:** Well, it can hardly be undertaken at all under the present conditions of uncertain funding. Nor is it the fault of the funding agencies that national problems are currently being addressed on a moment to moment basis, We seem to lack a clear perception of the multidisciplinary potential at the national laboratories, We need a lucid articulation of the long-term benefits that can come from fully developed life sciences within the national laboratories. We need to understand that this nation can afford long-term commitments to excellent science because that is what fashions powerful answers to our problems. While biomedical research has never been a primary mission of the national laboratories, it is nevertheless remarkable that the most powerful democracy on the planet Earth spends less each year on biomedical research in all its national laboratories than does any one of the world's major pharmaceutical houses on new-product development.

At the moment, hard-pressed funding agencies are constrained to seek immediate answers. We are behaving like a fisherman in an old boat. If the boat is sinking because of a hole in its bottom, he will either plug the hole or bail rather than invest in a new hull design that will eventually enable him to catch a hundred times more fish. The tragedy is that, if our nation, because of immediate and valid concerns for frugality, neglects the advantages of innovative research, we will have designed a self-fulfilling negative prophecy. Moreover, we will have missed extraordinary opportunities for productivity.

**SCIENCE:** *At this moment of fiscal retrenchment, do you see any partial solutions, any immediate and practical steps that can be taken?*

**BITENSKY:** We are having to perform a juggling act with our current funding. Some projects are supported by the National Institutes of Health. Programs relating to health effects associated with fossil and nuclear energy are largely funded by the Department of Energy. At present we receive less than ten per cent of our support from the Department of Defense. It is essential. if we are to serve the nation well, that stable funding



be provided both for our core facilities and for our basic and applied programs. With a more pluralistic, shared form of funding, perhaps deriving from the departments of Energy and Defense and from the private sector, problems at hand could be attacked much more effectively.

Ironically, at this moment, which combines extraordinary opportunity in biomedical research and serious fiscal uncertainty, perceptive administrators both in academia and in industry are out shopping for our brightest and most gifted research scientists.

**SCIENCE:** *How does long-term, high-risk research survive at all?*

**BITENSKY:** It is kept alive in the minds of scientists dedicated to it. Often there are wonderful surprises.

More than ten years ago at the Laboratory, Stan Ulam began to wonder how to describe mathematically the biological distance between two protein sequences. He interested other theoreticians, and they set about developing a rigorous mathematical definition of the problem. Using these mathematical

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approaches and protein sequence data, they tried to deduce phylogenetic trees and rates of protein evolution. Then, about five years ago, there were technological breakthroughs. Suddenly it became possible to determine the sequence of bases in DNA. The results have been quite unexpected in that the mathematical criteria developed for protein sequences have turned out to be useful. Since 1979 Walter Goad and colleagues in the Theoretical Division have been developing computer algorithms for the analysis of DNA and assembling a large library of known sequences in computer-readable form. There is a national program, which includes Los Alamos, for storing in the computer all of the known nucleic acid sequences of mammalian genes. Can the computer find algorithms that will examine DNA and distinguish protein encoding functions, gene regulatory functions, spacer functions? Can it tell whether two genes are related or derive from the same precursor? With this data base, it is possible to design specific nucleotide probes, which can be used to retrieve particular genes from cloned gene libraries.

**SCIENCE:** *Many of these things sound like dreams. Are we really ready to do them?*

**BITENSKY:** Fifty years ago few if any scientists or laymen would have believed that genetically modified bacteria would one day synthesize human insulin or human interferon, that organ transplants would prolong active life, that immunization and antibiotics could virtually eliminate infectious disease, or that certain forms of cancer would be curable with chemotherapy.

Molecular biology has just passed through a phase of remarkable growth in generating many new techniques. And the Laboratory is a natural center for such work because modern biomedicine is the handiwork of the physical sciences. Here the freshly emerging technologies of the physical sciences can provide future biomedical advances; here there is a compelling orientation to the needs of the nation; here each facet of science can interact with every other.

For example, in conjunction with the Center for Nonlinear Studies and the Applied Photochemistry Division, Life Sciences is attempting to learn how biochemical energy is communicated along a protein. The work involves theoretical calculations, Raman and ultrafast spectroscopy, and studies with pure proteins. Such work gets you into areas that a biochemist could not really look at alone; it depends upon a unique combination of talents in the Laboratory; it promises to tell us how molecules assembled in living systems produce signaling events and even muscular movement.

**SCIENCE:** *Is there any one concern that is most important to the Life Sciences Division?*

**BITENSKY:** Our most serious concern is that the nation realize it makes very good sense to invest in excellence in long-term research. In the war of time against the soul of man, we must not acquiesce to the needs of the moment. In this very trying period, when the nation cannot afford to indulge every option, we as a people must pay careful attention to priorities for the longer term. I use the term "pay attention," and attention is a very precious commodity. Over the last fifteen years the United States has allowed the proportion of gross national product invested in research and development to drop by twenty per cent. Over the same period of time, Japan, West Germany, and the Soviet Union have increased their investments in research by the same percentage or more.* In ways neither possible nor relevant for academia and industry, the national laboratories have a perpetual commitment and vigilant interest in the long-term defense and energy concerns of the nation. Too much is being left to chance with regard to assembling excellent biomedical research in the rich environment of physical sciences available at the national laboratories. We must plant the seeds now. We cannot, in good conscience as prudent scientists or concerned citizens, any longer neglect this remarkable window of opportunity. ■

***U. S. Senator John H. Glenn, "'Long Term Economic Rx: Research," Science Vol. 215, No. 4540 (26 March 1982), p. 1569.***

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