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THE END OF THE BEGINNING

by Robert L. Sinsheimer

A few hundred miles from here on the towering cliffs of gorges in Utah and Arizona one can read hundreds of millions of years of earth's history. On that immense scale a foot represents the passage of perhaps a hundred thousand years; all of man's recorded history took place as an inch was deposited; all of organized science, a millimeter; all we know of genetics, a few tens of microns. At odds with our need for stability, prophecy often strains our credulity, but if we remember that scale, what vision can seem too long?

It seems to me to be peculiarly appropriate to our era to ask, in all seriousness, that scientists emerge from their laboratories to exercise their prophetic vision—to become responsible prophets to the people. It has become quite evident that the prime mover of the tides of change sweeping our society is the ever-widening impact of scientific discovery. Those who would, for better or worse, anticipate the future must needs ask those who live on the surging frontier of science what social institutions may next be inundated and what social bonds may next be strained, perhaps to rupture.

The ancient profession of prophecy has a long and not very honorable history. Over the centuries the hardware, if that is the right word, has changed—from entrails to crystal balls to electronic computers—but the percentage of success has remained quite dismal. Indeed, the very persistence of the profession can only be attributed on the one hand to a deep, if dark, belief in causality and on the other to the importance of the issues. Most of us have a conviction that the future will unfold in an orderly manner out of the present. Such a belief is inherent in our culture; it underlies all our morality. If a man could not possibly be aware of the consequence of his actions, what basis could there be for moral judgment? And an orderly nature equally is the basis of our science. Science could never cope with a universe of caprice.

The importance of this problem, of anticipation in a world of flux, is truly transcendent. The injustice and the suffering that might be mitigated had we but a modicum of reliable foresight—*and* the resolution to use it—are so cruel a burden that alone they can justify the persistence of a profession with such a historically low batting average.

In this regard the importance of prophecy—the moral necessity of anticipation—becomes ever greater as we move increasingly into a world of our own making. In our time we are moving out of a world we never made—but were biologically more or less adapted to—into, for better or worse, a world of our own creation, a world shaped increasingly by the motivations and limitations of man alone. We can, and must, and will, direct the form of that world, and how well we do must depend increasingly upon our ability to anticipate the consequences of our acts. The very mission of prophecy is changing from one of almost frivolous whimsy, the role of the gambler's mistress, to one of deep moral responsibility.

But urgency is seldom a substitute for capability. Granted the necessity, can we really hope to do any better than the many oracles of the past? The difficulty of anticipating the future lies first in obtaining a clear view of the present, and second in recognizing those trends that would permit a calculation of the changes to be expected. The one reason that does lead me to hope that *we* may be more successful than were our predecessors lies in my earlier premise—that *science* has become the prime mover of change in our society. For of all human endeavor science is the most open, and its pattern of development would seem the most rational. Some of you may be thinking that that's not saying a great deal, and in any case it is the impact of scientific discovery upon man and society that we must consider, and what of rationality there? But I do think that we can know, and know well, the present status of

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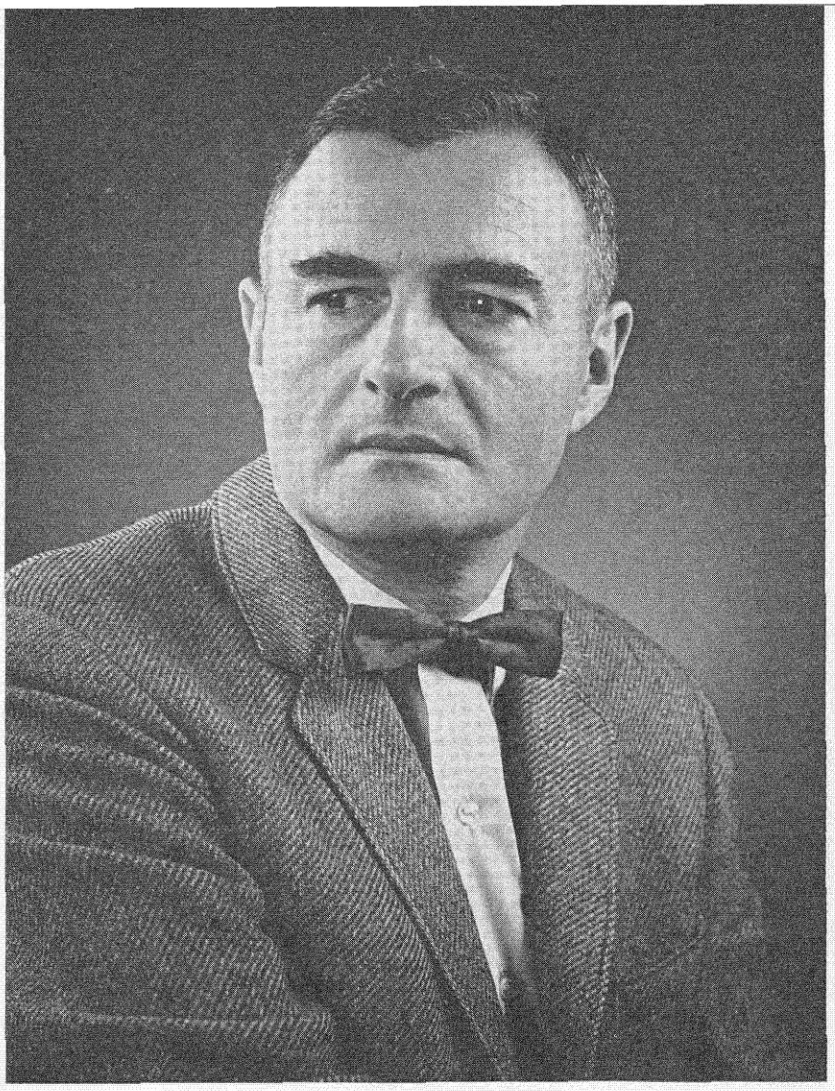

Robert L. Sinsheimer, professor of biophysics.

a science; and we can make quite plausible predictions about the more immediate developments to come in and from it, and this is a long first step.

What consequences may we expect from the recent extraordinary advances in molecular biology? I would like to consider this question on three levels: first, the direct consequences that we may sensibly expect from the applications of this new knowledge to outstanding questions in biology and medicine; secondly, since any such major advance in knowledge changes the whole intellectual climate in which students learn and scientists think, some of the potential consequences of this change in the *Zeitgeist;* thirdly, the impact of these practical and intellectual changes upon our society

The dramatic advances in molecular biology of the past few decades have laid bare the essential molecular mechanics of inheritance, and of the processes of cellular function and control. They have led to the discovery of DNA, the agent and the repository of two billion years of evolution; and to the decipherment of the universal hereditary code, the age-old language of the living cell.

They have led to the determination of the complete three-dimensional architecture of a protein catalyst, a molecule composed of over two thousand atoms, and thereby to an understanding of how this enzyme performs its unique and specific functions. They have led to the analysis and the mapping of the molecular pathways of biochemistry, including the degradative paths that provide usable energy and the synthetic paths that provide the complex and specific macromolecules, so characteristic of and essential to life.

In so doing, a secure base has been laid for *further* advances in our understanding of development and physiology and pathology—a base that can only be compared in this century with that which quantum mechanics provided for the development of modern physics and chemistry. And with this understanding will come the potentiality for intervention and the intelligent control of processes that have known only the mindless discipline of natural selection for two billion years. What we understand we can alter or repair, extend or duplicate, or even translate into other media.

It is probably as difficult for us today to envision the possibilities that will be provided by our new understanding for the control of the biological world as it must have been for our ancestors a century ago to envision the consequences that their new knowledge would bring in our physical environment. For instance, what reception would have greeted the prediction in 1866 that within a century we would transmit telepictures instantly from Europe to California. The analogous predictions that we can make today only seem brash or absurd, or fatuous or fantastic, or even inhuman; but they are all visibly etched on the near horizon.

Consider the proteins of cells, which serve as the catalysts of all the manifold and necessary reactions therein. They are also the structural elements, as in skin and tendon and hair; the contractile elements in muscle; the clotting agent in blood; the detector of light in vision.

We now know how nature makes the vast variety of proteins. We can carry out the process—as yet relatively feebly—in the test tube. But we will learn to do as well as nature. And then the chemist's mind will begin, gently, to introduce modifications; and soon we will make proteins nature never conceived, proteins with new permutations, new amino acids, and perhaps wholly different monomers.

Now, of course, in two billion years nature, by simple selection, has become very skilled; and I do not presume that we will ever make, say, a cytochrome that will perform better in a human cell than does the one nature already provides. But we may make proteins to catalyze reactions nature never conceived, and we may make fibers to perform tasks

that were never intended for natural fibers. And beyond the proteins we will make viruses in the test tube, and beyond the virus at some historic point we will make a self-reproducing cell—the second Genesis.

But before that day, as we understand life we can control life. This has been the historic pattern in physical sciences, and we have today a vast control of our physical environment. We will soon be acquiring a similar control of the biological world. Now the impact of science will strike straight home, for the biological world includes us.

How will you choose to intervene in the ancient designs of nature for man? Would you like to control the sex of your offspring? It will be as you wish. Would you like your son to be six feet tall? seven feet? What troubles you—allergy, obesity, arthritic pain? These will be easily handled. For cancer, diabetes, and phenylketonuria there will be genetic therapy. The appropriate DNA will be provided in the appropriate dose. Viral and microbial disease will be easily met. Even the timeless patterns of growth and maturity and aging will be subject to our design. We know of no intrinsic limits to the life span. How long would you like to live?

And in the end, after all these smaller steps to improve man's lot are taken, we may come to change man himself, his physique, his emotions, his intelligence, all of which are, in large part, the outcome of an inheritance pattern, which too can come under rational control. Not tomorrow. Perhaps not this century or the next. But it is only three centuries since Francis Bacon, and there are many centuries ahead.

In a sense, what I have been saying could have been said once Bacon projected his view of a world subject to rational laws that were comprehensible to man—if only he would approach nature with an open mind and with an unending reference to experiment as the source of truth. Or it could have been said once Mendel showed that the seeming complexity of inheritance could be rationally explained with a few assumptions concerning dual sets of genetic factors. But until now the means were mysterious—and doubt spawns in mystery. Now we have translated those genetic factors into physical entities, and the whole power of physical science is at our call.

These advances have also changed importantly the way man looks at life in the universe and at himself in nature. The kinship of man to the rest of the living world was, of course, demonstrated by Darwin a century ago; but it has now—in the universality of the hereditary code and in the detailed structure of common proteins—been documented anew on the most basic level and over a far wider range. For our molecules disclose our relation to life forms to which all superficial resemblance was lost countless aeons ago.

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Thus man becomes ever more surely a part of life, and in the process life has become ever more surely an integral part of nature. As we have penetrated the processes of the living cell, as the domains of mystery have receded, it has become ever more clear that all the properties of life can be understood to be simply inherent in the material properties of the complex molecules which comprise a cell. And thus that seemingly qualitative gap—self-evident to the most naive—between the living and the non-living has in our time been bridged. Life is but a property of matter in a certain state of organization, and, given an organization which can reproduce itself, then adaptation and natural selection and, consequently, evolution will be just as inevitable a process as is the action of the second law of thermodynamics.

It is then most natural, at least in the flush of our enthusiasm, to suppose that the same is true of the other great mysteries of biology, to suppose that the seemingly magic process of development—the growth of a man from a single fertilized cell—is also but a material consequence of the molecular organization of that cell. Indeed, it may be supposed that even the deepest mystery, the nature of mind and sensation and consciousness, will be understood in the end as a natural consequence of matter in a certain state of organization.

I do not pretend to understand how to bridge the seeming gap between matter and conscious sensation; but I suggest that having bridged one seemingly qualitative gap will give confidence to those who will bridge the next. In time we will come to understand the molecular and organizational basis of memory and emotion and intellect, and we will comprehend the strange spectrum of sensations and the dimensions of consciousness.

We must ask what the impact of these changes will be upon society—and vice versa—for there is an interaction between science and society. The

prospect is awesome in its potential for deliverance or, equally, for disaster.

Much of the structure of our society is very naturally determined by the biological aspects of man. Indeed this state is so natural, and the boundary conditions of our society are so interwoven with the biology of man, that it is often difficult to dissociate them and to see the changes that will become necessary as we change our biology. The life span of man—the size, the sexuality, the diseases, the hunger, the intellectual range and capacity of man, the simple density of man on this planet: these factors do form and underlie our society. And as these change—and the changes have already begun—so must our social structures and our ways of life.

Even some of the most elementary, in the scientific sense, of these prospects, such as the control of progeny gender, will send shock waves through our society. We have throughout history relied upon nature to provide essentially equal numbers of men and women. Shall we continue this ratio? And if not, how shall we arrange it when the choice is ours? When this prospect is combined with the already pressing problem of the expanding world population, it seems ever more clear that in the future world the right to give birth to life, as is today the right to take life, will have to be controlled to preserve some semblance of balance. But how this will be achieved, I do not know. It merits much thought.

Likewise, even modest changes in the life span of man—say a factor of two—would rack our social structure almost beyond recognition.

Eventually we will surely come to the time when man will have the power to alter, specifically and consciously, his very genes. *This* will be a new event in the universe. No longer need nature wait for the chance mutation and the slow process of selection. Intelligence can be applied to evolution.

How might we like to change our genes? Perhaps we would like to alter the uneasy balance of our emotions. Could we be less warlike, more self-confident, more serene? Perhaps. Perhaps we shall finally achieve these long-sought goals with techniques far superior to those with which we have had to make do for many centuries.

Most likely we would like to improve our intellectual facilities. Presumably this can be done. Even nature has had only a limited experience in the evolution of intelligence. It can hardly be thought to have achieved perfection. When cerebral mechanisms are understood, they can doubtless be improved and rearranged—if one thinks this is more desirable than duplicating the process with faster and less expensive transistors.

One may wonder if a brain can really act to improve itself. I think so—within limits. The modes of improvement that the brain can conceive are doubtless limited by its own patterns of thought. Wholly different thought processes might be possible that it could never envision, and this raises a venerable question. Can we *really* change anything? Are we not the prisoners of our nature and our culture—merely passengers on a fantastic streetcar named evolution? Can there be—as I have implied—a free will for a species? I do not know, nor do I think we can know—certainly not now, and perhaps never. Man is psychologically the most plastic, least programmed animal; and by coincidence or by design he is self-aware. Thus he knows conflict, and thus he knows hope.

There are those who will be concerned with the ethics of the potential modification of man, yet it seems to me this issue poses a quandary that is beyond ethics. The foundation of ethics is foresight. It is our ability to forecast the consequences of our actions that engenders our responsibility for them. But how can we possibly predict the ultimate consequence of our alteration of ourselves? Each small step will lead inexorably to another, in a cumulative, positive feedback mechanism to patterns of life and forms of knowledge and even systems of thought beyond our scope. We will have need of hope.

Ours is an age of transition. After two billion years, this is the end of the beginning. It would seem clear, to some achingly clear, that the world, the society, and the man of the future will be far different from that we know. Man is becoming free, not only from the external tyrannies and caprice of toil and famine and disease, but from the very internal constraints of our animal inheritance, our physical frailties, our emotional anachronisms, our intellectual limits. We must hope for the responsibility and the wisdom and the nobility of spirit to match this ultimate freedom.

Alfred Whitehead said, "The art of progress is to preserve order amid change and to preserve change amid order." We must, I believe, devote much more thought to the achievement of that balance in a world always impelled toward change by the anguish of the human condition, and always inclined to disorder by the mindless flux of statistical law. We must ask that the changes we introduce be orderly and with humanity aforethought. At Caltech, and in all of science we have been, in a sense, children, spewing change into society with scant thought for the consequence. We in science are growing up now. Our toys become more potent. The little games we play with nature are for great stakes, and their outcome moves the whole social structure. We must accept our responsibility.