Whither Molecular Biology?

by ROBERT L. SINSHEIMER

It is precisely the unprecedented potential of molecular biology to reconstruct the world of life, so long accepted as given, that requires us to reconstruct our way of life

I AM REMINDED of one of Sherlock Holmes's celebrated cases in which the critical clue lies in a series of seemingly misspelled words. Here, too, it may be that the critical question will be, not *whither* molecular biology, but *whether* molecular biology? As has become the case with nuclear science, questions of molecular biology have become issues of public policy.

Ordinarily, an attempt to foresee the future of a scientific discipline such as molecular biology would begin with a tour of the current frontiers of the field. In the nature of science such an excursion would inherently include a description of adjacent contours recently crossed. One could then proceed, as adroitly and imaginatively as possible, to project the likely future contours and paths, out of the internal logic of the discipline.

In this case, however, it is not at all certain that molecular biology will be free to develop solely according to the dictates of its internal logic. Molecular biology is simply too important. Its insights and its techniques impinge too directly upon too many vital public concerns. Thus, external forces may well channel its future in directions not entirely congruent with those defined by its internal logic. Indeed, I suggest they already have. And the form and consequence of such interactions are not so easy to foresee.

Let me, then, attempt first to sketch some of the directions in which I think molecular biology *would* develop out of its internal logic. Let me then attempt to describe the external forces which I suggest have and will impinge upon this development, and then let me attempt to foresee some likely consequences of these interactions.

The central theme in molecular biology to date has been the recognition that the genes serve as the information bank and command center for the cell (and thereby in part for the organism). We have come to appreciate the constant reference to, the constant involvement of, the genes in the life of the cell. We have established the outlines of gene information storage, replication, and expression. In bacteria we have now a substantial understanding of the modes of control of gene expression.

In cells of higher organisms, however, with an order of magnitude and more greater genetic content, the genetic control mechanisms are necessarily more intricate — and we still lack an authoritative understanding of such mechanisms and their interactions. Various plausible proposals have been advanced for the regulation of genes in batteries corresponding to various states of differentiation. The validity of specific proposals remains to be established.

Varied proposals for control processes effective at other levels — between making of DNA and syntheses of protein — have been advanced with more or less compelling evidence.

The magnitude of effort expended in this field and the steady development of technique and insight make it virtually certain that we will achieve a grow-

ing understanding of the mechanism of gene control in higher organisms. This understanding will carry within itself the keys to the understanding of preprogrammed differentiation and development, as well as of cellular response to all manner of external stimuli — from hormones to drugs, from carcinogens to narcotics, from antigens to transmitters, from radiation to cell-cell contact.

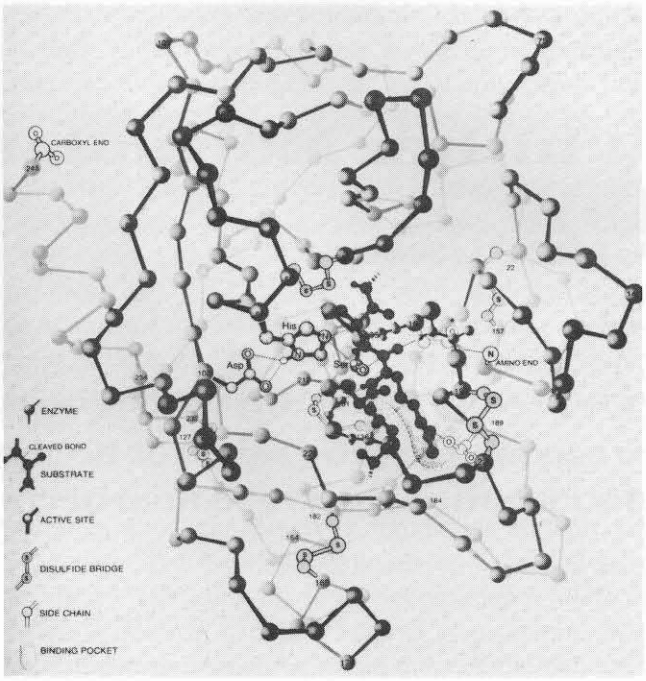
And out of this understanding will develop the opportunity to intervene in the state of differentiation of the cell for varied purposes. Because we have not had such opportunity, I expect we most often tend to accept the particular differentiated state of a cell of a higher organism as given and fixed. We thus forget that each cell, bearing the entire genome, has potentialities far, far beyond those it expresses at any one time. The understanding of the control system would permit us to unlock those potentialities, in whatever combination we might choose. The clinical impact of such a capability must be profound.

Understanding of the control mechanisms may also clarify the current state of confusion as to the function of much of the genetic material — the DNA — of higher organisms. Current insight only permits us plausibly to account for perhaps 10 percent of the DNA of, say, a mammal. Various hypotheses suggest that the bulk of the DNA is involved in the command and control mechanisms — or alternatively, that much of the DNA is currently functionless, free to mutate, and is thus a reservoir of future genes, a glimpse of evolution in process.

In view of the critical importance we attach to DNA it is clearly essential that we achieve a firm understanding of the role of the bulk of this substance. Somewhere, wrapped also in this enigma, lie the keys to the understanding of other current conundrums — of the origin and maintenance of assemblies coding for families of structurally related proteins, and of special DNA sequences that may be involved in duplication and recombination of genes, as means of gene permutation and gene amplification.

But information storage and expression and control are hardly the sole business of a cell. Cells must survive and reproduce — they must literally do things. And for these purposes they need and have machinery. And a second great accomplishment of molecular biology has been to provide a growing insight into the nature and function, the architecture (above), of the molecular machines that do the work of the cell.

We have come to appreciate that even single-enzyme molecules are intricate machines — skillfully adapted to grasp their substrate, to draw it into an environment favorable to the catalysis, and then, the deed done, to release the fragments while returning to the initial state ready for the next cycle. We have learned how the activity of an enzyme can be controlled by simple gating mechanisms which control access to critical regions of the molecule — mechanisms that can be irreversibly displaced as in the activation of an inactive proenzyme (such as chymotrypsinogen), or reversibly modulated by the biochemical addition and removal of small blocking groups (such as phosphate or acetyl or adenogyl).

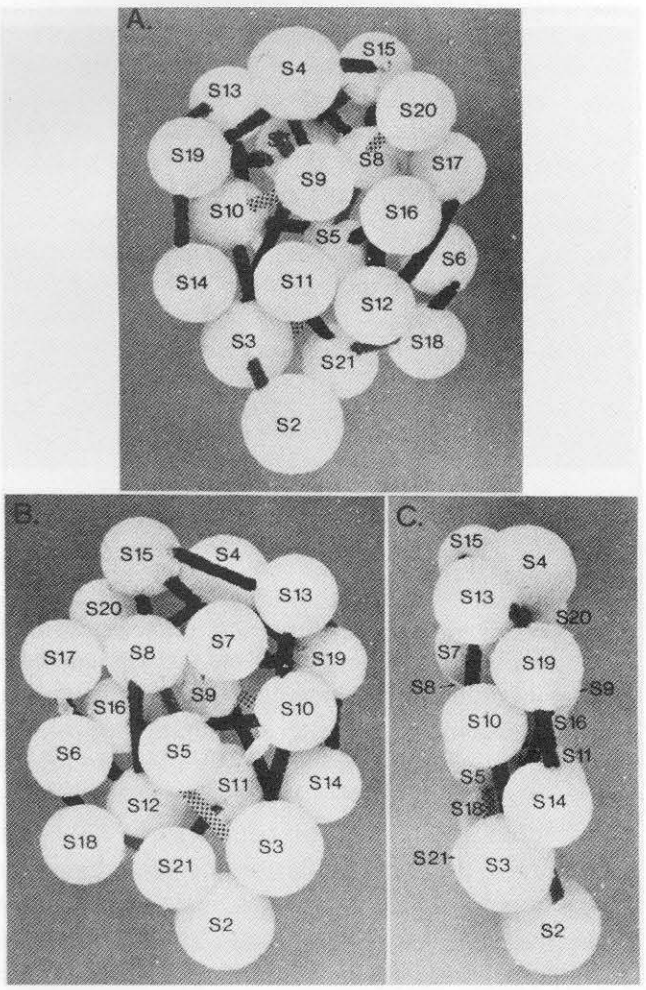


Even single-enzyme molecules are intricate machines — as shown by this molecular model of the interaction between the enzyme trypsin and its substrate.

Multienzyme assemblies are even more evidently machines. For instance, a complex involving 10 or 12 proteins mediates DNA replication; its structure is yet to be elucidated.

The special architecture of the chromosome must certainly relate to its varied roles in the several stages of the life cycle; the nuclear pores, those gatekeepers of the inner sanctum, must monitor and regulate nuclear-cytoplasmic traffic in response to unknown commands.

The ribosome involving some 50-70 proteins and three RNA molecules is a machine of extraordinary versatility, able to translate *any* RNA molecule with appropriate recognition signals (the password, as it were) into its corresponding polypeptide chain. The details of its intricate organization, the structure of its



A three-dimensional model, seen from the top (A), bottom (B), and side (C), illustrates the spatial relationships between the proteins of a ribosomal subunit.

active sites, the mechanisms of its processes (above) are all under intensive study.

As an instance, the extraordinary action of complement — the multienzyme machine found in blood and employed by the immune system to destroy the invader, once it has been recognized as alien — is now well understood. Following fast on this is the appreciation of the clinical consequences of deficiencies or defects in one or another of the elements of this complex defense mechanism.

The achievement of motion — contraction or transport or propulsion — requires an elaborate multimolecular machinery to convert chemical energy into mechanical work. The essentials of this machinery in its more enduring forms — as in cilia and muscle — are now increasingly clear (right). We have also come to appreciate that more transient machines are assembled and disassembled on short notice within the cell to achieve changes of shape, amoeboid motions, ruffling, streaming, and so on.

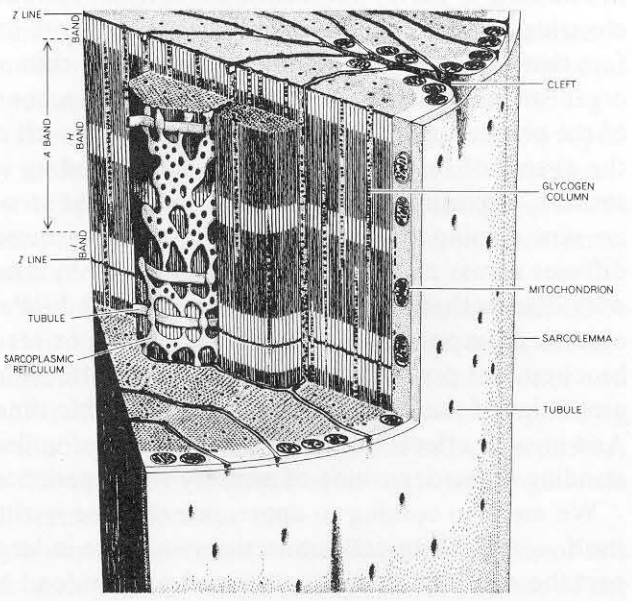
The provision of energy requires even more intricate machines — the mitochondria and the chloroplasts. These discrete organelles segregated within the cell retain for obscure reasons small satellites of autonomous genetic material together with their own protein-synthesizing machinery.

The membranes of the cell are quasifluid machines of extraordinary surface-to-volume ratio. They contain the gatekeepers, the sensors, the packagers, and exporters — the elements involved in the interaction of the cell with the outside world. The surface structures must in some way communicate with the command centers of the nucleus, but the mechanisms of such communication are at present unclear.

Our admiration for these extraordinary devices is enhanced by another circumstance. *Our* machines must be built; molecular machines can self-assemble. This is both self-evident and astonishing. Each component must not only perform its task but must also contain the appropriately designed connecters to couple it to its proper neighbors — and to nothing else within the cell.

The self-assembly of the ribosomal subunit can be reproduced in the test tube, and such studies have provided considerable insight into some details.

Virus particles are elaborate machines, and their



Cutaway drawing of a striated muscle fiber. The achievement of motion requires an elaborate multimolecular machinery to convert chemical energy into mechanical work.

self-assembly has been studied in elaborate detail.

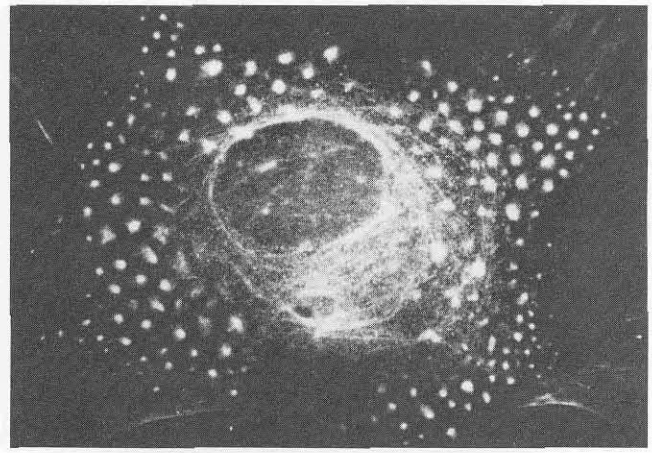
Almost all of this intricacy and elegance is the expression of preprogrammed patterns. We need only recall how an entire bird develops within the egg with no outside intervention to realize the potential latent in such preprogramming. But in the course of evolution Nature has developed more flexible patterns of growth, more open-ended patterns of development capable of adaptive response to environmental circumstance. These mechanisms, which we understand much less well, culminate in the central nervous systems and their associated sensors and detectors — and particularly, of course, in the central nervous systems of higher organisms, birds and mammals, primates and man.

These structures and their capabilities return us to the concept of information receipt and processing and storage, but on a very different level as regards diversity of input, ease of recombination of information elements, and flexibility to develop integrated patterns of processing and response.

Through these organs, these machines of a different order, the external world becomes represented in the internal, and the resultant interaction plays a potent role in the individual development and reactivity.

The evident importance of the electrical signals in these quite different machines and the extraordinary intricacy of their architecture — the wiring, the connections — for some time diverted attention from the evident fact that the elements of these machines are living cells, with the many capabilities of living cells, in addition to their specialized capacity to conduct electrical impulse. It also diverted attention from the fact that this adaptive machinery resides within an organism and that it must recognize and take account of the physiological state of the organism as well as the events of the external world, as reported by its sensors, to produce an adaptive response. And so we are now coming to appreciate that when a transmitter diffuses across a synapse to an adjacent neuron it not only causes that neuron to produce and conduct an electrical impulse — it also initiates longer-term biochemical processes that may in turn affect the properties of the neuron for some considerable time. And in such effects may lie the beginnings of understanding of the deposition of memory and experience.

We are also coming to appreciate that the wiring itself — the cell-to-cell connections — while in large part the result of a preprogrammed pattern, can be varied, certainly functionally and perhaps anatomically, by the effects of early experience, and indeed that the organism has specifically provided for this opportunity in critical periods.



Use of a fluorescent antibody reveals the nodes of the filamentous network that forms the cellular cyto-structure.

It is also becoming apparent that there are neurons in critical sectors that monitor and are responsive to indicators of the body physiology — to hormones, to factors inducing that mysterious change of psychic state we call sleep, and very likely to many others. Very recently it has been recognized that there are endogenous substrates (polypeptides) for the opiate receptors — those molecules on the surfaces of certain neurons to which the opiates bind to thereby produce their extraordinary effects. The function and possible pathologies of these endogenous substrates will surely be of the greatest interest.

Such belated recognition of the significance of biochemical traffic between the central nervous system and the body, in both directions, is certain to have major implications, both clinical and psychological. This is, of course because the central nervous system is more than a processor of sensory data — it is the seat of mood and affect, sensation and thought.

That the brain is chemically differentiated, that it is conceivable chemically to influence different sectors differentially and thus affect differentially sense and mood — even perhaps memory and lucidity — suggests the basis for the development of a molecular psychobiology of a significance to rival molecular genetics.

We *could* then project a future for molecular biology as a logical continuing development, providing increased understanding of these systems for information storage and processing and expression at varied levels, and increased resolution of their associated biological machinery. Such a projection could be reasonably straightforward and offer fascinating vistas.

However, such projections ignore two great changes which are now taking place and which, I suggest, are very likely to introduce major discontinuities into the smooth evolution of molecular biology.

One change is a qualitative transition within the science itself. Molecular biology has crossed a threshold from a purely analytical science to a synthetic science. I refer, of course, to the recombinant DNA technology which permits us to explore biological processes by construction and innovation as well as decomposition. The other change is in the public perception and valuation of science in general. The larger society is both more appreciative of its need for science and more apprehensive of the fruits of science — and is thus increasingly insistent that it play a role in the direction of science.

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These changes clearly interact and reinforce each other. For the invention of synthetic biology, the capability literally to design new organisms, greatly augments the power of biology, both to meet the needs of society and to stir its apprehensions.

With respect to the former, we have already seen the tidal pull upon the patterns of scientific funding, and thereby research and training, exerted by the public concern with certain diseases and disabilities. To the extent that the tide has moved in the same direction as the stream of molecular biology we have been able to flow with it — as in those studies of cell biology which clearly relate to the cancer problem. In other areas, as in heart and pulmonary diseases, the synergism has been much less effective — and still other areas of, for instance, bacterial molecular biology have been left as dwindling tidal pools.

I think it likely that this trend and the associated pressures will continue. We may expect molecular biology to contribute, and to be expected to contribute, ever more effectively to the relief of the infirmities of the human organism — disease and aging, addiction and depression, and indeed, to all the defects latent in the machinery of the body and, increasingly, the mind.

Molecular biology may be expected to contribute more importantly to the relief of certain infirmities of the social organism — to population control and mental health. Further, as society begins to appreciate that molecular biology can contribute significantly to other critical problems — as in agriculture and, very likely, in the field of energy — strong pressures will develop to deflect the flow of molecular biology into directions appropriate to those technologies. We would surely benefit from improved understanding of photosynthesis or nitrogen fixation. It does not seem inconceivable that with imagination we could learn to employ biological energy transducing systems (such as that found in the purple halobacteria) to convert solar energy into usable chemical energy on a massive scale. Such ventures would attract attention and resources to areas of molecular biology currently in relative neglect.

More broadly, while surely inferior to the ideal of support of science for its own sake, I think the development of multiple sources of support and understanding, albeit mission-oriented support, for molecular biology will be to the good. While it is graceless to deplore the hand that feeds you, I believe the predominant support — even though it has been truly enlightened — of molecular biology by a single agency dedicated to medicine has, in fact, already distorted and limited our perspectives.

However, the input of societal pressure will, I expect, not only be directed and positive; it may well be, in certain fields, negative and restrictive — at least to the degree that we may well be required to seek alternative modes to advance our science. I am thinking again of the recombinant DNA area although similar issues may arise one day out of molecular psychobiology when that develops.

The recombinant DNA technology was developed by molecular biologists as a means to solve their scientific problems. However, as a technology it has many, many other applications and implications, some of vast import.

With but modest extrapolation recombinant DNA technology literally makes available to us the accumulated gene pool of the planet to reorder and reassemble as we see fit. It makes this capability available not only to scientists but to entrepreneurs, to flower-fanciers, to militaries, to subversives — to all sectors of society.

In our consideration of the potential hazards of this technology, as exemplified by the Guidelines of the National Institutes of Health, we have predominantly been concerned only with the potential for immediate health hazards that might arise in the course of scien-

tific investigation. I believe this is a very limited perspective which arises in part, inadvertently, out of the sustained impact of the NIH role as a major source of research support in this field. In truth — and we should be aware — we have but little knowledge of the resilience, the coherence, of the intricate web of life support systems of the planet. The possible environmental and evolutionary consequences of this development — the numerous and varied societal consequences — have not yet been adequately addressed. To make my point, one may ask would we have developed the same guidelines under the aegis of a different sponsor?

I think the larger society may well, for its own good reasons, impose major restraints upon the introduction of recombinant DNA technology with its almost incalculable consequences. If so, then molecular biology may well be required to develop alternative ways to achieve its objectives, scientific or applied. Such means are by no means inconceivable, if likely more difficult. If there is a shortage of pancreatic insulin, must it be made in free-living organisms? Chemical synthesis, ribosomal synthesis, tissue culture synthesis are all conceivable.

I suggest we can foresee biology becoming increasingly, although not wholly, a molecular science

Fractionation, and DNA synthesis methods comparable in power, if not elegance, to cloning are also conceivable. The deficiencies of our existent techniques need not oblige us to take risks, small risks perhaps, but in truth incalculable risks, with the only biosphere we have.

Restraint need not mean prohibition, but rather a more thoughtful and orderly progress across a dangerous terrain.

Thus, I suggest we can foresee reductionism triumphant — or nearly so — and biology becoming increasingly, although not wholly, a molecular science. And we can see, emergent from this scientific progress, a new and most powerful applied science — a biomolecular engineering, of which genetic engineering is but the first form — intended to shape the world of life to human purpose, as we have already done to so much of the inanimate world.

But that history will not simply repeat. Society is now aware of the process — the progression from science to engineering to technological and social change — and is, determinedly, groping toward some measure of control over the direction and pace of the sequence.

And, unlike inanimate matter, living matter will not stand still after we have reshaped it. It will reproduce itself and evolve as it has always done, in ways probably beyond our skill to predict.

The external world — the larger society — thus is certain to impact upon the future of molecular biology. If I may draw an analogy, the development of the central nervous system provided a means for internal representation of the external world, past and present, which could then help to shape the development and reactivity of the individual organism. This accomplishment clearly proved to be advantageous and adaptive. We shall have to develop analogous means to represent the external world — the larger society — in the development and reactivity of our science, while maintaining at the same time our scientific integrity. And vice versa, we shall have to make known to the larger society the needs, the capabilities and, with insistence, the intrinsic worth of our science. Such developments will provide increasing and varied opportunities for molecular biology to contribute to human welfare.

As scientists we have not been required to think much beyond our immediate scientific problems — and they are often difficult enough to consume our energies and efforts. If we are called now to realize a larger vision, it may be some comfort to realize that it is our own success that has brought us to this horizon. It is precisely the unprecedented potential of molecular biology to reconstruct the world of life, so long accepted as given, that requires us to reconstruct our way of life.

We are becoming creators — makers of new forms of life, of creations that we cannot undo, that will live on long after us, that will evolve according to their own destiny. What are the responsibilities of creators — for our creations and for all the living world into which we bring our inventions? These are novel questions to ponder.

It is but 32 years since the discovery of the chemical nature of the gene. That we are today discussing how best or whether to deploy genes is the measure of how far we have come and how fast.

We may look in the index of the future under "whither molecular biology" but, with concern — and without conceit — I suggest the answer may be found under "whither humanity." □