Chapter 3

The New Biology

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Chapter 3
The New Biology

Of all the areas of science and technology where rapid advances are now occurring, probably none will have more direct and profound implications for individual rights and responsibilities than molecular biology. This has come to be called "the new biology. " This field of research is producing dramatic new knowledge derived from the increasing ability to map and manipulate the genetic materials in the cells of microorganisms, higher plants and animals, and people; and from far-ranging explorations into biochemical factors in physiological and mental functions.

From the new biology flow two major streams of applications. One deals with genetic engineering in industry, agriculture, and management of the natural environment. The second consists of tools and techniques for analysis, prediction, correction, control, and enhancement of the human body, brain, and behavior.

The first has already raised several direct constitutional issues related to the right to patent new "engineered" life forms, and the right of scientists to carry out experiments that some people perceive as imposing significant risks to human safety or to the environment. It is likely to raise other constitutional questions in the future. The second, knowledge of human biology, affects assumptions about what constitutes human nature, what people are capable of, and thus what they can be held responsible for. New technologies based on this knowledge will also increasingly present people with the necessity for new decisions about life and death, reproduction and inheritance, culpability and punishment.

In order to probe some of these potential challenges in later chapters, it is helpful to review briefly the basic premises and promises of the new biology. Those readers who are already well informed about this area may wish to skip this chapter, which provides a summary in nontechnical language. For those who know little about the new biology, it will be worth some effort to read carefully the following section, as a primer for the discussion of potential constitutional issues that follows in later chapters on genetics, public health, and medical interventions.

MOLECULAR BIOLOGY: WHAT'S IT ALL ABOUT?[1]

In molecular biology the traditional disciplines of biology, chemistry, and physics converge and overlap in the study of the detailed structure and functions of biological macromolecules. These are very large complex molecules made up of several subgroups of atoms. Cells, the basic building blocks of all living organisms, are generally made up of such macromolecules.

Until very recently, biochemistry dealt mostly not with macromolecules, but with small molecules such as vitamins, hormones, and amino acids. This research had many practical applications in nutrition, medicine, and agriculture, and was relatively quickly commercialized in the form of specific products. Macromolecules, in contrast, are made in and retained within living cells and carry out the basic cellular functions. During the first two decades of molecular biology-roughly, the 1950s and '60s– research on macromolecules yielded few practical applications that could give rise to commercializable technologies.

This changed dramatically in 1974 with the development of recombinant DNA techniques. DNA is the basic material in genes. During

[1]Much of the material in this chapter, not otherwise attributed, was prepared for the Office of Technology Assessment by Dr. Bernard Davis, Professor Emeritus of Bacterial Physiology, Harvard University, in the form of a contractor report "The New Biology," May 1987.

conception the DNA in egg and sperm combine and so transmit traits from one generation to the next, from parents to offspring. Along with this continuity, DNA allows for variability, since the traits from two lines of inheritance-two parents-are combined and mixed. An ability to analyze, map, and manipulate DNA opened up both deeper insights into living processes and immense prospects for practical applications. A review of some key steps in the short history of molecular biology, especially the recombinant methodology, shows vividly how much unforeseen knowledge we have gained. It also shows that the advance of science and technology depends only in part on orderly, step-wise research; occasional unanticipated breakthroughs open up new territories that in turn rapidly spawn new information and understanding.

Start With Bacteria . . .

The study of bacteria played a key role in the emergence of molecular genetics. The very small size of these single-celled organisms—about one thousandth the volume of an average human cell—had always been a major obstacle to dissecting their internal structures. There was no science of bacterial genetics until the 1940s—no one had observed either the transfer of genes between organisms or mutations in bacteria. But in 1944 (when pneumonia was a leading cause of death), research on pneumococcus showed that the material of genes is DNA and that it can be transferred between bacterial cells.[2]

Bacteria offer several advantages for the study of molecular genetics: their relative simplicity, rapid multiplication (as many as three generations per hour), and the ease of selecting even very rare mutants from populations of billions of cells. Moreover, the relatively simple viruses that infect bacteria (which are called bacteriophages) have even greater advantages for many studies. Analysis of their life cycle has laid the foundation for understanding the viruses of animals and plants, and gave us the ability to rapidly identify and characterize the AIDS virus, as will be described in chapter 5.

An important consequence of microbial genetics has been the recognition of the remarkable unity of biology at a molecular level. The living world is enormously diverse. Millions of species have adapted to their environment through astoundingly varied structures, functions, and behaviors. But at a molecular level all organisms-man as well as microbe-make their nucleic acids and proteins from precisely the same building blocks, and these acids and proteins function in essentially the same way. The inherited differences between organisms—between, for example, a person and an earthworm-appear to be determined by differences in the sequence of the basic building blocks comprising the genes.

Such basic unity in the midst of diversity gives us, with the development of bioengineering, the ability to make useful products such as insulin by inserting human genes into bacteria. The bacterial cellular mechanism can then produce insulin, illustrating the fundamental similarity in basic proteins and genetic structures. This close biochemical relationship between two extremes of biological complexity-the human and the bacteria—is evident throughout the living world and provides strong evidence for its evolutionary continuity.

James Watson and Francis Crick, in 1953, demonstrated the structure of DNA. Within DNA the basic building blocks are chemical bases, of which there are only four kinds: adenine, thymine, guanine, and cytosine, known as A, T, G, and C. In order for genes to be passed on from one generation to another, DNA must replenish itself. The fact that DNA within the cell is double-stranded, and that complementary bases are paired-A always with T, and G with C—gave scientists an immediate clue to how replication occurs. Thesequence of each strand-the order in which its

[2]The discovery was made by Oswald Avery. Until then it was generally assumed that chromosomal proteins carry genetic information and DNA played some secondary role. The importance of the discovery was not widely recognized at the time. Avery never received a Nobel Prize. Lubert Stryer, *Biochemistry,* 2nd ed. (San Francisco, CA: W.H. Freeman & Co, 1981), p, 562; or G.J.V. Nossal, *Reshaping Life: Key Issues in Genetic Engineering* (Cambridge University Press, 1985).

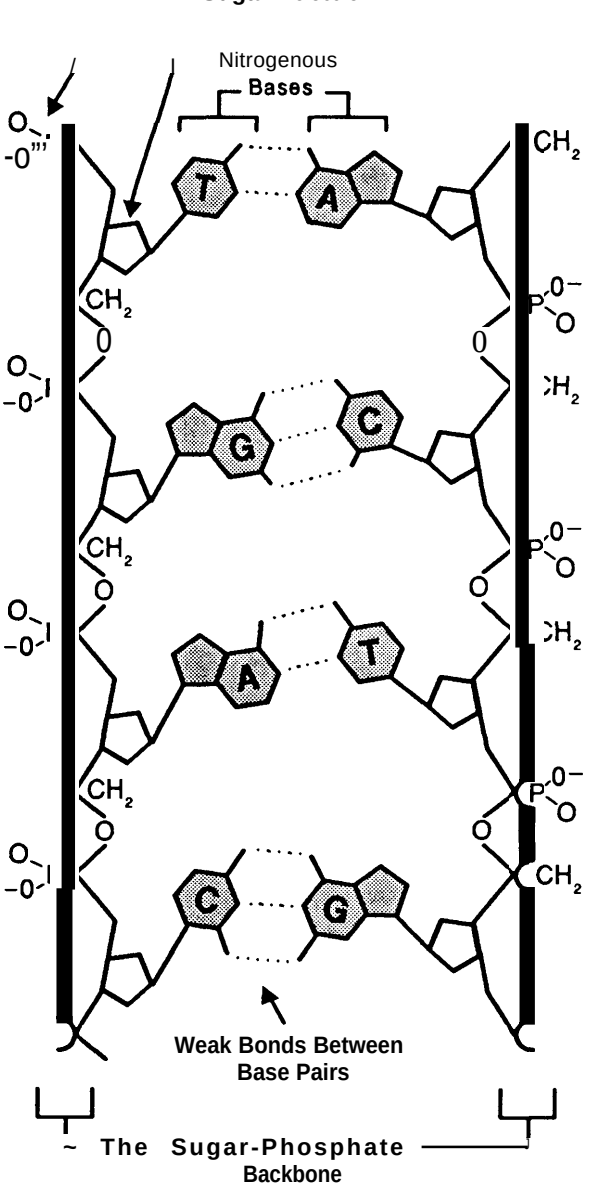
building blocks are arranged-serves as a template for the synthesis of its complementary strand, and hence for the formation of two double-stranded molecules from one. (See figures 3-1, 3-2). Moreover, mutations could now be explained as errors in the pairing of bases during replication.

The research that has grown from the explanation of DNA by Watson and Crick has provided an enormous amount of detailed information about the chemical and biological properties of DNA. Each gene is a sequence of bases within a chain; within bacteria the length of that chain is about a thousand times the diameter of a cell. To accommodate this length within the cell, the DNA chain is tightly folded. The genetic information itself is linear, coded much like sequential sentences in a printed book or electronic signals on a magnetic tape.

There are many kinds of errors, or "misprints. " Mutation eventually turned out to be much more complicated than was originally thought. Sometimes chromosomes (or strings of genes) become rearranged, or one base is substituted for another, or bases are duplicated or deleted when they should not be. Some sequences seem to be particularly transposable; they are often transferred to another site in DNA.

Some of these transposable elements also can be incorporated into viruses that can carry them to other cells, to other individuals, or even –although rarely-to individuals belonging to other species. This also contributes to the increase of genetic variety. Some scientists even suggest that the role of viruses in causing disease may be only a byproduct of a more fundamental evolutionary role in expanding genetic variety. As an analogy, there are only a few bacteria that cause disease, compared to those that play essential roles in the cycle of

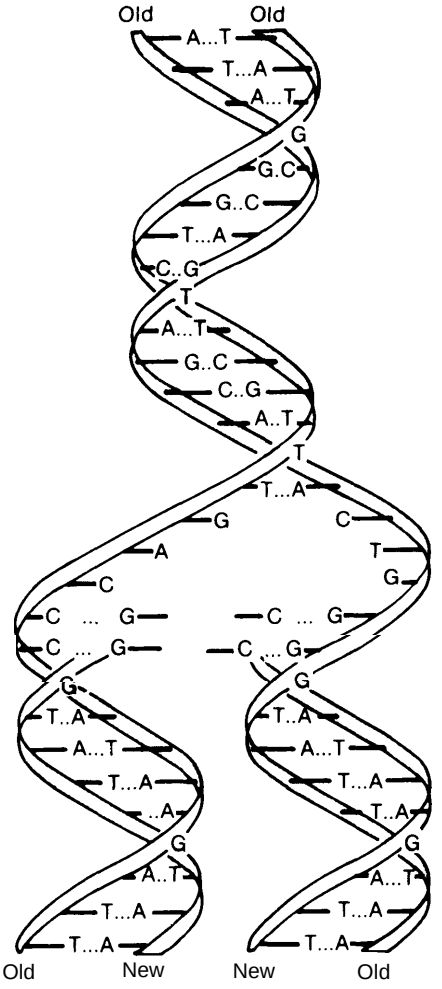
Figure 3-1 .–The Structure of DNA



The four nitrogenous bases, adenine (A), guanine (G), cytosine (C), and thymine (T), form the four letters in the alphabet of the genetic code. The pairing of the four bases is A with T and G with C. The sequence of the bases along the sugar-phosphate backbone encodes the genetic information.

SOURCE: Office of Technology Assessment, 1988.

Figure 3-2.—Replication of DNA



When DNA replicates, the original strands unwind and serve as templates for the building of new complementary strands. The daughter molecules are exact copies of the parent, with each having one of the parent strands.

SOURCE Off Ice of Technology Assessment

matter between the organic and the inorganic world.

From another perspective, however, mutations are rare exceptions. DNA is transmitted from generation to generation with extraordinary accuracy. This accuracy depends not only on the inherent chemical stability of DNA, but on repair mechanisms that recognize and correct most errors in replication and most of the genetic damage caused by radiation, chemicals, or other environmental factors.

The information contained in genes directs the formation of the other molecules that comprise the core of the working machinery of cells –RNA and proteins. In this process a DNA sequence, by "un-pairing" its bases, gives rise to a complementary RNA sequence, and this "messenger" RNA is then translated into proteins. Each successive set of three bases in messenger RNA calls forth a specific amino acid. Amino acids are linked together to forma proteins. This translation of RNA to produce proteins occurs with a remarkably low error rate.

Several different regulatory mechanisms that affect the expression of specific genes have been recognized. Such regulatory mechanisms allow even the simple bacterium to adjust the formation of its components to various environmental circumstances. Appropriate human cells "turn on" antibody genes when the body is invaded by a disease organism. The regulatory elements or mechanisms are key factors in the bioengineering synthesis of useful proteins through the use of recombinant bacteria, as described below.

The more complex regulatory processes in the cells of higher organisms, which are of great importance for medicine and pharmacology, are as yet much less well understood. For example, it is not yet understood why certain processes (e.g., loss of a limb) are effectively irreversible in higher animals, but not in plants.

Recombining DNA: How and Why?

A number of additional discoveries in the fields of bacteriology and molecular genetics led to the development of recombinant DNA methodology, which is popularly called bioengineering. Before this development, the problem of isolating the different genes in a chromosome seemed unsolvable, because they are sequences in a giant chain and physical methods for breaking that chain simply yield random fragments. The breakthrough came with the discovery in cells of "restriction en-

zymes, which destroy unwanted DNA by cutting or cleaving it at a specific sequence. Restriction enzymes can be used in the laboratory to cleave DNA purposefully into a set of fragments with known ends that can be relinked or recombined with other fragments that have complementary ends, by using other enzymes.

By using restriction enzymes and ligation (linkage) enzymes, scientists can now splice a DNA fragment into an appropriate unit and multiply it indefinitely (i.e., "clone" it) by inserting it into an appropriate cell that then multiplies. After years of effort, a simple procedure has been developed to genetically modify the bacterium *Escherichia coli* or *E. coli.* Bacteria contain a single, very long circular chromosome that contains most of the genetic information necessary to function. The chromosome of *E. coli,* a common bacterium living in the human gastrointestinal tract, is some 4 million nucleotide base pairs in length. But like most bacteria, *E. Coli* contain other "accessory" genetic elements that carry genes involved in reproduction and resistance to drugs. These small circular units of DNA are called plasmids and can be transferred from one bacterium to another.

The entire "library" of genes of a mammal, containing around 3 billion base or building block pairs, can be stored in the bacteria in a single test tube. Such a mixture of perhaps 10 billion bacteria will contain thousands of different recombined genes, but the "library" can be separated into "books," or smaller pieces of DNA containing several genes, and each "book" or piece can be inserted indifferent bacteria. Ingenious techniques have been developed for efficiently selecting those cells that have incorporated a particular gene.

What Goes On in a Cell?

Molecular biology has two major branches: molecular genetics and macromolecular structures. The first branch was described above; it aims at determining how genetic information is transferred from DNA to RNA and finally to production of proteins. The second or structural branch of molecular biology aims at determining how these proteins, in turn, carry out biological functions through specific interactions; for example, how insulin controls the storage and processing of sugar. This branch too is contributing to both streams of future technological development, that leading to commercial applications for industry and agriculture, and that focusing on the human body and brain.

As they study biochemical reactions, scientists are attempting to develop enzymes to affect not only naturally occurring compounds but also synthesized or novel organic compounds. Genetic variation in the microbial world is so rapid that microbiologists can now accelerate natural evolution by selecting mutant bacteria with enzymes having the capacity to attack a specific organic molecule.

Researchers are learning that a small number of genes can generate large numbers of unique proteins. For example, antibodies are specialized proteins that attack and destroy foreign substances, or antigens, thus protecting the body from disease organisms. This process requires very specific physical binding of the antibody to the antigen. Specificity results from the unique amino acid sequences of antibodies that are encoded by genes. Although it is known that the body can generate in excess of a million different types of antibodies, there are just a few hundred antibody genes. Recently it was discovered that this enormous number of antibodies can be generated by mixing, matching, and splicing a small number of genes together. It is now known that natural gene rearrangements of this kind are responsible for the generation of many kinds of proteins.

Short synthetic protein chains are already under trial as vaccines. The analysis of the interactions of drugs with their receptors in living cells is also having a revolutionary effect on pharmacology.

[3]An *enzyme* is a complex protein that catalyzes a specific biochemical reaction within the body; that is, causes the reaction to occur without the catalyst enzyme itself being used, changed, or destroyed.

The proteins in cell membranes, including the receptors for hormones and drugs, were long a mystery to biochemists. They seemed part of an insoluble debris. But new laboratory techniques, including the use of certain detergents to make them soluable, have made them accessible to study. Biochemists are now able to make artificial membranes that reproduce some natural biological functions. It is not yet clear how far this approach can go toward reconstructing cells from their components, or toward "tissue engineering" formedical purposes.

In the future, there maybe nearly unlimited possibilities for designing synthetic protein chains for specific purposes. Enzymes produced to order by engineered organisms will be used in the chemical industry, perhaps replacing chemical reagents that are more risky to workers or to the environment.

Enzymes and Proteins: Regulating Life

In the memory of a computer, information is stored in an intricate pattern of switches, each of which may be "off" or "on," represented by O or 1, so that information is put into a code, like 01001001110. Genetic information is stored in a different way, in the linear sequences of four different chemical bases within a giant molecule. Thus it uses a 4-letter code rather than the 2-letter code of 0/1.

For day-to-day conduct of cellular business, cell functions are regulated by still another means of transmitting biological information —special proteins that sense the presence or concentration of some molecule and react to it. This key discovery came about through research that had a more limited aim: to explain how bacterial cells stop making a certain amino acid when it is supplied to them in the medium in which they are grown. In this feedback response, the initial enzyme that begins the process of creating an amino acid is directly inhibited by the end-product of that process, i.e., by the presence of amino acid. This spares material and energy for other purposes when more amino acid is not needed. Enzymes thus act as valves controlling the flow through a pathway from raw material to end-product, each enzyme specific to a particular starting material.

The mechanism by which this occurs involves the ability of many proteins to shift between two stable alternative shapes or conformations; this is called allostery. The same simple principle has provided a general explanation for an enormous variety of biological phenomena, from the expression of a gene, to the actions of drugs on the body, to the secret of mechanochemical coupling resulting in movement in biological systems. It has been useful in explaining how muscle fibers work, the migration of cells in embryonic development, and the mechanisms by which some cells, called phagocytes, engulf and digest foreign bacteria, allowing the body to resist infection.

The understanding of this and other regulatory mechanisms is certain to contribute to the understanding and control of disease, to the development of drugs, and to the manufacture of desired proteins by genetic engineering.

Mapping the Human Genome

Soon scientists will have mapped the complete DNA genetic sequence of the common bacterium *E. coli*, with its 3 million base pairs. Some scientists argue that we should now mount a major national effort to do the same for the human genome (i.e., complete set of chromosomes), which is about 1,000 times larger.

There are two alternatives for further work, ‘‘mapping, and "sequencing" the genome. The difference is important because of current policy debates about which way to proceed. At present, small regions of the genome concerned with specific functions are being sequenced. These regions are identified in two ways: the sequence of a known protein is used to locate the corresponding gene, or the abnormal form of a gene associated with a disease is located through genetic comparisons and then is used

to identify the normal version. To continue along this path would involve studying key sites on the human genome; physically, in terms of the succession of restriction enzyme cleavage sites, and genetically, in terms of the genes as they are identified. Detailed sequencing of the various regions, base by base, would be done gradually, with priorities set by interest and importance rather than by location—i.e., the work would "skip around" with gaps being filled in slowly (See figure 3-3.).

This program is in fact being carried out now, in many laboratories, and the information is being collected and correlated. It has revealed unexpected parallels between sequences in genes with very different functions. This indicates that as organisms became more complex and as they therefore increased the number of their genes, new genes evolved from older ones in branching patterns, much like the branching pattern of the evolution of species through modification of earlier organs.

The alternative approach is mapping or complete systematic step-by-step description of the entire human DNA sequence, containing possibly 100,000 genes and over 3 billion bases. Only a few hundred genes have so far been described, less than 1 percent of the total. Current techniques can produce rough sequencing of about 20,000 bases a day, and are rapidly improving. One approach would be to map the structure of DNA in sections some 40,000 bases long. Sections of DNA of that length can be cloned into special vectors called "cosmids," in such a way that these partial maps would overlap. Mapping of the complete genome would be the largest single biological project ever undertaken.[4] A major governmental initiative toward this end has been proposed, involving the establishment of a few major research centers to carry out the work with centralized coordination. It is highly controversial.

[4] "Sequencing the Human Genome," *Issues in* Science *and Technology*, Spring 1987. See "Prologue," p. 25. This seminar in print includes: Walter Gilbert, "Genome Sequencing: Creating a New Biology for the Twenty-First Century, pp. 26-35: Leroy Hood and Lloyd Smith, "Genome Sequencing: How To Proceed, pp. 36-46; and commentaries by David Baltimore and Francisco Ayala, pp. 48-56.

The advantages of comprehensively mapping the human genome are that it would make it much easier and faster to link a newly identified gene with a disease or human function. Currently, a gene must be located through a painstaking search for genetic markers before it can be isolated and its bases sequenced for further study of its functions. Mapping the full genome would mean that when biologists want to study a specific protein within the body, analysis of a bit of its amino acid would make it possible to go to the genome database and locate the specific gene that guides the production of that protein. Advocates say this would dramatically accelerate achievement of the goal of fully understanding human inheritance and its limits. Possibly diseases that depend on the interaction of several genes, or that have alternative genetic causes, could be understood. There would also be spin-off benefits for many other areas of biological research, including ecology, immunology, and cancer control.

Mapping the entire genome would be a large and ambitious undertaking, probably taking 10 to 20 years, and with a cost estimated by some experts to be at least $3 billion. Critics fear it could divert research funds from other research that they think is more urgent. Some sections of the human genome, it is thought, will be much more difficult to clone and map than others, and some scientists suspect that the technology is not yet up to the task.

Some biologists argue that 90 percent of the effort of such a project would be wasted because it is now believed that only about 10 percent of DNA codes for proteins and the rest is "irrelevant" or "junk." Advocates respond that we do not really know what genetic material is irrelevant to our needs, and that the effort to filter out the junk would in any case be more time-consuming than systematic mapping.

Allowing the U.S. Department of Energy (DOE) to take the lead in mapping the human genome has been considered as one possibility, on the grounds that this would be a natural extension of DOE research in molecular bi-

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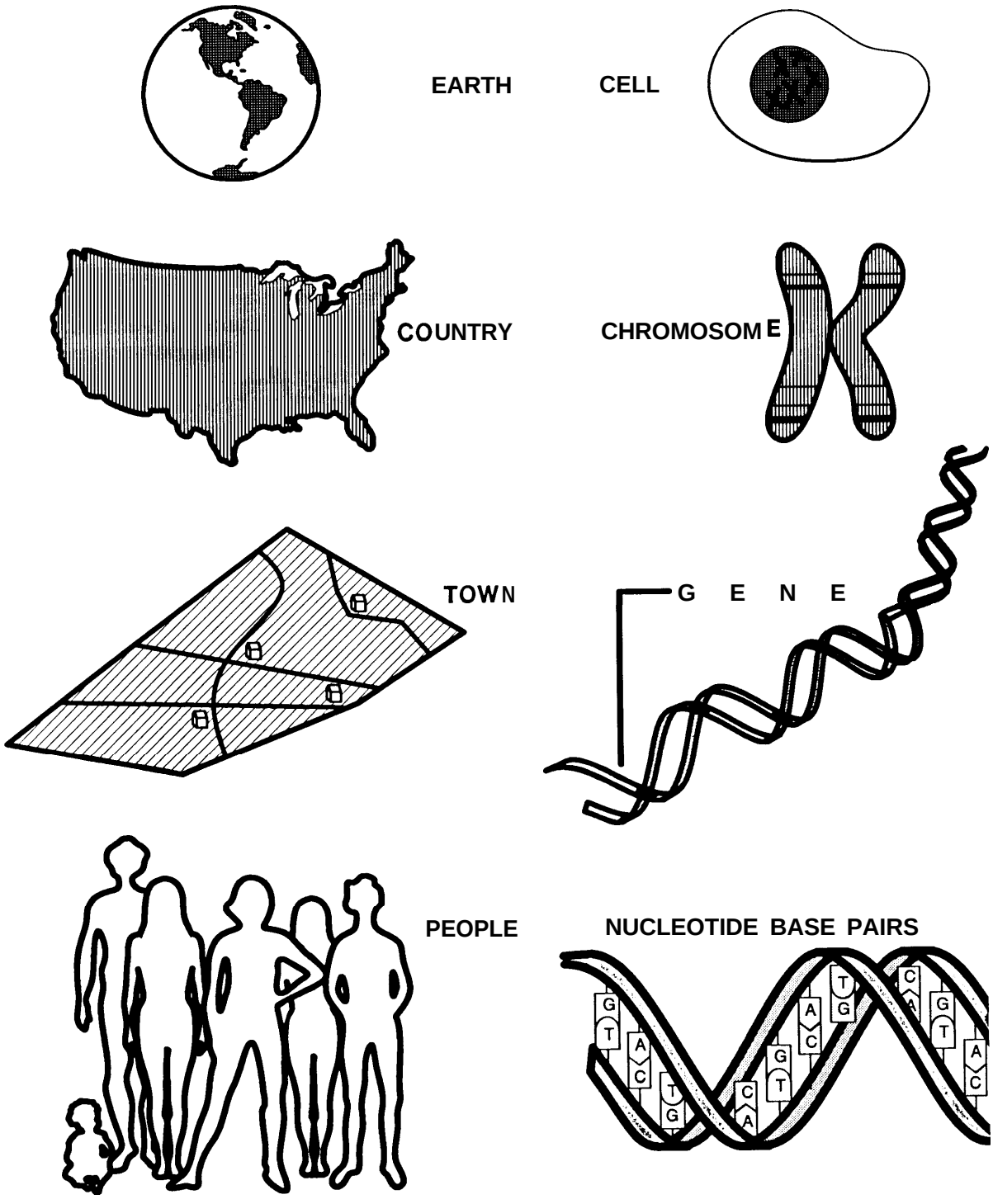
Figure 3.3.—Comparative Scale of Mapping



The number of base pairs of DNA in human cells is roughly comparable to the number of people on Earth. The scale of genetic mapping efforts can be compared to population maps, with chromosomes (50 to 250 million base pairs) analogous to nations, and genes (thousands to millions of base pairs) to towns.

ology (focusing on mutations that result from radiation or energy production) and would take advantage of DOE-funded scientific instruments and staff at national laboratories. Alternatively, the project could be led by a new, directed effort of the National Institutes of Health (NIH). An NIH-led effort would build on a much larger base of biomedical research. These and other strategies for carrying forward genome mapping efforts has been widely debated inside and outside of government in the last 2 years. Most likely is a set of projects funded through two or more Federal agencies, with formal or informal means of coordinated planning.

The situation in mid-1988 is that there is no single human genome project but instead many projects, in NIH, DOE, and other government laboratories and in universities and private sector laboratories. They aim at establishing and enhancing databases about DNA sequences, markers, and gene structure and expression; creating chromosomal maps; and developing new instruments, analytical techniques, and other scientific resources for biomedical research. No agency or organization, and no national government, has made a commitment to massive sequencing projects, or to a unitary, single focus program of research like that of the Apollo Project, the Manhattan Project, or other celebrated government research initiatives. Recent reports by the National Academy of Sciences[5] and the congressional Office of Technology Assessment[6] concluded that any such initiative would be inappropriate. They suggest, rather, that the Federal Government should, through funding and oversight, encourage and coordinate the continuing enhancement of databases and resources in many cooperating units and centers of research.

[5]National Research Council, *Mapping and Sequencing the Human Genome* (Washington, DC: National Academy Press, 1988).

[6]U.S. Congress, Office of Technology Assessment, *Mapping Our Genes– The Genome Projects: How Big, How Fast?* OTA-BA-373 (Washington, DC: U.S. Government Printing Office, April 1988).

The Evolutionary Record

The new field of molecular evolution provides more direct evidence for evolutionary continuity than even the fossil record. For example, man and chimpanzee, species which separated only around 10 million years ago—a short time in evolutionary history, have about 99 percent of their DNA sequences in common. This similarity indicates that man and chimp have a relatively recent common ancestor, compared to the much smaller genetic overlap between man and other species. DNA changes over time, due to mutations that are not eliminated, and the more similarity there is in the DNA of two species, the shorter the time in which they have been developing separately and thus diverging. There are decreasing degrees of homology, or genetic similarity, between man and increasingly distant organisms down to the lowest of the vertebrates. By contrast, bacteria have been diverging from each other not for thousands of years but for several billion years, and they show sequence homology only between very close species; that is, different bacteria may have very little overlap in DNA sequences. Some of the gaps in the evolutionary record are likely to soon be clarified and closed by such molecular comparisons, and some current misunderstandings and misinterpretations may be identified and swept away.

Evolution has implications not only for describing the origin and development of our species but also for increasing our appreciation of its rich genetic diversity, and for the still richer genetic diversity in our environment at large. This diversity could be needlessly reduced by careless or misguided agricultural and environmental management practices.[7] With respect to humans, a deeper understanding of the value of the wide variety in nearly all human traits enormously enriches life and literature, and when combined with understanding of the basic unity of life, as revealed by molecular biology, can further complement the already strong moral, political, cultural and re-

[7]U.S. Congress, Office of Technology Assessment, *Technologies To Maintain Biological Diversity*, OTA-F-330 (Washington, DC: U.S. Government Printing Office, March 1987).

ligious grounds for treating all races and all individuals with equal consideration and respect.

Tools of the Trade: Innovations in Conducting Biological Sciences

Progress in science depends on technical as well as conceptual advances. As biochemistry expanded its scope it has become increasingly dependent on elaborate (and expensive) instruments.[8] Also of major importance has been the use of computers. Automation and computers greatly facilitate the accumulation of data. While the investigator sleeps, his instruments continue to collect successive samples in a fractionator, to measure radioactivity, to determine or synthesize base sequences in genes. Indeed the rate of production of data is overwhelming the ability to publish it; a case in point is DNA sequence information.

The focus of biochemistry on larger molecules, and the simultaneous focus of cell biology on ever finer structures, has had another fundamental benefit. It has done away with the troublesome range where cell features were too small to be studied by microscopy but too large to be defined chemically. The field of cell biology increasingly overlaps that of molecular biology, and any line between biology and organic chemistry is becoming artificial.

An even more fundamental breakthrough has been the development of monoclinal antibodies. An animal produces antibodies in response to the presence within its body of a disease organism. In the ordinary antibody response, an "antigen" or stimulus (such as a protein on the surface of a virus) stimulates the formation of a protein molecule (antibody). The antibody is shaped to fit the antigen like a lock fits a key. The antibody covers the antigen so that it cannot latch on to another body cell. This prevents the virus from invading the cell and replicating itself.

The difficulty is that a normal antibody response leads to the formation of hundreds of different antibodies, differing with respect to the small region on the protein surface that each is attracted to and binds. The distribution of antibodies elicited by a given antigen varies somewhat from person to person, and even in the same person at different times. This made it hard for scientists to study the formation of antibodies.

There is a kind of cancer that attacks antibody-producing cells, called multiple myeloma. The cancer makes the "sick" cell reproduce itself uncontrollably. The new or daughter cells are clones of (i.e., identical with) the original cell. Scientists learned how to fuse an antibody-producing cell with a myeloma cell to get a cell that is called a hybridoma, which both produces one species of antibody and replicates itself over and over. These identical antibodies are called monoclinal antibodies, and are a powerful tool for analyzing the process of antibody formation. (See figure 3-4.) Their specificity allows them to be used, for example, to carry fluorescent markers or poisons to cancer cells. Monoclinal antibodies can be accurate and thorough biochemical scouts, spies, and assassins in the service of medicine. They have nearly unlimited potential for diagnosis, therapy, and analysis, and a growing industry has sprung up to produce them.

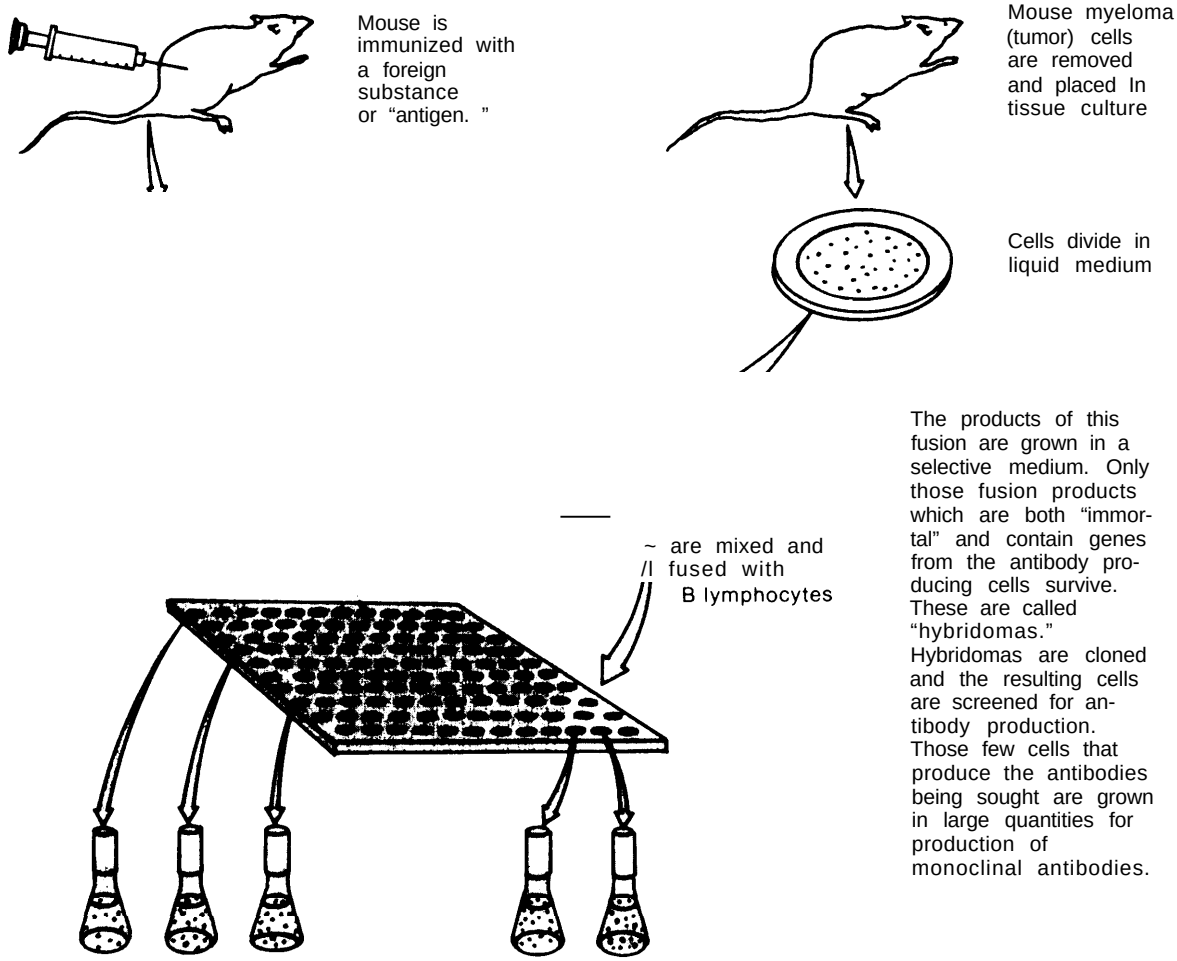
The Changing Environment for Biological R&D

The development of recombinant DNA and monoclinal antibody techniques have had a significant impact on the relationship between biomedical sciences and industry. Until recently most research in biology has not had much potential for commercial applications. But now a substantial number of the leading researchers have become involved in commercial enterprises.

It is clearly desirable that scientists doing basic research also encourage the development of applications that will benefit society through better health, improved agriculture, or increased economic productivity. In the United States, such benefits are perhaps most likely to be realized when the initial discovery is developed and marketed by an industry.

[8] For example, high-speed centrifuges, chromatography columns, flourescence cell sorters, electrophoresis apparatuses.

Figure 3-4.—Preparation of Monoclinal Antibodies



SOURCE Off Ice of Technology Assessment, adapted from Y. Baskin, "In Search of the Magic Bullet, " *Technology Review*, pp. 19-23

But there may also be problems associated with this changing relationship. Scientists who are also university faculty members may be tempted to spend too much time on commercial activities, and too little time on teaching. Students may be attracted to those areas promising the most immediate commercial payoff while other lines of basic scientific research get too little attention. There may be an adverse impact on the openness of scientific communication and sharing of knowledge. Concern about priority in discovery-for either winning prizes or patenting-could encourage scientists to postpone publication of preliminary or intermediate results, as could industrial secrecy.

FROM SCIENCE TO TECHNOLOGIES: THE USES OF NEW BIOLOGY

Bioengineering in Industry and Agriculture

People have throughout history domesticated various microbes by empirical selection of genetic variants with improved properties –for example, in making bread, wine, cheese, and antibiotics. Now, directed manipulation of genes through bioengineering can further improve strains. Also new strains of selected properties can be designed without waiting to select from variants that nature offers. The use of enzymes may increasingly replace traditional methods of organic chemistry in manufacturing processing, especially if biological processing proves to be more environmentally benign than older methods. Engineering of microbes could also increase both the efficiency and versatility of the conversion of biomass into energy and other useful products, or solve the problem of economically producing single-cell protein for food.

A successful early application of the new biology has been the use of recombinant bacteria to produce mammalian proteins. One of the first was the human growth hormone, used to treat children who otherwise would not grow to normal stature. Another early product was bovine hormone to increase milk production in cows. A third was human insulin for the relatively rare diabetic people who are allergic to insulin derived from other animals. A more *re*-cent product is tissue plasminogen activator, to dissolve the blood clots that may cause coronary thrombosis or strokes. These products from engineered microorganisms have the added advantage that they do not risk contamination with lethal human viruses as can occur with hormones extracted from human tissues and glands. The variety of products under development is growing rapidly.

Manipulation of DNA will supplement, rather than supplant, traditional methods of strain improvement in domesticated plants and animals. But bioengineering is different from conventional techniques in that it can produce changes in more stable portions of the genome not ordinarily changed by selective breeding. With animals, the extent of possible alterations through genetic engineering may be limited because the traits one would wish to alter often involve a large number of undefined genes, rather than being determined by a single gene. With plants, somewhat more extensive changes may be likely. Promising possibilities include enhanced resistance to pests, drought, or temperature extremes, and changes in nutritive value and flavor. Currently, there is extensive research on the possibility y of incorporating in various plants the set of genes responsible for nitrogen fixation, thus removing the need for expensive nitrogen fertilizer. However, since these genes are found naturally only in bacteria, it is not yet certain that they will function or will remain sufficiently stable within a plant.

Technical problems have been encountered both in achieving strong expression of inserted genes even in bacteria, and in preventing destruction of the resulting proteins before they are harvested. Since genes can also be cloned in cultured mammalian cells and in yeast cells (which are more similar to mammalian cells than are bacteria), future production of mammalian proteins may well be shifted to these organisms. Moreover, though the knowledge of molecular genetics of higher plants is so far not well developed, it is conceivable that cloning into these organisms will eventually prove economical; some optimists suggest that a single field of corn could meet the world's need for insulin.

Some scientists hope that eventually it may be possible to preserve the DNA of rare species that are threatened with extinction. It has been suggested that inserting preserved DNA into the egg of an existing closely related species could allow us to reconstitute an extinct species, or that related DNA might be modified for that purpose. These applications are speculative at present, but not beyond the realm of possibility.

One constitutional issue, that of patenting of engineered organisms, has been addressed

by the Supreme Court, which allowed the patenting of a genetically altered bacterium.[9] The Patent Office, citing the Supreme Court decision, extended patent protection to other bioengineered plants and animals. In April 1988, Harvard University was granted a patent on a genetically altered mouse, the first patent to be issued for higher life forms.

Soon thereafter at a meeting sponsored by several national church groups, a panel of ethicists and theologians called this "a matter of deep philosophical and spiritual concern" because it portrays animals 'as human creations . . . rather than as God's creation or subject of nature. . . .'" O The patenting of animals, and of human cells and tissues, raises issues that are now being debated in Congress. Two bills before the 100th Congress as it nears adjournment call for a moratorium on granting animal patents. Court cases challenging the government's decision to allow experimental release of engineered organisms for field trials also have some implicit constitutional implications and will be discussed in chapter 4.

The Biology of People

The new biology is having a profound effect on the sciences and practice of human genetics, medicine, and public health. As it does, many complex public policy issues are being raised, and many of them have constitutional aspects and implications that will be explored in later chapters.

While genetic counseling has been done for along time, it was practiced mainly on the basis of knowledge of the health and life experience of parents and grandparents and statistical analysis of health records of the offspring of people with similar heredity. Several radically new techniques are now being developed: genetic screening for hereditary diseases associated with known genetic defects, prenatal diagnosis of disease or defects through testing of fetal tissue or cells, and human cell therapy. These will be discussed in chapter 4.

Diagnostic Tools and Vaccines

Molecular and cell biology have revolutionized both basic and applied immunology. Monoclinal antibodies and fluorescent dyes or tags have provided particularly valuable tools. Growing knowledge of the complex immune response will surely make it possible to enhance protective responses and to prevent damaging allergic responses. Autoimmunity, the abnormal formation of antibodies or immune cells that attack normal body constituents, is recognized as a factor in some chronic diseases and is strongly suspected in others; these include pernicious anemia, juvenile diabetes, multiple sclerosis, arthritis, and ulcerative colitis. Antibodies and other visible agents are widely used with microscopy to reveal the distribution of cell components. Their chemical coupling to powerful toxins or drugs promises to provide a means of targeting these agents to specific cells.

Advances in immunology have also made possible simple and sensitive diagnostic tests for infectious agents, which are also much faster than cultures and other traditional methods. One example is differentiation between streptococcal throat infection (which requires antibiotic treatment) and viral infection (for which there is no specific treatment). Simple home tests have been developed for many diseases.

Vaccines, which stimulate protective antibody formation, were formerly prepared by modification of either viruses, intact bacterial cells, or toxins. With better understanding of the immune response and improved methods for purifying or synthesizing macromolecules, it is possible to use specific components of the pathogenic organisms, or synthesized protein sequences, to make much more effective and non-toxic vaccines. This should be particularly effective against viruses, which offer fewer

[9] *Diamond v. Chakrabarty*, *477* U.S. 303 (1980).

'('United States Patent No. 4,736,866, Apr. 13, 1988. The meeting of ethicists and theologians was sponsored by the National Council of Churches, the Humane Society, the Presbyterian Church, the New Creation Institute, "and other groups, " as described by David E. Anderson, ''Halt Urged on Patents of Engineered Animals, " *The Washington Post*, Apr. 30, 1988, p. B8. Quotations are taken from that article.

unique features for selective attack than do bacteria.

The methods of molecular biology are also being applied to studies of protozoal parasites. Some experts believe that prospects are bright for vaccines for parasitic diseases, such as malaria or trypanosomiasis, that are major causes of death in the Third World. Others are less optimistic, although tending to agree that such vaccines will ultimately be developed. The problem is that some microbes—including some viruses and bacteria as well as protozoa –have a capability of making reversible genetic changes that permit them to replace a surface antigen with various alternative antigens that cannot be neutralized by the same antibodies.

Targeting Cancer

Animal cells, unlike bacteria, undergo differentiation and organ formation, and these processes involve intricate interactions with neighboring cells. Accordingly, the regulation of cell growth has been much more difficult to study in animals than in bacteria. It is the regulation of cell growth that is disrupted in cancer.

Recombinant DNA methodology has already dispelled some of the mystery of cancer, by tracing the origin of some cancers to alterations in the amount or structure of various genes called oncogenes. These gene changes explain why viral infection, radiation, or mutagenic chemicals as well as spontaneous mutations might all cause cancer. Moreover, researchers are exploring the effects of these genes on regulatory mechanisms and on the cell surface.

Molecular genetics has led to drugs that interfere with DNA replication and thus in a limited way with cell growth, and potentially with cancer. Growing understanding of the biochemistry and immunology of cancer offers promise of greater future advances in prevention or cure and unlike many other advances in medicine, they may decrease rather than increase the costs of controlling cancer.

Human Body and Brain Enhancement

Gene therapy is aimed at curing well-defined hereditary diseases. But bioengineering might also theoretically be aimed at enhancing desired traits or creating new traits or new physical or mental capabilities. This possibility has often been raised in speculation and in fiction, with some scenarios going as far as the creation of superior and inferior classes of people.

In fact, the technical possibilities for significant enhancement through genetic engineering appear limited. Genetic manipulation in humans is likely to be restricted for a long time at least to addition or replacement of a single gene, and there are only a few known single genes with significant effects generally agreed to be desirable. If one assumes that the traits society might be tempted to enhance would be intelligence (or more precisely, some aspect of intelligence), memory, strength, size, athletic ability or some other specialized talent, each involves a large and as yet undefined number of genes. Anyone attempting to manipulate such traits would be facing a formidable task.

For many years, however, neurobiologists have been studying conduction of electrical impulses along nerve fibers and the chemical transmission of impulses from one cell to many others. Specific functions in the brain have been identified and localized in specific regions. It has been known for some time that some hormones, distributed throughout the body, influence both physiology and behavior.[11]

Now science is identifying a variety of neuropeptides, hormones that are released within the brain and modulate functions such as blood pressure and digestion. It is increasingly likely that neuropeptides will prove to be involved in controlling mood or emotions, although none have yet been shown specifically to do so under physiological conditions. It is even possible that a biochemical explanation may be

[11]U.S. Congress, Office of Technology Assessment, *Impacts of Neuroscience—Background Paper, OTA-BP-BA-24* (Springfield, VA: National Technical Information Service, March 1984).

found for violent, aggressive, or antisocial behaviors. Such knowledge could be expected to lead to medications or treatment for a range of conditions, such as emotional disorders; it could also lead to less beneficial forms of behavior control or mind control. According to Dr. James L. McGaw, director of the Center for the Neurobiology of Learning and Memory at the University of California, Irvine, "The basic science of neuropeptides and neurotransmitters . . . is exploding at the present time. Dr. Herbert Weingartener, Chief of Cognitive Studies at the National Institute of Mental Health, added, "We're sitting on a revolution that rivals quantum physics in the 1920s."[12]

A second line of research is also leading to new theories and new knowledge about the genetic basis of mental and behavioral traits—the study of identical twins, including pairs that were separated at birth by adoption. A series of studies at the University of Michigan has been widely reported; this research entails both biological and social science research and may provide clues for further genetic research.

The molecular basis of memory is being worked out in simple animals. In higher animals analysis of the paths and mechanisms of communication between different regions within the brain is providing new insights into the ability of the brain to integrate information, much like a computer but with complex branching rather than more linear connections.[13] There could be ways to enhance the functioning of these pathways and possibly the storage of information; already clinical tests of such chemical aids are underway.

Individuals appear to differ widely in the speed of the search-and-find processes in their brains that produce complex responses to an input of information. The molecular genetics of development suggests that one source of differences in this aspect of "general intelligence"[14] might be differences among individuals in certain proteins of their synapses; whether these proteins can ever be 'enhanced" is highly controversial at present.

Advances in neurobiology will almost certainly have major impacts on the understanding and treatment of various mental illnesses. A better understanding of the role of biological factors and the role of social factors could eliminate unwarranted blame for mental illness that has been attributed to the family environment or to other aspects of society. Recent indications that genetic factors may play a decisive role in some kinds of manic-depressive illness have focused attention on biological factors in other mental illnesses.

The brain, with its hundred billion or more cells and a thousandfold greater number of connections, seems likely to provide a virtually endless challenge for molecular scientists. Many people, however, may find that their discoveries, or even their hypotheses and research, are unsettling and disturbing. They bring into question familiar assumptions about human nature, responsibility and freedom, and basic equality among people.

The Control of Aging

The branch of biology with the most recalcitrant gaps between empirical description and molecular analysis is developmental biology, or the study of how cells and organisms mature and age. Scientists still lack adequate knowledge of the mechanisms by which cells in a developing embryo differentiate, move, and relate to neighboring cells in an orderly way to yield a coherent set of organs. They do understand or are beginning to understand some of the key features: how genes are selec-

[12]Both are quoted in Michael Schrage, "Soon Drugs May Make Us Smarter, " *Washington Post,* Feb. 3, 1985, p. Cl.

[13]For a good journalistic account of this line of research, see George Johnson, "Memory: Learning How It Works, New *York Times Magazine,* Aug. 9, 1987, pp. 16-34ff.

[14]The definition and the use of the term "intelligence' is frought with difficulties, both technical/scientific and political. It is probably best, from both standpoints, to think of multiple kinds of "intelligences' or mental capabilities, with people *differ*ing in performance across the range both individually, as compared with other individuals, and among and between groups or populations. Quite distinct from questions of definition or measurement of intelligence or intelligences, is the mystery of various forms of dyslexia, or defects in specific aspects of handling language.

tively turned on or off, how concentration gradients of chemicals released by cells influence neighboring cells, and how cells find and adhere to each other. They are still far from understanding in detail how nerve fibers extending from specific cells in the brain connect with other specific cells in other brain regions. It is generally anticipated, however, that advances along these lines will now proceed rapidly and the results will be translated into major medical advances in the years ahead.

Despite the progress in cell biology, the basic mechanism of aging in higher organisms is not understood—even in terms of whether the key changes occur in genes, intracellular structures, membranes, blood vessels, the immune system, or all of these. The general increase in life span is a product of improvements in prevention and treatment of infectious and other diseases, as well as in nutrition and sanitation, rather than a product of specific interference with the aging process. If life were sufficiently prolonged, or aging and natural death sufficiently delayed, then the birth rate might need to be lowered to avoid problems of overpopulation. A lowering of the birth rate might come about either by a general consensus of individuals, by public policy intervention, or by some natural adaptation. Such interference does not seem to be in sight now, but if it comes about it could radically alter the normal process of generations with major social consequences.