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PREFACE

With the enormous growth of the National Institute of General Medical Sciences it became evident that to responsibly administer a broad program of research grants, research training grants, and other awards, a special effort should be made to use all sources of the latest research information and assess these in the light of achievements in the various disciplinary fields. Consequently, at the request of the Director, Frederick L. Stone, each of the discipline-oriented Training Grant Committees, composed of scientific consultants, undertook a status assessment of their fields. This included evaluations of research accomplishments and the research training activity, including their respective needs, and some projective views on areas of future concern.

At the outset it was recognized that to deliver a meaningful and useful document would be an arduous task, requiring a perspective transcending the discipline in order to perceive the over-all impact of biophysical research on cognate fields. Nevertheless, the Biophysical Sciences Training Committee undertook the challenge, seeking the widest possible consultation within the time allotted. The result, less than comprehensive, with gaps in documentation and justification, and reflecting, perhaps many of the biases of those who made the final synthesis, must be viewed as only an initial effort. If this is to be followed in succeeding years with more penetrating analyses of the various areas of active concern, then perhaps the series will possess a persuasion greater than the individual reports.

This document in much the same form received initial distribution among the staff and consultants comprising the Advisory Committees of the National Institutes of Health in early 1967. In that it may be of interest to the entire scientific community, as well as to those involved in all aspects of scientific research, research training, its support and administration, the Committee has suggested that it be published and thereby made available.

FRED M. SNELL

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SUMMARY

This report, an assessment of the current status of the biophysical sciences, is in three parts: Structure and Support of Science, Biophysical Science, and Recommendations. The organization is such that the first part provides the broad perspective for the next which describes the biophysical sciences in some detail. The first two parts provide the scientific basis for the Recommendations.

STRUCTURE AND SUPPORT OF SCIENCE

In this part recognition is given to the fact that most of "science" has been a product of this century and, indeed of the last three decades. Science and its support have now become visible and scientists must recognize more than in the past their responsibility to justify their goals. The goals of the basic and fundamental sciences and the goals of the technological and applied sciences are to gain knowledge and understanding of natural phenomena and to utilize these for the benefit of man. Basic science is the support science of any mission-oriented endeavor.

The decision process that relates to the ultimate support of any basic scientific research project is complicated and involves several levels. The highest levels are largely political and administrative decisions that relate to the establishment and support of missions, the cost of which are now a visible portion of the Gross National Product (GNP). The lower-level decisions become increasingly weighted with scientific considerations. The criteria for making rational judgments are well-defined only at the final level that determines which is or which is not a project worthy of support.

The biophysical sciences have emerged as an identifiable interdisciplinary activity during the past two or three decades. They have matured into a most significant component of science. We have defined them as including that component of the interface between the physical sciences on the one hand and the biological and medical sciences on the other which gives more than the usual emphasis to the approaches of physics, physical chemistry, engineering and mathematical analysis.

BIOPHYSICAL SCIENCE

In this section, the Committee analyzes in considerable detail biophysical science, its research interests, its contributions to knowledge and understanding, its impact upon neighboring sciences, and the status of its research and research training. We finally suggest some areas that appear particularly significant for future exploitation.

Activity within the biophysical sciences can be conveniently classified according to the levels of biological organization: molecules, cells, organs, and populations. The greatest activity is directed toward the molecular level, although cellular biophysics comprises a close second. Organ biophysics is becoming increasingly important but little attention has been directed toward studies of populations. Instrumentation and theory are additional significant activities.

In recent years there have been innumerable contributions stemming from the biophysical sciences. Many of the contributions have been of such great significance as to have revolutionized many fields of biological and medical science. We point to cell culture techniques and fundamental radiation studies. We mention the development of radioactive tracer methodology that has seen wide application and is destined to see even more in clinical medicine. We note the impact stemming from the elucidation of DNA structure. We discuss cell membranes and the nerve impulse, the contractile system, the plasma proteins and protein structure, our knowledge and understanding of which are largely a product of biophysical scientists' work.

The impact of the quantitative and analytic approaches upon the biological sciences has been that of a revolution. The effect has been primarily that of a unification of this science. Emphasis is now being given to the similarities of molecular mechanisms rather than to differences among species. The medical sciences have strongly felt the impact in terms of medical research, especially basic medical research, but in contrast to biology, medical education has been less responsive. The impact on the physical sciences is readily apparent and the changes that are occurring in portions of physics, physical chemistry, mathematics, and engineering are certainly significant.

Research training in the biophysical sciences has developed largely in the past decade. Ph.D. enrollments have risen rapidly. Support for this training, derived largely from the National Institute of General Medical Sciences, is about 15% of the total research training effort, although research support from both the National Institute of General Medical Sciences and the National Science Foundation amounts to about 20% of that available.

Future areas for biophysical research that have enormous potential are numerous. We indicate but a few: molecular regulatory processes with their many significant possibilities, and molecular neurobiophysics in which there is at the present time a lack of understanding. We also emphasize the importance of elucidating the mechanisms of cell replication and neuronal interaction and suggest that we need better conceptual formulations of the latter to effect significant progress. We point to the important field of cell and tissue preservation. We urge greater attention to population problems. We stress the fact that theory will assume an increasingly important role contributing significantly to true understanding. Instrumentation needs, especially those that refine our observational limits and allow us to process the wealth of biological and medical information are paramount. We conclude by indicating that present and future problems in biomedical research are and will be more difficult than have been those in the past. Basic science following a quantitative and analytical approach will assume an increasingly important role.

RECOMMENDATIONS

In this section, we urge that the National Institute of General Medical Sciences press for adoption by the National Institutes of Health of the following actions: *We recommend that the growth of both training and research in the biophysical sciences be set at an annual rate 3–5% greater than the average for all biomedical sciences.* This is a studied recommendation that reflects our considered opinion concerning the merits of the quantitative and analytic approaches of the biophysical sciences and the desire to strengthen these in the biological and medical sciences.

We recommend an annual review, at the highest level within the National Institutes of Health, of the long-range plans for biomedical research and its rate of growth. This recommendation reflects our concern that the support of basic science in the health-oriented mission of the National Institutes of Health must continue to comprise a significant portion of the total support, and that the rate of growth of total support should approach that of the GNP in a smooth and orderly fashion.

STRUCTURE AND SUPPORT OF SCIENCE

INTRODUCTION AND PERSPECTIVE

Science has played an important role in human society and culture emerging over the course of only a few centuries, beginning as an activity and pursuit engaged in by only a few natural philosophers. Its growth has been phenomenal. Science now engages a significant portion of our society and attracts a large segment of the educated public. With this evolution has come a greater social and cultural responsibility.

Yet scientists themselves have, in general, tended to remain aloof, nonpolitical, and often naive concerning nonscientific matters. Perhaps they have expected their role to be understood. Perhaps they have assumed a universal acceptance of the importance of science. Perhaps they are taking for granted that their endeavors, so important to them and, they believe, to society, are deserving of support.

As science has grown, so has its support. At the present time, especially in this country, the amounts directed toward science have become very visible. It is apparent, therefore, that future science must be justified—justified in terms of its achievements and probable achievements. Science must compete with all other significant endeavors that comprise our social and economic expenditures. Within the limits of resources available, science must justify its support in relation to the over-all goals of our peoples, our societies, our nations, and our world. Some scientists say that science justifies itself. Perhaps this is so; it should be explicable in rational and logical terms for all to see. Let us advance arguments, then, and let them determine the extent to which our resources are directed toward science. Surely, there must exist an optimum level of scientific activity, both in regard to manpower and economics.

The emergence, growth, and development of science has been marked by its being partitioned into disciplines, subdisciplines, and fields of specialization. Each discipline, subdiscipline, or field is characterized by its methods, approaches, techniques, and achievements. Based upon the scientific method, i.e. observation, experiment, description, hypothesis, test and theory, the contributions of each of the disciplines have added to our over-all knowledge and understanding.

With the evolution of science and its division into disciplinary areas, there has nevertheless been unity of purpose. The principal goals of science remain clear: the elucidation of natural phenomena, the understanding of our universe, and the utilization of this understanding for the benefit of man.

Knowledge is founded on observation and experiment. These represent the facts of nature. Understanding involves the assimilation of knowledge into self-consistent frameworks, through logical explanations, through theory. Though facts may be numerous and diverse, science attempt to correlate them by devising a rational explanation, a theory. To gain this knowledge and this understanding is the pursuit of "basic science."

The utilization of knowledge and understanding for the benefit of man comprises our applied science or technology. Today, technology is ubiquitous. It permeates our society and culture and affects our everyday lives, even down to the minutest detail. It has also penetrated science itself, contributing significantly to the advances that can be made in our knowledge and understanding. Science is comprised of both basic approaches and technological applications. Each discipline is comprised of both, but in varying degrees. What is to be remembered, however, is that all technological advances and their applications have been derived from basic scientific achievements. Thus, basic science supports technology, assists basic science in its further advances, and simultaneously translates advances to benefit mankind.

The disciplinary categorization of scientific endeavors as well as their division into basic and applied fields has evolved naturally, largely owing to the diversity and breadth of nature itself. These categorizations now largely determine the organization of science within our academic and research institutions. The organization has both its good and bad features. On the plus side, the factor of identification together with the healthy competition that exists for attracting keen minds, has led in our free society to the strengthening of disciplines according to their productivity and achievements. However, on the negative side may be pointed out the tendencies of parochialism, professionalism, and narrowness that such disciplinary organization engenders. Often the more mature and older a discipline, the more it suffers from its own internal structure and rigidity. In fact, it even expends effort toward self-preservation. These fatcors are not part of science itself, but reflect the fact that science is composed of human beings. It is to be added that parochialism has occurred and developed in spite of the realization on the part of many that truly significant achievements are not necessarily made within the realm of an identifiable discipline but rather at the interfaces between previously established disciplines.

Recent years have seen the emergence of a number of interdisciplinary areas. Communication between disciplines is being established. Fruitful new areas are evolving. In part this is a reaction to parochialism, to traditionalism and professionalism. Individual scientists are crossing from one field to the other. Perhaps the most significant of these interdisciplinary areas is that which lies between the physical sciences on one hand and the life sciences and medical sciences on the other. This large interdisciplinary zone has become so important that the prefix "bio" has now been attached to a number of formerly fundamental disciplines; physics, chemistry, mathematics, and engineering. In this report we direct our attention to the biophysical sciences, a broad interdisciplinary field that has seen enormous success in terms of its significant achievements. In this report, we intend to examine the scope of the biophysical sciences and point out in a selective manner some of its significant contributions. We wish also to examine the impact the biophysical sciences have made upon neighboring scientific fields. A portion of our evaluation will involve the current status of the biophysical science education, research, and research training. An additional, significant portion of the evaluation must involve an assessment of what the future holds, realizing that prediction can be based only upon current knowledge and understanding. Manifestly, therefore, prediction points to the obvious and it must be borne in mind that the unpredictable is often as significant as the predictable, if not more so.

This report is to be considered an initial report, to be refined, documented, modified, and strenghtened, at least on an annual basis, in the years ahead.

BASIC SCIENCE, TECHNOLOGICAL SCIENCE, GOVERNMENT, AND THE PROCESS OF DECISION

There are some additional points of perspective that bear not only on the biophysical sciences but upon all science and its relation to society. We shall attempt to outline the various successive levels of decision that ultimately determine the federal government support of a given research project. We shall suggest where scientists may play a more responsible role and also where criteria that affect decisions are needed. We shall attempt to provide a better picture of the role of basic science in relation to the more technological aspects and we draw upon an analogy to better illustrate this relation.

Government support of science in a free democratic society involves many successive levels of decision. Scientists are accustomed to dealing only with the final levels that involve principally scientific judgments. It is important that they become aware of the others. For purposes of this report, we choose to identify five levels:

Level 1 At this level, decision is made as to what portion of the GNP should be channeled into science and technology. This decision, either directly or indirectly derived, is largely a political one. The Executive branch of the government does exert some influence. Discussions relative to this level of decision are well stated in a number of the essays comprising the National Academy of Sciences Report to the Miller Legislative Committee. ("Basic Science and National Goals," NRC-NAS Report, 1964). The report of the Wooldridge Committee ("Biomedical Science and its Administration," Report to the President, February 1965, Appendix III) also contains a discussion of criteria for determining levels of Federal support of health research.

Level 2 This level concerns decision as to what should comprise the principal scientific missions to be supported from any governmental allocation to science. Again, these decisions are largely political with perhaps more opportunity for administrative and executive influences. It is at this level that decisions must be reached as to how much money should go into the health needs of our country and others, how much should go into exploring space, into studying the universe, and into studying our own planet. Each project at this level is in effect a mission whose goals are broadly defined and clearly delineated. Obviously, some scientific judgment is required to reckon with factors of feasibility.

Level 3 At the third level, decision must be made as to what proportion of the total budget for each mission should be allocated to the so-called support sciences and what proportion should be allocated to the more technological sciences.[1]

It is at this level that scientific judgments become of great importance. However, criteria determining this decision process are woefully lacking and, as a result, decision is largely arbitrary and biased. Opinion properly expressed is convincing to some but detestable to others. It necessarily embodies a high amount of subjectivity. In making decisions at this level, basic science in reference to the technological aims of any mission has frequently been represented as the necessary overhead expense, a portion that should be kept as low as possible. It becomes clear, however, with the many contributions that basic science has made to technological developments, that it should not be considered as mere overhead. It has attracted the elite of the scientific talent and it is the most prestigious of scientific pursuits. It deserves, therefore, the dignity of identifiable support.

In considering criteria that affect decision at this level, three factors should be borne in mind: (*a*) Basic science has been notable for making unexpected discoveries, and thereby opening up new avenues, new approaches, and often new missions. (*b*) Basic science has provided and is providing a large resource of expertise. These experts are a national asset, pursuing their own research interests in basic science, but available in times of crisis to apply their expert knowledge to technical developments. (*c*) Basic science has provided the most fruitful breeding ground for education and training, not only for those who choose to stay in the basic science, but also for those who wish to apply this knowledge in technological sciences. Individuals so trained are in general more

[1] We use the term "support sciences" for the fundamental and basic sciences, and "technological sciences" for the applied sciences.

broadly based and more fundamentally trained than those whose training is derived within the technology itself.

At this juncture, it is perhaps well to draw upon an analogy to illustrate the role of basic science in any mission-oriented endeavor. Let a seed represent an idea that possesses a sufficiency of substance to justify the initiation of a mission. We plant the seed and it grows. The initial growth is small but visible; it represents the initial achievements of this mission. These are sufficient to inspire confidence for the mission's defined goals. However, this initial success has been entirely based upon knowledge and understanding that existed within the seed. The young shoot must now send out a root system, hidden from casual observation by the public. However, it is this root system that gives the shoot its support; it nourishes it and it permits it to bear its leaves and fruits. The root system is thus analogous to the basic science componet of any mission. The stalk or the tree trunk, the leaves and the fruit are the technological achievements that become visible to all. Some missions must have more extensive root systems than others, but all must have some to assure a stable and worthwhile mission. If the roots find themselves in inadequately fertilized soil, the visible portion of the mission is affected; a less than optimal product results. Too much fertilizer leads also to an inadequate root system that cannot properly support the goals of the mission. Thus at this level of decision, criteria need to be established to determine the correct and optimal amount of financial resources that are required for the basic support of the technological science in any mission.

Level 4 At this level, decisions bear upon the allocations to be made among the various disciplines or areas that relate significantly to the goals of the mission: both basic disciplines and technological disciplines. Here again, inadequate criteria exist to guide these decisions. At the present, decisions are not insensitive to pressures that arise from the disciplinary areas. Increased effort should be made to seek out those disciplinary areas of particular promise for any mission and thus satisfy the requirements of planned programming.

Level 5 At this final level, decision must be reached in the allocation of funds to individual projects within each discipline or area. Scientists have proved themselves capable at this level to make reasonable and valid judgment. The panel system adopted in particular by the National Institutes of Health and the National Science Foundation is time-tested and has proved to be an effective means of distributing support. The panel system is not entirely free of criticism. Two principal ones are often voiced. The first relates to the dependency of approval on what is termed "grantsmanship." The other has been directed towards what would appear to be a tendency for any applicant to direct his project more towards the "sure thing" than toward that involving considerable risk. In this regard, it is difficult for any research investigator to exploit his intuition. All intuition must be rationalized in order to obtain approval. Applicants tend therefore to avoid more imaginative projects and place before review panels those which are more pedestrian in character.

SCOPE OF THE BIOPHYSICAL SCIENCES

Historical

It is only within the past two or three decades that the biophysical sciences have emerged, matured, and been given identifiable recognition. However, there is a longer history and this lends considerable emphasis to the significance of interdisciplinary effort. Some individuals date the origin of biophysics with the origin of science. Perhaps this is so, for the inquiry into things living has always comprized a prime motive for the study of things physical. More definitively, however, a possible identifiable beginning is the work of Leonardo da Vinci with his pioneering studies on the flight mechanism of birds. Other individuals would relate the origin of biophysics to the work of Galvani some three centuries later, during the last part of the 18th century. His observations on the excitability of frog muscle laid the foundation for the study of bioelectricity and indeed of the physics of electricity. At about the same time, the contribution of Lavoisier removed much of the mysticism about combustion. His quantitative experiments with animals demonstrated unequivocally that respiration involved oxygen consumption analogous to physical combustion and thus the stage was set for a study of all metabolism. Darwin, through his keen observation and quantitative assessments, was perhaps the first biological theorist, theorizing on the origin and evolution of the biological species. In the 19th century many other names stand out in the development of the biophysical sciences. Faraday set the foundation for modern electrochemistry and modern electrobiology. The contributions of Helmholtz on vision are the basis for all modern considerations of color perception. One of the earliest and most significant applications of mathematics and statistics to biology was the contribution of Mendel. He laid down the rules of heredity, but in terms of abstract quantities. In 1879 Flemming described the chromosome, but it has been only in recent years that these abstract quantities have been identified with molecular structures and processes. Also in the 19th century, the name of Willard Gibbs stands out. This thermodynamicist clarified most of the quantitative considerations associated with heterogeneous equilibria, which are relevant at every turn in the study of the function of biological systems. Finally, the discoverer of X-rays, Röntgen should certainly be included as a contributor to 19th century biophysical science.

The 20th century naturally brings many more contributors. We note only a few among the many. The work of Sir Henry and Sir Lawrence Bragg, although originally not specifically directed toward the solution of biological problems, established the base for current investigations of the molecular structure of biological macromolecules. The contributions of Peter Debye, Irving Langmuir, and A. V. Hill in terms of modern biophysical chemistry, membrane problems, and quantitative physiology are outstanding.

The contributions of the last few decades overwhelm the science historian. Many of these are so well-known that detailing them at this point is unnecessary. Suffice it to say that Nobel awards have been made to many individuals whose contributions have been a part of the interdisciplinary biophysical sciences. Among these, we would include Pauling, Watson, Crick, Wilkins, von Bekesy, Jacob, Monod, Stanley, Calvin, Perutz, Kendrew, Hodgkin, and Huxley.

From this brief historical review, one becomes aware of the fruitfulness of the interdisciplinary approach. These contributions serve in part to define the scope of present-day biophysical science and they have certainly provided much of the stimulation that has led to the almost explosive growth of this area that is now occurring.

Biophysical Sciences among Other Sciences

Clear limits and boundaries between the biophysical sciences cannot be readily defined. The fact is that the biophysical sciences represent primarily an interdisciplinary endeavor and as such provide a continuum of effort between disciplinary fields. The interfaces between the physical sciences (chemistry, physics, engineering, and mathematics) and the biological and medical sciences are many, and the biochemical interface and the biostatistical interface are fairly well-defined in our minds. We choose to call biophysical science that component of the interface that gives more than the usual emphasis to the approaches of physics, physical chemistry, engineering, and mathematical analysis.

In addition to biophysics per se, biophysical science thus includes large portions of biophysical chemistry, bioengineering, and biomathematics, and certainly has activity at all levels of biological organization. The biophysicist may be educated in any of these disciplines. It is with his knowledge and understanding of the physical principles that he directs his attention toward solutions of the problems of the biological and medical sciences. His contributions to the physical sciences themselves, however, are not to be discounted. The impact of the biophysical sciences on the physical sciences will be discussed later, but in illustration, we point out that much of the base of modern mathematical statistics has risen from the considerations of the multivariable problems of biology. We may further predict that the discoveries made concerning the *modus operandi* of living systems will have an ever-increasing influence on the technology of the physical sciences. After all, living systems have evolved ways and means of achieving their ends that have survived the rigorous selective procedures of time, with complexities and high degrees of reliability, and within very small physical dimensions. They are time-tested molecular machines.

BIOPHYSICAL SCIENCE

COMPONENTS OF BIOPHYSICAL SCIENCE

The study of living things by the methods of biophysical science is made at all levels of organization of the biological systems. The levels of organization form a convenient means to categorize the activities of the biophysical scientists and delineate further the scope of this interdisciplinary area. For our purposes we recognize four levels: the molecule, the cell and its organelles, the organ, and the population. We characterize each of these in terms of the interests and activities of the contributing biophysical scientists.

Molecule

A large component of the more recent investigative endeavors of biophysical scientists is focused on the molecular level of organization of biological systems. So significant has been the activity at this level that it has given rise to the term "Molecular Biology." Molecular biology is, however, somewhat broader than molecular biophysics. Molecular biophysics includes only that portion of molecular biology which relates to the more physical aspects. Biophysical science is concerned not only with the detailed structure of molecules that comprise the living systems, but is equally concerned with the relation that this structure bears to biological function. It is interested in the organizaion of molecules that comprise the information system, the hereditary material, and the means whereby this information is transcribed and determines the structure of other molecules.

Biophysical science is interested in enzyme catalysis and the detailed mechanisms of the chemical transformations that enzymes effect. It has a primary interest in the nature of molecule-molecule interaction, which leads to an understanding of supramolecular organization. It is also concerned with the interaction of smaller molecules, the nature of which must be considered in any theory of fluids and fluid behavior. Biophysical science is interested in the interaction of radiation with matter and is concerned not only with the mechanisms of the primary event but also in the utilization of this interaction to study many of the events of cellular function including genetic transmission and molecular synthesis and its control. Biophysics may use the approaches of the solid-state physics. It utilizes the techniques of X-ray crystallographic analysis, electron microscopy, modern analytical techniques of spectroscopy, ultracentrifugation, gas chromatographic analysis, and many other techniques that in many instances biophysicists have assisted in developing. The molecular biophysicist also feels free to utilize the techniques of the biologists involving microbial, viral, and cell culture and has often elaborated on these techniques and introduced a variety of new ones.

Cell and Organelle

At these next higher levels of biological organization, there has also been a large amount of biophysical investigative activity. These investigations involve all varieties of subcellular and cellular structures and the relations that these bear to the wide variety of cellular functions, both general and specialized. At this level biophysics is concerned with how molecules become organized into identifiable and unique biological structures. It is equally concerned with the mechanisms by which these structures carry out their detailed functions. Biophysical science is interested in molecular synthesis and the interrelations of this to cellular control which comprises much of the beauty inherent in organization of the biological system. This interest includes general cell functions such as DNA synthesis, organization of chromosomes, the cell division process with its partitioning of genetic material, as well as a host of specialized functions. Among the more specialized functions are those of active transport, nerve impulse propagation, enzyme secretion, contraction, and other forms of energy transduction. Many, if not all, living cells are able to transport a variety of molecules selectively. Many become specialized to do so, and transport a variety of molecules across their entire structure. Knowledge and understanding of the mechanisms involved is paramount. The nerve impulse is a most significant biophysical phenomenon, and the relation between nerve impulse and memory is one of our most pressing problems. Another significant biophysical problem is the transduction of chemical energy into mechanical energy, as carried out by muscle cells and other contractile elements such as flagellae.

The biophysicist is more concerned with the quantitative, analytic, and deductive approaches derived from the physical sciences. His instruments are sophisticated. He uses the electron microscope, the ultracentrifuge, and modern analytical techniques. He has developed a large number of microtechniques that are applied to his problems, the microelectrode, the microspectrophotometer, and methods for microanalysis. Furthermore, he is able to analyze quantitatively his experimental data, build hypotheses, and subject these to mathematical analysis with physical models.

Organ

Cells are organized into tissues, tissues into organs, and organs into entire living units, and these levels also interest the organ biophysicist. Many significant problems exist. A principal problem is the organization and function of the central nervous system, the manner in which information is sensed by peripheral sensors, the manner in which this information is subsequently translated into signals that are transmitted to higher stations, the manner in which these stations process this information and pass it on to even higher levels for further processing, storage, utilization, and the like. Biophysicists knowledgeable in modern communication theory and control theory are especially interested in these systems. How do cells interact to behave in a coordinated fashion? How do tissues and organs interact to likewise behave in an integrated fashion? What are the mechanisms responsible? How does one go about elucidating these mechanisms? Here the analytic approach of the control system engineering scientist plays a significant role, reducing the complex behavior to a level which can be handled by mathematical operations or computer simulation. The organ biophysicist is also concerned with the specialized functions such as cardiac, vascular, respiratory, and renal function. The organ biophysicist is characterized by his ability to capitalize on the approaches of the physical scientist. He makes use of the most sophisticated instrumentation and analysis. Many organ biophysicists are in a position to devise model systems that simulate the biological, and in fact are active in devising a variety of artificial organs for use by medical scientists.

Population

The population level or organization has perhaps attracted the least attention from physically oriented scientists. The problems are those of quantitative ecology, the relation of species to species, and the analysis of these relations. Population biophysics is also concerned with the relations of large numbers of people to machines and how machines can better serve the purposes of man. It is interested in artificial intelligence and learning, and the need to understand intelligence itself. Although this level has not yet felt the full impact of the biophysical sciences, there are many features which suggest that it is a sensitive area for further exploitation.

Other Components

Although the principal activities of the biophysical sciences are focused upon the elucidation and understanding of biological systems, there are other activities that are not readily classifiable according to the level of biological organization outlined in the foregoing section. Some of these other activities have been alluded to above, but perhaps should be amplified. Many of these focus not upon the biological problems per se but are directed more towards development of appropriate instruments and techniques to be used in biological investigations.

Those well acquainted with physics and its applications are in a good position to make significant advancements in new instrumentation and new technologies. Biophysical science has contributed to many of these developments and the resulting instruments are widely used in a variety of investigative endeavors not only by the biophysical scientists themselves but also by biological and medical scientists and, indeed, physical scientists. An inclusive list would be enormous, but any list must include the ultracentrifuge (analytic and preparative), electrophoretic apparatus, light scattering apparatus, and chromatographic techniques, both analytic and preparative, which are all commonly employed in modern biophysical research at the molecular and cellular levels. We must also mention the electron microscope. Here, important refinements have been made that hopefully will improve both resolution and contrast. New techniques that impinge upon the use of the electron microscope have been devised including techniques of tissue fixation, staining, embedding, and thin sectioning.

Also to be included are the variety of spectroscopic techniques, electromagnetic, optical, and mass spectroscopy. Biophysical scientists have certainly contributed to the techniques associated with X-ray diffraction used in the determination of molecular structure.

Automatic methods of data collection as well as new means for analyzing it and utilizing the computer to control data collection are evolving. Special mention should be made of chemical analytic techniques and associated instrumentation for they have virtually revolutionized analytical chemistry. These include chromatography in one form or another–liquid phase, vapor phase, and thin layer chromatography–and on occasions the coupling of chromatographic separation with mass spectroscopic analysis. Biophysical science has led to the development of new electronic circuits for particular purposes and also for microtechniques, transducers, and recording apparatus much of which is now employed in many disciplines.

In addition to instrumentation, biophysical science has given emphasis to the role of mathematical models in the analysis of biological systems. This has allowed the design of more specific and significant experimental approaches in a number of instances. The use of computers by the biophysical scientists has become as commonplace as among the physical scientists, and biophysical science has to a significant degree contributed to computer development.

Another activity is that of fabricating artificial organs and prosthetic devices. These are finding application in medicine and patient care. The artificial heart is a current notable example but there are also sensing devices for the blind, sensing devices for the deaf, and cognitive devices for the recognition of patterns that may come to play an important role in routine medical diagnosis. Also biophysical science is contributing to the automation of clinical laboratory testing, to the analysis of this data, as well as other clinical information that comes to bear upon the ultimate diagnosis of a disease state. It is not difficult to predict what the impact of these developments will be upon the practice of medicine.

DISTRIBUTION OF INTERESTS AND ACTIVITIES

Because of the breadth of the biophysical sciences, and the fact that they impinge upon so many related disciplines, it is difficult to document with any precision the extent of activity at any of the levels of organizations outlined above. The biophysical scientist characteristically publishes in a variety of scientific journals representing those of all the physical sciences as well as the biological and medical sciences. He characteristically participates in the activities of several scientific societies. So diverse has been the activity and its communication that it was not until 1957 that a scientific society representing the interest of the biophysical scientist was organized in the United States. The Biophysical Society attempts to bring together the host of biophysical interests, endeavors, and problems and to give emphasis to the unity that exists in approach to solutions of biological and medical problems. Commencing with only several hundred participants, it now has a membership of over 1400. A principal activity has been to sponsor the Annual Meeting wherein biophysical scientists at every level of endeavor report on their scientific findings and enjoy the cross-fertilization that comes about from discussions with colleagues. An appreciation of the diversity of interest represented in the society can be had from Table I. Here are classified according to field the number of contributed papers and the number of sponsored symposia for the first nine annual meetings. It is apparent that the interest in molecular biophysics as represented by biophysical chemistry, protein and macromolecular chemistry, nucleic acid chemistry, and viruses and bacteriophase, comprises the principal segment of interest. Subcellular and cellular biophysics comes second with its representation in transport and membrane phenomena, contractility, ribosomes and protein synthesis, and radiation biophysics. The interest at the organ level is not to be discounted, especially in terms of the number of symposia that have been devoted to the

TABLE I

SCOPE OF THE BIOPHYSICAL SCIENCES AS REPRESENTED BY CONTRIBUTED PAPERS AND SYMPOSIA AT 9 ANNUAL MEETINGS OF THE SOCIETY

	Contributed	Symposia
Biophysical chemistry	128	5
Protein and macromolecular chemistry	170	6
Nucleic acid chemistry	176	3
Genetics	33	5
Viruses and bacteriophage	111	8
Radiation effects—radiation biology	115	5
Ribosomes, protein synthesis	101	5
Subcellular structure	26	1
Photosynthesis and photobiology	100	4
Cellular structure	10	1
Cellular function, control	76	4
Bioelectric phenomena	40	2
Nerve function	99	1
Muscle and muscle proteins, contractility	110	8
Transport and membrane phenomena	164	3
Microorganisms	22	
Effect of physical agents, cryobiology	95	1
Sensory biophysics	48	9
Electrocardiography	23	1
Circulation, hemodynamics	63	3
Central nervous system	15	8
Mathematical models, theories, and analysis	102	3
Computers and information processing	41	4
New techniques: instrumentation	53	5
Extraterrestrial		3
Total	1,921	98

central nervous system, sensory biophysics, and information processing, i.e. 20% of all the symposia. Population biophysics has played only a minor role to the present time. The Biophysical Society has also helped in the development of the International Organization of Pure and Applied Biophysics (IOPAB) which in this past year has joined the International Council of Scientific Unions to become the International Union of Pure and Applied Biophysics. The international organization has sponsored two International Congresses as well as a number of international meetings of its various Commissions. These developments attest to the recognition that the biophysical sciences are receiving on the international level.

Eight years ago, the Biophysical Society initiated its official publication, the *Biophysical Journal* published by The Rockefeller University Press. In the few years of its existence, its circulation has grown from several hundred to nearly 2000 subscribers. Its initial volume was approximately 500 pages. It is now approaching 1500 pages per volume and it has recently become a monthly publication. Although the communications appearing in the *Biophysical Journal* represent only a small fraction of those stemming from biophysicists, an appreciation of the scope may be had from Table II. Here are tabulated the number of papers published categorized by the level of biological organiza-

TABLE II

SCOPE OF BIOPHYSICAL SCIENCES AS REPRESENTED IN *BIOPHYSICAL JOURNAL*

Field	Level								Total
	Molecular		Subcellular		Cellular		Organ		
Chemistry	Proteins	10	Ribosomes	9	Microorganisms	5			
Biophysical	Nucleic acids	16	Nucleus	4	Biosynthesis	2			
Quantum	Polysaccharides	3	Viruses	8					
Theoretical	Biophysical	9	Bacteriophage	4					
	Kinetics	1							
	Enzyme	4							
	Total	43	Total	25	Total	7			75
Physics	Structure	7	Structure	2	Structure	1	Biomechanical	6	
Biomechanical			Radiation	3	Membrane phenomena	6	Bioelectrical	2	
Classical	Radiation	4					Physical agents	2	
					Bioelectrical and excitation	7			
E and M					Growth and division	2			
Quantum					Sensory	3			
Radiation					Radiation	5			
Solid State					Physical agents	3			
	Total	11	Total	5	Total	27	Total	10	53
Mathematics	Transport	2	Kinetics	3	Transport	8	CNS	4	
Theoretical	Kinetics	3			Nerve	12	Bioelectrical	3	
Models	Coding	1			Muscle	1	Circulatory	1	
Systems					Sensory	1			
	Total	6	Total	3	Total	22	Total	8	39
Total		60		33		56		18	

tion as well as by the most closely related discipline among the physical sciences. It is evident that the principal activity of the biophysical sciences has been at the molecular, subcellular, and cellular levels of biological organization.[2]

SELECTED CONTRIBUTIONS OF THE BIOPHYSICAL SCIENCES

To identify, describe, and place in perspective the many contributions of the biophysical sciences is an impossible task. We choose, therefore, to describe a few of the major contributions and point out their relevance and significance. In assessing significance we will look primarily for the effects the contribution has had upon the field, upon neighboring fields, and upon neighboring disciplines. Another yardstick will be the degree to which a contribution has opened up new fields to future exploration. We will not forget the value of a concept, the impact of which can often be enormous. In other sections, we will discuss more fully the impact of the biophysical sciences upon neighboring disciplines, and the potentialities of the biophysical sciences in terms of possible areas for significant future research.

Significant contributions are rarely the product of a single individual. More often than not they represent the accumulated effort of a large number. We cannot in this brief report, therefore, assign credit where credit is due for undoubtedly many omissions would be made.

The initial development of quantitative mammalian cell culture techniques has been due largely to a group of biophysical scientists. The techniques have been exploited by a large number of investigators in a large number of disciplines and as a result, a number of significant advances have been made. The quantitative study of the effects of ionizing radiation upon mammalian cells was made possible by these tissue culture techniques, opening up a still larger area of important radiation research and fundamental investigation. Although X-radiation had been applied on a more or less empirical basis in the treatment of cancer, quantitative cell culture studies have resulted in promising therapeutic improvements. These researches have given a rational basis for the combination of surgical removal of a cancer and radiation therapy, reducing the hazard of malignant spread, since the malignant cells can be killed without comprising the normal healing of the wound. Other fundamental studies have shown that if DNA is replaced by certain of its halogenated analogs, there is a resultant increase in the sensitivity to ionizing radiation. These findings have led to modification in clinical radiation therapy that is currently under evaluation. They have also led to a greater understanding of the mechanisms involved in radiation sensitivity and, in fact, have promoted the devolopment of antiradiation drugs which offer substantial protection against radiation damage.

The introduction and development of radioactive tracer techniques were based upon the accomplishment of biophysical scientists. Prior to their use, biologists had no basis on which to formulate a concept of the stability of biological structures. The use of these techniques, together with the associated instrumentation, has completely revolutionized our concepts as to the functioning of the biological system at the molecular level. Most of the constituents that go to make up these systems are found to be in a dynamic state constantly being synthesized and destroyed. With these techniques, biochemists have now

[2] A survey of the scientific journals and all biophysical literature, although not attempted for this report, would be of great interest and would likely provide quite a different picture of the scope and distribution of activity.

elucidated most of the metabolic pathways by which chemical transformations are effected and from which energy for cell function is derived. It is to be further added that the concept of the dynamic state made possible by the introduction of radioactive isotopes is now providing a firmer base for evaluation of disease states. One can now study the dynamic processes of disease and measure these quantitatively. This is providing greater acuity for pathological diagnosis and, indeed, in many cases, has contributed to extending our knowledge of disease from a clinical syndrome to a molecular disturbance. Using these approaches, a number of diseases have now been recognized as inherited errors of metabolism, and in a few instances a rationale for therapy has been devised. Phenylketonuria (PKU) is a prominent example.

Radioactive isotopes have played a major role in elucidating the nature of the self-duplicating process of DNA. Through their use the inherent stability of this genetic material was elucidated, and more recently extensive repair systems have been discovered which are able to replace damaged segments of this important information-bearing substance.

At the clinical level, radioactive isotopes are used more and more. They are being exploited in the visualization and localization of cancers, in the assessment of organ function, and for actual therapy. ^{131}Iodine is now indispensable in the diagnosis of all thyroid disease.

The elucidation of the detailed structure of DNA has perhaps been one of the most remarkable and significant achievements of this century. The story is a dramatic one, and so widely appreciated that it need not be detailed here. Suffice it to say that it was the result of the combined efforts of a large number of biophysical scientists as well as others. The final proposed structure collated X-ray diffraction data and genetic data into a beautifully simple model. The deduction of this structure has given us a rational understanding of genetic function at the molecular level. It is now giving us a rational understanding of information transfer, protein synthesis, elementary cellular function, etc. The discovery opened up innumerable new avenues of approach in molecular biophysics; in fact, the implications are beyond the imagination of current technology. Among these are the possibilities of genetic modification or modulation of existing cells. This may ultimately lead to control of growth processes, developmental processes, and elimination of unwanted genetic material. It will ultimately provide us with a rational basis for considering a whole host of disease processes, as well as normal processes, and may thereby point to a medicine and its practice based totally upon rational inference.

Our knowledge and understanding of the structure and functions of cellular membranes has come largely from the contributions of biophysicists. Original conjectures of the structure based upon light microscopy, birefringence studies, and surface behavior of lipids have been to a large measure confirmed. This has been achieved largely by use of the techniques of electron microscopy and X-ray diffraction, and these membranes are now known to consist of a bimolecular layer of lipids, together with proteins, organized in lamellae about 100 A units thick. Biophysical studies have revealed that these membranes have amazing properties of selective permeability, are the site of a variety of bioelectric phenomena, and have a dynamic function related to the excitability first described by Galvani. Through the investigative efforts of a number of individuals, we now have a reasonable but as yet incomplete understanding of the nerve impulse and its propagation. Cell membrane excitability is certainly one of the fundamental processes of living systems, and its elucidation will probably open up many fruitful avenues for further exploitation. Currently we have no firm basis for understanding the nature of neuronal interaction, and thus there is no real basis for understanding the function of the central nervous system. This is a prime requisite for the understanding of behavior and all of its manifestations in both health and disease.

In addition to the phenomena of excitability associated with biological membranes, it is well known that these membranes are intimately related to a variety of other cell functions. The processes of absorption of foodstuffs through the intestinal mucosa, the preservation of salt and water balance by the kidneys, the secretion of hormones by both excrine and endocrine glands, the secretion of digestive enzymes, and even the processes of transfer of genetic material from the cell nucleus to points of protein synthesis, are all intimately associated with biological membranes. It is not difficult to imagine or to predict that, with increased understanding of membranes and the associated transport systems, a more rational basis for modifying and modulating these transfer processes will become commonplace and deeply affect the medical sciences.

Our present-day knowledge and understanding of another fundamental biological process, contraction, is largely attributable to the efforts of biophysical scientists. This fundamental process involves the conversion of chemical energy into mechanical energy. The energetics of the process attracted the interest of the noted biophysicist, A. V. Hill. It is now known that the process involves at least two or three primary protein molecules which, deriving their energy from adenosine triphosphate, a product of metabolism, interact to bring about the structural alteration. The structural relations among these proteins have been studied by the techniques of electron-microscopy and X-ray diffraction, and the results suggest that contraction involves a linear interdigitation of at least two kinds of these proteins. As yet, details are lacking and our understanding is incomplete. The process of contraction is triggered by an electrical event that takes place across the cellular membranes and is found to penetrate the muscle cells. Here again, a complete elucidation of the mechanisms involved will undoubtedly have a major effect, permitting rational considerations of heart disease, vascular disease, and a variety of other diseases.

Certain protein systems are of particular usefulness in medical science. The plasma proteins represent such a system, since they are easily accessible for laboratory analysis, and can be introduced relatively easily into the bloodstream as therapeutic agents. Work during World War II, based strongly upon biophysical principles and methods, did much to increase our understanding of these proteins and to make serum albumin, gamma-globulin, fibrinogen, and other human plasma proteins available for transfusion therapy. On the other hand, much remains to be accomplished in this field, and practical applications of advances here should be rather immediately applicable to medical practice. The plasma also represents a tissue where all of the protein components are easily available for purification and study, and hence this system is useful for the isolation of many purified proteins. Certain of these, and especially the plasma lipoproteins, represent our best model systems for protein-lipid, protein-polysaccharide, and protein–small-molecule interactions. Such systems surely occur in other less accessible tissues, and must also be studied from these sources.

Finally, we come to the achievements of biophysical scientists in determining the complete three-dimensional structure of a number of the protein molecules. This has been a major achievement that has been dependent to a large degree upon the techniques of X-ray diffraction and amino-acid sequence analysis. Knowledge of the complete structure of several proteins taken by itself does not seem so important or significant. However, this knowledge has confirmed the existence of helical structure, first postulated by

Pauling, an important concept in structural organization. Also, it now opens the way for wholesale determination of protein structure which searches for underlying principles involved in higher-order structural organization, and even supramolecular organization. Since there appears to be a direct relationship between amino acid sequence and the nucleic acid sequence, as has been shown by recent superb biophysical researches, crystallographic determination of protein structure will permit "fingerprinting" the gene and open up entirely new vistas involved in the understanding of cell functions. The principles of structure will also go far in the final elucidation of the mechanisms of enzyme action and, thus, the nature of regulation and control.

IMPACT OF BIOPHYSICAL SCIENCE UPON NEIGHBORING SCIENTIFIC FIELDS

There is no denial of the fact that the penetration of physical science into biology has brought about a major revolution in the biological sciences. There is little question that, in turn, the penetration of biological challenges into the physical sciences has had significant consequences. The realization that biological systems may be investigated with the same kinds of approaches as are employed by the physical scientists has greatly matured biology from an earlier stage of qualitative description and classification. At the same time, this realization has brought an enormous unifying force to biology and all of its subdisciplines. Emphasis is now directed at features common to all living systems, rather than to differences.

Biological Sciences

The growth and development of biology has been characterized by early and repetitive fragmentation into subdisciplines, such as botany, zoology (invertebrate and vertebrate), bacteriology, ecology, taxonomy, etc. These subdisciplines gave rise to specialists such as the plant and animal cytologist, the plant physiologist, the microbiologist, the vertebrate zoologist, etc. However, none of these subdisciplines or fields have been immune to the penetration of the approaches of the physical sciences. The botanist has now become concerned with the molecular structure of plant viruses, and employs techniques derived from the biophysical sciences to analyze the structure as well as the functional penetration and injection of the genetic material into the plant cells. He employs cell culture techniques and inquires into the mechanism whereby the viruses direct the synthesis of more virus. The zoologist, instead of focusing on many species differences, now directs his attention toward the mechanisms of life processes. He is concerned with structural entities as determinants of function. He also recognizes that the modern botanist shares many of his own interests. The microbiologist directs his attention toward inquiry into synthetic mechanisms at the molecular level, and shares this information with his colleagues in botany, zoology, and many of the other subdisciplines. The modern ecologist has before him quantitative techniques for inquiring into the relationships between the various forms of life. He now constructs mathematical models, analyzes them, and thereby gains greater insight into the ecological structure that exists. The science of systematics or taxonomy has before it an entirely new molecular approach. The recognition that DNA is the primary genetic material has led the biophysical scientist to search for common denominators in sequence of the nucleotides in the various levels of evolutionary evolvement. He has found similarities in the information content in these molecules in terms of this sequence and has learned that the bacteria, the yeast, and indeed, animals, have sequences that are identical or nearly so.

The impact that the biophysical sciences have had on the education of the biology major and the biology graduate student is evident. At the undergraduate level, curricular changes are evolving and have already been instituted in our larger universities. These curricular changes come with the recognition of the importance of the physical sciences and mathematics. "Freshman" biology is vanishing as the entering biology major is advised to obtain fundamental grounding in physics, mathematics, and chemistry. This enables biology to be presented at a level of sophistication heretofore impossible, greatly augmenting an advancement of the student toward the investigative frontiers. There is current heavy emphasis upon the molecular component of biology and this is providing a unifying thread that prevails throughout all of the subdisciplines. In fact, at a number of our universities, the entire academic structure of biology is being revamped and the traditional compartmentalization into separate academic departments is giving way to fusion and merger into departments of biological science or departments of life science. Undoubtedly, these changes would come about more rapidly were it not for the predominance of the classical approaches in a large number of departments. It is not infrequently found at the present time that the entering undergraduate biology major is better equipped to deal with the concepts of modern biology in terms of the quantitative and analytical approaches than is his professor. Heretofore, biology has attracted and trained that segment of our scientific society who have felt little interest in the techniques of quantitative analytic science. This fact has made for the current deficiency in many departments of biology whereby entering students gain no encouragement or opportunity to exploit further the physical and mathematical techniques that they have already acquired and that will ultimately be required. These techniques will thus atrophy from disuse. This deficiency is being counteracted at many of our academic institutions by a loosening of the curricular structure, allowing the undergraduate major to reinforce his physical background with courses outside of the department and at the same time pursue in greater depth his chosen line of interest.

At the graduate level, the impact of the biophysical sciences is also evident. Here again there is heavy emphasis upon molecular biology and molecular biophysics. New courses and instruction are now commonplace and include such titles as "Ultrastructure," "Physical Chemistry of Macromolecules," and "Molecular Genetics." Here again we see a loosening of curricular requirements, with less emphasis upon the broad fields of biology and greater emphasis upon the foundation sciences of physics and mathematics. Furthermore, we see a change in the character of the entering graduate student. Now it is not infrequent that a physics major, or a mathematics or chemistry major, directs his attention towards the biological field. All of these developments are encouraging, but could be further stimulated.

Medical Sciences

The impact of the biophysical sciences on the medical sciences is evident both at the basic science and at the clinical science levels. Modern departments of anatomy are now almost unrecognizable in terms of the traditional composition and emphasis that these departments provided a few decades ago. Emphasis is now upon ultrastructure. The electron microscope is almost ubiquitous. Investigative endeavors extend beyond the morphological as keen interest develops in the functional relations that impinge upon the structural. The modern anatomist is concerned with electron stains and improvements in histochemical techniques, and enormously interested in means to gain another order of refinement in microscopic resolution.

It has already been pointed out in the previous section how radioactive isotopes have enormously influenced and revolutionized biochemistry. Biochemistry has also felt the impact of other approaches and techniques derived from the biophysical scientist. Biochemists are now interested in the physical properties of the constituents that go to make up the biochemical machinery. Their interest is in the enzymes, the structure, and the relation of the structure of the active site to its function, and the exploitation of the full gamut of modern instrumentation in an effort to achieve their ends. In fact, it may be said that among all of the basic medical sciences, biochemistry has been the most responsive to developments occurring among the biophysical sciences. Certainly at the molecular level of investigative pursuits, there is little that differentiates the modern biochemist from the molecular biophysicist. In this respect the impact is complete.

Physiology is another basic medical science that has undergone considerable change as a result of the influence of the biophysical sciences. Perhaps most obvious has been the increased utilization of sophisticated instrumentation. This has permitted the recording of physiological variables originating from the most micro of transducers to the simultaneous recording of a large number of physiological variables. It is becoming rather commonplace to see sophisticated techniques of handling data and analyzing them being used. The use of computers is widespread. The formulation of mathematical models is not unusual. Many physiologists may now become interested in modern information theory and control theory. The words "feedback" and "control" have become routine in the vocabulary of the physiologist. In recognition of the impact of the biophysical sciences, many physiology departments have become departments of physiology and biophysics.

The current situation in microbiology is analogous to that in biochemistry. Modern departments of microbiology have acquired the complexion of the molecular biologist interested in gene structure and its transformations, interested in the molecular architecture of viruses and in the biophysics of virus-host interaction. Many departments have seen the development of cell culture techniques and these are being exploited further in the interest in the immune response in terms of cell surface behavior. One also sees interest in the mechanisms of protein synthesis and concern for elucidating the primary mechanisms that lead to immune bodies specific for a stimulating antigen.

The current situation in pathology is quite analogous to that in anatomy, both having felt the impact of the biophysical sciences' modern techniques that are being brought to bear upon their problems. Pathological investigations are now at the ultrastructural level, examining the morphological changes associated with disease. Molecular pathology is a term that will undoubtedly acquire greater significance and importance with the further acquisition of knowledge concerning the detailed role of biological molecules in the disease process.

Finally, among the basic medical sciences, we come to pharmacology. Here again we see the enormous impact of molecular biophysics. Drug action is now being interpreted in terms of molecule-molecule interaction. Receptor sites are being investigated not just in terms of dose response, but with the use of modern sophisticated instrumentation, electromagnetic spectroscopy, and the like. Furthermore, there has been a gradual influence to replace the empirical approach of the past with a rational approach using molecular orbital theory in the design of new drugs that increase the desired effects and diminish the unwanted side effects. The term "molecular pharmacology" has come into being and there has, in fact, been established a *Journal of Molecular Pharmacology*. Many other influences that parallel those in biochemistry and physiology could be mentioned, but suffice it to say that the impact has been significant.

We now turn to the clinical sciences and note that the impact of the biophysical sciences has been no less than in the case of the basic medical sciences. The impact, however, has been different and it differs more qualitatively than quantitatively. The influence has been less at the molecular and cellular levels of organization, and far greater at the organ level of organization. Likewise, the clinical sciences have felt an enormous impact from instrumentation, leading to improvement of diagnostic techniques. They are yet to feel the full impact of the application of information systems. In every clinical department, however, we now find clinical investigators utilizing the techniques of the basic medical sciences which have, to a significant degree, been derived from the biochemical and the biophysical sciences. The clinical investigator is becoming more basics oriented. He is finding it necessary, in order to understand the problems of medicine, to undertake laboratory research. He is no longer content with clinical observation. Perhaps this can be attributed in part to the influence of the biophysical sciences, if not directly, then certainly indirectly. We have seen introduced into the clinic the concept of molecular medicine. The fact that a disease can result from a minor molecular change and can be understood in these terms is of great conceptual significance. The classical example of such a molecular disease is sickle cell anemia.

In the way of improved diagnostic techniques, the widespread use of radioactive isotopes has already been noted. In addition we are seeing the introduction of automatic computer-controlled techniques in the diagnostic and clinical laboratory. We are seeing the introduction of ultrasonic techniques, especially in attempts to visualize soft tissue masses. We are seeing refinements in radiological examinations. The use of image intensifiers has considerably reduced exposure to ionizing radiation. Radiologists are becoming aware of the problems of pattern recognition, and are acquiring interest in means to automatically examine diagnostic films to eliminate the normal. Similarly, cognitive systems for the recognition of abnormal EKG patterns and EEG patterns are being developed. As has been pointed out already, many developments are taking place in the field of artificial organs.

Medical education has perhaps been less responsive to the influence of the biophysical sciences than has biology. This may be due to the presence of a greater component of the stabilizing influences of tradition. Also, medical education is stabilized through the influence of creditation boards and licensing requirements. Nevertheless, there are some curricular developments that are coming about. In many institutions some instruction is taking place on an interdepartmental basis, which is in recognition of the unity of the science.

There has been some increase in the emphasis being given to the physical sciences, but at the present time the entering medical student is often more equipped to handle quantitative analytical considerations of life processes than is his instructor. It is not infrequent that one sees a medical student who has majored in the physical and engineering sciences with the intent of applying this knowledge to the solution of a variety of medical problems. Unfortunately, however, for the most part, the physicians who are being graduated today will find difficulty in comprehending the many technological advances that will occur within the next ten to twenty years. Medical schools are aware of this, but have not as yet fully responded. Notwithstanding the fact that there is some recognition of the biophysical sciences, as shown by the establishment of separate departments in some instances, the impact is largely confined to the medical science research endeavors.

Physical Sciences

The impact of the biophysical sciences on the physical sciences has been less dramatic than in the case of the biological and medical sciences. The physical sciences have had a history of interest in biology, and often have been directly motivated by biological problems. In fact, more often than not it has been the physical sciences that have spawned the development of the biophysical.

With the exception of high-energy physics, every other field of physics has felt the influence of the biophysical sciences to some degree. One frequently finds theoretical physicists concerned with the statistical mechanics of macromolecular behavior. Solid-state physicists are often concerned with biological materials. Radiation physicists direct their attention to the nature of interaction of radiation with matter and often deal with biological matter. Not infrequently the involvement of the physicist in biological problems is great enough that, indeed, he becomes a biophysical scientist.

Mathematics has seen some interesting developments. On the one hand, there is the pure mathematician who sees such inherent beauty in his abstract and logical formalism that he gives no thought or hint of its possible applicability to reality. On the other hand, the applied mathematician is motivated by his desire to inquire more deeply into the nature of physical and biological matters, utilizing the powerful deductive reasoning inherent in his approach. A reasonable segment of mathematical activity has been directed towards the life sciences, especially in the field of biostatistics. More recently, biomathematics has developed with contributions from many other fields of mathematics. Perhaps some mathematicians will look to biology to stimulate and guide their mathematical developments toward the comprehension of the complexities of life processes. A large segment of applied mathematics is now being directed towards computer science. Here we also see the influence of the biophysical sciences, and it is not unusual to find individuals concerned with the processes of learning, artificial intelligence, analysis of complex networks, and simulation of a variety of systems.

There is no question that departments of chemistry have been strongly influenced by biochemistry. The impact of biophysical chemistry is also noteworthy and it is not unusual to find significant activity of this nature being carried out within chemistry itself. Physical chemists in the past have had a tradition of investigating simple systems in the quest for understanding the laws of nature. More and more, however, they are directing their attention towards more complex systems often including the biological. They have now become interested in nonequilibrium processes which is clearly the result of the influence of the biophysical sciences. The physical organic chemist is also now concerned with molecules of primary biological significance. The theoretical chemist is interested in such problems as random coil-helix transformations, lattice models, molecular orbital theory, and the like.

In the last three decades engineering has evolved from a "handbook" science to an applied physical science. In this evolution the biophysical sciences have not been without effect. Many schools of engineering give bioengineering identification and support. In addition, many fields in engineering have felt the impact of the biophysical sciences including industrial engineering, chemical engineering, mechanical engineering, electrical engineering, and even civil engineering. Perhaps electrical engineering has been the most affected and it is not uncommon to find large segments of biologically directed activity within these departments. Such activity may include the information and communication sciences, computer science, cognitive systems analysis, etc. A study of man in relation to machine, behavioral psychology, the principles of optimality, all come into industrial engineering science. Chemical engineers are now concerned with transport processes coupled to simultaneous chemical reactions and find that the biophysical scientist is likewise interested in these problems. Finally, we find a significant influence in engineering in terms of the development of new instrumentation both for scientific use and for direct use in patient care such as pacemakers, artificial organs, and a variety of other prostheses.

Education both at the undergraduate and graduate level in the physical sciences is seeing gradual change. In part this change is being effected as a result of the influence of the biophysical sciences. At the undergraduate level the most significant change is that towards greater curricular flexibility permitting the physical scientist greater exposure to other scientific disciplines including biology. Likewise the mathematician has an opportunity to explore other sciences and the engineers have evolved options that lead to specializations in bioengineering. All of this is healthy and lends emphasis to the unity that exists in science in spite of its division into scientific disciplines.

At the graduate level we note that there are more and more individuals who, once having received undergraduate preparation in the physical sciences, direct their attention toward biology. This is due in part to the many challenges that exist in biology but may also be an expression of the fact that physical science research has become largely a group effort with little opportunity for individual expression. Owing to the sequential nature of education in the physical sciences the physical science major is in a much stronger position to enter biology than vice versa. Biological science on the other hand is characterized more by its breadth than its depth and in general the physical scientist at the graduate level experiences little difficulty in acquiring biological knowledge.

We have taken note of the great impact that the biophysical sciences have exerted upon their neighboring sciences, biology and medicine on the one hand and physics on the other. Alvin Weinberg (*Minerva,* Winter, (1963), page 159) has made a strong point that in establishing the significance of any scientific discipline one should assess this in terms of the impact that it has made upon neighboring areas. If this is accepted as a criterion of significance, then certainly the biophysical sciences must be rated at the top.

BIOPHYSICAL SCIENCE RESEARCH AND RESEARCH TRAINING

Directly identifiable research and research training in the biophysical sciences has largely come into being in the last two decades. Prior to this, biophysical research activity was rather widely distributed and associated with other disciplinary areas. There existed very few, a handful at most, graduate programs in the biophysical sciences. Individuals interested in this interdisciplinary area had to seek their own avenues for obtaining research training and experience. Indeed, the field at this time was characterized by individuals who had made the transition from the physical sciences on their own initiative.

With the recognition of achievement and success came identification. With the identification came visible financial support, both governmental and nongovernmental. Research programs became established, flourished, and proliferated. More and more support became available in large part through the National Institutes of Health. The programming efforts of this agency provided significant stimulation in the field and resulted in its clear identification. With the proliferation of research came demands for the creation of training programs to provide additional, well-qualified personnel.

In spite of the identification given to the biophysical sciences by some granting agencies, the boundary conditions are not clear. Thus it is difficult at the present time to estimate reliably the extent of biophysical research and its dollar support. Much of the

TABLE III

NATIONAL INSTITUTE OF GENERAL MEDICAL SCIENCES

Research grant awards by discipline—FY 1965 and FY 1966

	Fiscal year 1965			Fiscal year 1966		
	No.	$	%$	No.	$	%$
All program areas	1,838	51,629,329	100.0	1,653	54,906,925	100.0
Biochemical sciences	866	22,780,661	44.1	814	24,801,700	45.2
Biochemistry	332	10,718,033	20.7	270	9,672,831	17.7
Chemistry	247	4,598,263	8.8	221	4,511,890	8.2
Enzymology	117	3,206,660	6.2	118	3,558,620	6.5
Biophysical Sciences	110	2,916,284	5.6	121	3,310,292	6.0
Pharmacology-Toxicology	43	931,837	1.8	51	1,688,621	3.1
Biology	5	121,055	0.2	21	1,374,446	2.5
Other*	12	288,529	0.4	12	685,000	1.1
Biological sciences	597	15,912,039	30.8	497	16,377,422	29.8
Genetics	206	6,841,876	13.3	180	6,353,329	11.6
Biology	148	3,359,655	6.5	129	4,406,501	8.0
Physiology	98	2,293,477	4.4	71	2,071,767	3.8
Biochemical sciences	79	1,881,161	3.6	56	1,575,813	2.9
Microbiology	37	866,159	1.7	38	1,208,318	2.2
Other‡	29	669,711	1.2	23	761,694	1.3
Biophysical sciences	238	8,298,158	16.1	232	8,838,371	16.1
Biophysical sciences	109	3,258,304	6.3	113	3,956,059	7.2
Biophysical chemistry	63	1,598,411	3.1	52	1,601,722	2.9
Bioengineering	11	1,330,890	2.6	17	1,266,901	2.3
Biomathematics	27	1,070,970	2.1	16	645,845	1.2
Other§	28	1,039,583	1.9	34	1,367,844	2.4
Medical sciences	137	4,638,471	9.0	110	4,889,432	8.9
Anesthesiology	6	1,144,774	2.2	7	1,439,453	2.6
Pathology	37	1,130,545	2.2	29	1,087,533	2.0
Surgery	26	769,755	1.5	27	818,628	1.5
Other‖	68	1,593,397	2.9	47	1,543,818	2.8

* Includes minor support in Anesthesiology, Behavioral sciences, Biomathematics, Genetics, Microbiology, and Nutrition.

‡ Includes minor support in Anatomical sciences, Biophysical sciences, Endocrinology, Medical sciences, Pathology, Pharmacology-toxicology and History of life sciences.

§ Includes minor support in Anatomical sciences, Behavioral sciences, Biochemical sciences, Biological sciences, Genetics, Radiology and Medical sciences.

‖ Includes minor support in Anatomical sciences, Behavioral sciences, Biochemical sciences, Bioengineering, Biological sciences, Biomathematics, Epidemiology, General medicine, Other medical sciences, Pharmacology-toxicology, Physiology, Radiology, and History of life sciences.

TABLE IV

NATIONAL SCIENCE FOUNDATION

Division of biological and medical sciences dollar value of grants awarded by program and fiscal year (In thousands)

Program	FY 1960	FY 1961	FY 1962	FY 1963	FY 1964	FY 1965
Developmental	1,706	2,440	3,207	3,995	4,160	4,389
Environmental	2,592	3,069	3,922	4,681	3,814	4,613
Genetic	2,136	2,383	3,015	3,812	4,422	4,341
Metabolic	3,096	3,007	4,394	4,493	4,555	3,815
Molecular	5,559	4,622	7,052	8,030	9,550	9,564
Psychobiology	2,161	2,342	2,600	3,332	3,630	4,129
Regulatory	3,573	3,450	4,642	5,180	4,587	5,001
Systematic	2,771	2,683	3,138	3,939	5,118	4,811
General	1,270	3,283	890	1,640	1,518	2,630
Total	42,865	27,279	32,860	39,103	41,355	43,293

Note: The above data are from Division records and therefore may not agree with analogous data available in the official records of the Foundation. Detail will not add to total because of rounding.

support is still implicit in other areas and not explicitly identified, primarily as a result of the manner in which granting agencies have organized their research project reviewing procedures. Current levels of research support in all programmed areas from the National Institute of General Medical Sciences is reproduced in Table III. For the fiscal year 1966, the total dollar support was slightly over $12 million, amounting to approximately 22% of total research support. In Table IV, we summarize data from the National Science Foundation listing the dollar value of grants awarded by program and fiscal year. Here the biophysical sciences are not identified as such; however, if we assume that approximately half of the activity in molecular biology, half of regulatory biology, and one-quarter of genetic biology is of a biophysical nature, the dollar support for fiscal year 1965 totals about $8,300,000, representing about 20% of the total support. Comparable figures from other governmental granting agencies are not available, although it is well-known that significant support comes from the Atomic Energy Commission, the Office of Naval Research, and the National Aeronautic and Space Administration, among others.

In response to the demands for well-trained personnel in the biophysical sciences, a significant number of graduate Ph.D. programs have been established in the past decade. The total graduate enrollment in these programs in the academic year 1964–65 was 503 students. Although this number is small in comparison with other basic medical sciences and other biosciences and represents only 2.8% of the total bioscience enrollment, it is, nevertheless, significant. Furthermore, this figure indicates a 20% increase from the previous academic year and thus leads in percentage growth among all of the biosciences.[8] An indication of dollar support from the National Institute of General Medical Sciences for research training in the Biophysical sciences is obtained from Table V. Support for the fiscal year 1966 amounted to about $6 million representing some 15% of the total available from this source. Our best estimates indicate that in fiscal year 1966, a total of 654 students received support from biophysical sciences training grants, compared with 790 in biochemistry and 506 in physiology. To this total must be added

[8] Data obtained from *Resources for Medical Research*, Report No. 9, May, 1966.

TABLE V

NATIONAL INSTITUTE OF GENERAL MEDICAL SCIENCES

Training grant awards by discipline-FY 1965 and FY 1966

	Fiscal year 1965			Fiscal year 1966		
	No.*	$	%$	No.*	$	%$
All Program Areas	723	36,367,104	100.0	728	41,175,017	100.0
Biochemical sciences	187	9,299,487	25,6	195	10,923,287	26,5
Anesthesiology	11	384,958	1,1	16	983,557	2.4
Biochemistry	86	4,725,803	13.0	87	5,086,434	12.4
Medicinal chemistry	5	152,868	.5	6	259.543	.6
Nutrition	20	653,308	1.8	20	685.928	1.7
Pharmacology	53	2,957,664	7.9	54	3,373,594	8.2
Clinical pharmacology	3	122.054	.4	3	153,139	.3
Toxicology	9	302,832	.9	9	381,092	.9
Biological sciences	291	13,667,722	37.6	281	14,022,781	34.1
Anatomical	47	2,279,990	6.3	44	2,424,319	5.9
Behavioral	26	1,296,430	3.6	27	1,525,008	3.7
Genetics	41	2,690,258	7.4	38	2,657,828	6.5
Laboratory animal	6	210,857	.6	6	273,124	.7
Microbiology	68	2,720,082	7.5	66	2,794,370	6.8
Multibiological	27	1,491,050	4.1	27	1,536,844	3.7
Physiology	76	2,979,055	8.1	73	2,811,288	6.8
Biophysical sciences	84	5,431,950	14.9	83	6,048,397	14.8
Biometry	39	2,479,088	6.8	36	2,552,019	6.2
Biomedical engineering	11	584,501	1.6	15	951,691	2.3
Biophysical	33	2,347,837	6.4	31	2,492,706	6.1
Continuing scientific development	1	20,524	.1	1	87,981	.2
Medical sciences	161	7,967,945	21.9	169	10,144,552	24.6
Bio-information	2	46,333	.1			
Epidemiology	19	1,055,417	2.9	15	1,069,613	2.6
Evaluation	4	33,722	.1	4	39,711	.1
Experimental colleges	4	305,959	.9	3	321,498	.8
Medical scientist	3	331,087	.9	4	640,716	1.6
Medical student	27	1,312,977	3.6	24	1,224,830	2.9
Multimedical	6	547.087	1.5	5	449,106	1.1
Pathology	84	3,930,791	10.8	76	3,954,214	9.6
Radiology	5	214,776	.6	16	1,169,568	2.8
Surgery	7	189,796	.5	22	1,275,296	3.1

* Number constitutes number of active programs and not number of awards.

another 238 in biometry and 115 in bioengineering. These figures are most certainly low for they do not include students who, although enrolled in biophysics programs, obtain degrees in a disciplinary field through which the training program is administered such as physics, chemistry, physiology, or electrical engineering.

TABLE VI

NATIONAL INSTITUTE OF GENERAL MEDICAL SCIENCES RESEARCH FELLOWSHIPS BRANCH

Distribution of approved research career development award applications by disciplinary area

	Number of awards	Amount recommended
Anatomical sciences	3	$ 48,286
Anesthesiology	5	134,405
Biochemistry	20	374,832
Biophysical sciences	10	173,589
Cell Biology	8	125,913
Genetics	12	231,021
Microbiology	8	145,961
Pathology	4	79,494
Pharmacology	4	68,308
Physiology	7	130,238
Surgery	2	51,904
Toxicology	1	16,530
Total	84	$1,581,477

Not insignificant is the support channeled through career development awards to the biophysical sciences. This data appears in Table VI, where it is to be noted that 12% of the awardees are in biophysical sciences.

For the most part, the quality of biophysical research training as currently represented in the 84 programs receiving support from the National Institute of General Medical Sciences appears to be high. Students entering these graduate programs are derived largely from the physical sciences. They enter this interdisciplinary field with enthusiasm and vigor. The programs are unique in terms of their flexibility. They may be tailored to the individual and in general are very closely coupled to investigative endeavors. The final product or output from these programs appears to be excellent, although insufficient time has elapsed for statistically valid judgments to be made as yet. Suffice it to say that the graduate student upon receiving his degree has no difficulty in obtaining an academic position. Even though the number of academic positions in biophysics is not large, the graduate is welcome in basic medical science departments as well as in departments of biology. In fact, he is eagerly sought by these other disciplines. This fact gives confidence to those engaged in education and research training in the biophysical sciences and leads them to expand and strengthen their programs to meet the demands of the future.

It should also be added that the existence of identifiable training in the biophysical sciences has had a strong influence on neighboring sciences. Students identified with biophysical sciences have stimulated the minds of graduate students from other disciplines, providing encouragement to graduate students in the physical sciences to enter the biophysical. They influence the graduate students from the basic medical and biological sciences to acquire more in the way of a good physical science background. In fact, it is probable that these graduate students receive this advice more often from their colleagues in the biophysical sciences than from their own faculty advisors at the present time.

FUTURE AREAS FOR BIOPHYSICAL RESEARCH

The problem of identifying areas likely to produce significant research achievements in the near future is difficult. Very often the most significant results are those that are unpredicted. However, the achievements of the recent past have opened up entire new vistas of investigative areas in both the medical sciences and the biological sciences. Many of these areas are now ripe for harvest and additional research is likely to open up even further vistas permitting much broader and more encompassing concepts to be formulated for the biological sciences.

At the molecular level, at least three areas should be mentioned. First, with our present understanding of molecular genetic control, the position is clear to investigate in a comprehensive manner all molecular regulatory processes that determine the temporal and spacial coordination of cell behavior. It is now known that a degree of regulation is obtained by controlling the synthesis of appropriate enzymes involved in the various cell functions. However, very little is known as to how this genetic expression is modulated. Also, very little is known concerning the finer regulatory control that governs specialized functions of cells. The synthesis of antibodies appears to be under the general control of messenger RNA but, in its final stages of formation, what makes an antibody specific for a given antigen is completely unknown. An understanding of this specificity and its regulation is imperative, and would affect all those instances in which the immunological system is implicated—autoimmune disease, allergies, and organ transplants. Understanding of all these regulatory mechanisms opens up the possibility of rational interference, the implications of which are not difficult to imagine. The conceptual value alone would drastically influence our current views of disease processes, and this understanding is very likely to point to possibilities of rational therapy at the molecular level.

Second, and again related to our understanding of molecular genetics, is the area of developmental biophysics. This area involves the problems of cell growth, differentiation, and development of specialized tissues. The mechanisms whereby undifferentiated cells evolve into a well-differentiated structure is undoubtedly a complex sequence of events and must, in the views of many, involve specific chemical mediators. Search for these mediators, with concommitant gain in understanding of these processes, must have far-reaching consequences. Not only will the consequences relate to the problems now posed by anomalous embryonic development, but the implications that it bears to organ replacement are enormous. It is not beyond the imagination that once the mechanisms are understood it will be possible to induce the regeneration of specific organs damaged from trauma or by the normal processes of senescence, and thereby achieve a rejuvenation that would otherwise be impossible. To the degree that progress can be made in this area, it is likely to be one of the most significant in terms of our principal current medical problems, impinging upon all of the degenerative diseases, such as the rheumatoid diseases, heart and vascular disease, as well as cancer.

Third, the area of molecular neurobiophysics would appear to be important in terms of what is likely to be achieved. Molecular information storage is now a well-established concept, but how the central nervous system operates even as a memory system is not at all understood. Parallels have been drawn to the genetic; however, there exists at the present time no rational basis or good hypothesis as to how electrical events of the nervous system can be translated into permanent and retrievable structural information entities. Intensive effort along this line will udoubtedly reveal the pattern and thereby open up entire new vistas for exploitation in the search to understand the central nervous system. Although the implications are somewhat beyond the imagination at the present time, there is little question that gains in this area will certainly influence the entire field of behavioral sciences.

At the cellular level one can identify several areas where investigations are likely to lead to fruitful gains. Ultimate understanding of the detailed molecular mechanisms of energy requiring transport processes will undoubtedly open up many new avenues to be exploited for the rational treatment of many disease processes. Similarly, the detailed understanding of the mechanism of nerve impulse excitation and propagation will undoubtedly point towards a clearer path for investigating all aspects of central nervous system functions. A detailed understanding of the muscle contractural system is very likely to exert a significant influence upon a variety of medical problems and our current means of dealing with these, as well as point to significant new possibilities for engineering developments and applications. Finally, problems involved in cell replication and division and their control are certainly most important. Elucidation of these problems will bear a direct relation to our understanding of cancer no matter what may be the etiology, and will undoubtedly suggest means of rational and specific interference that will do much to bring these diseases under control.

At the organ level of biological organization, the problems of understanding central nervous system functioning remain paramount. Although there is some question as to whether this field is currently ripe for significant investigative endeavors, its importance in terms of fruitful outcomes is overriding. It would appear that complicated direct experimentation on the brain to obtain detailed knowledge of both temporal and spacial electrical potentials has little hope of leading to an ultimate understanding. On the other hand, it would appear that considerable progress could be made in formulating conceptual mechanisms as to how the central nervous system operates. These conceptual mechanisms would in turn suggest crucial and significant experiments that may ultimately prove or disprove a particular concept.

The area of tissue preservation, impinging directly on present medical problems and future therapeutic approaches appears amenable to biophysical approaches. Long-term blood preservation is as yet unsolved. This involves not only the fundamental considerations of structure and structural stability, but also the problem of viral hepatitis, the detection and selective destruction of this infectious agent. Equipment design for efficient processing of blood for storage and its subsequent retrieval for use are problems for the biophysical engineer. The preservation of other tissues and entire organs for subsequent transplant is currently a pressing problem and requires diligent biophysical approaches to effect a satisfactory solution.

Finally, at the organ level, the understanding of regulatory and control mechanisms is likely to make a significant impact on the concepts of disease processes. Certain aspects of these mechanisms, especially those that attempt to formulate the problem in a precise and unambiguous manner that can be subject to a systems analysis and subsequent experimental tests, are likely to be particularly rewarding.

At the population level of biological organization, there exists a large number of significant problems that lie unexploited by current techniques. It is felt that gratifying gains can be made with attempts to formulate behavioral and sociological problems in a more quantitative and analytic fashion. It is only in this way that we will be able to ultimately approach a true understanding of cultural values that form such an important portion of cultural conflict. No one will deny that as populations continue to expand, sociological and cultural misunderstanding become ever-increasing and critical problems.

Theoretical biophysics and instrumentations for biophysical research are two broad areas that cut across all levels of biological organization and deserve special mention.

Since the biological and medical sciences have emerged from the embryonic stage of observation and description, it now becomes apparent that considerably more effort should be devoted towards theory. Theory has characterized a large segment of the physical sciences and is destined to become a much more significant segment of the biological sciences. In giving theory and theoretical approaches greater emphasis, we look for two primary and significant gains. Theory serves to codify a large body of knowledge into an understandable and clearly delineated concept. The theory provides a degree of predictiveness which should serve to guide the diligent experimentalist in undertaking the more critical and thereby more significant experiments, thus avoiding a large amount of pedestrian research.

In regard to instrumentation and the devolopment of new techniques, there are always obvious needs. The electron microscope has received a great deal of attention. The needs for further refinement both in this technique and the technique of field emission microscopy have been well pinpointed in a recent conference sponsored by the National Institute of General Medical Sciences and thus need not be amplified here.[4] There is also a great need for further developments at the light microscopy level of resolution, especially in terms of spectrophotometric observations that will provide simultaneously both good spacial resolution and temporal resolution. Such instruments would play a valuable role in a large amount of biophysical research at the cellular level of organization. Many other microtechniques are in demand that will impinge significantly upon the problems of biological organization and the large degree of heterogeneity of structure that is observed. In addition, we need to devise new techniques for dealing with the large amount of information that will be forthcoming as we proceed to examine biological function at the microscopic and molecular level. We need a greater degree of automation in handling this information, processing it for a more rational deductive analysis. Instruments providing microanalysis are urgently needed and perhaps these could be best coupled to the developments of the microbeam electron microscope that is currently in the developmental stages.

At the clinical level involving all of diagnosis and patient care, there is urgent need for clinicians to have assistance in formulating the wealth of information derived from clinical histories, physical examinations, laboratory examinations, patient progress reports and therapeutic regimes into more quantitative and meaningful assessments. This is requisite prior to expecting significant progress in the exploitation of electronic data processing techniques to assist in medical diagnosis and patient care. Progress is being made on aspects of these problems such as the automation of clinical laboratory examinations and the design of cognitive systems for pattern recognition. However, in all probability, significant new techniques of analysis must be devised, such as extensions of those dependent upon Bayes' Theorem and cluster analysis or even radically new approaches.

In concluding this presentation of possible areas for immediate and future research that are likely to lead to significant results, a comment as to what constitutes scientific progress is perhaps in order. In general, progress is all too slow, halting, and erratic. Significant breakthroughs come all too infrequently. The rate of progress appears to be inversely proportional to the maturity of a scientific field. An immature field is characterized by research that is largely observational and based upon empirical approaches.

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[4] See "High Resolution Microscopy in Biomedical Research" and covering Memorandum dated 31 May 1966, to Participants, Conference on Electron Microscopy, from Chief, Research Grants Branch, NIGMS.

Such has characterized much of the medical and biological research of the past. It has been enormously successful. One need only point to the fact that there has been a virtual eradication of infectious disease that so significantly affected our average life span. However, we did not have to know the nature of a virus to develop vaccines that protect us from them. We did not have to know about the mechanisms of action to find antibiotics effective against so many pathogenic bacteria. We did not have to make a very penetrating deduction to realize that cancerous growth can often be removed by surgical intervention. Although great strides have been made in the medical sciences, the next generation of medical problems—the ones currently under attack—represent those that are at least ten times more complex than those that have been solved in the past. The problem of cancer is closely coupled with normal cell development without which we can understand very little. The problem of abnormal development, mental retardation, degenerative diseases, the problems of senility, and the problems of behavior are all problems that are internal to the biological system itself. Their solution will be closey coupled to our knowledge and understanding of basic, fundamental biological processes. These arguments point to only one thing—greater significance and importance must be attached to obtaining knowledge and detailed understanding of these fundamental biological processes. Thus, even greater emphasis must be placed on basic science if we are to continue to make the strides that have characterized the past.

RECOMMENDATIONS

We recommend that the growth of both training and research in the biophysical sciences be set at an annual rate 3–5% greater than the average for all biomedical science.

The future rate of growth in the biophysical sciences depends primarily on the rate of growth of science in the United States. "The Wooldridge Report"[5] estimates that biomedical research expenditures should increase from 0.25–0.35% of the Gross National Product in a period of about eight years. If we assume an annual growth rate of 5% in the GNP in constant dollars, this means a doubling time in biomedical research of some eight years, or an increase of about 8.5% per year. The President's Commission on Heart Disease, Cancer and Stroke[6] recommends a more rapid rate of growth both for "The Development of New Knowledge" (Appendix A, Chapter 7), and for "Training for Research" (Appendix A, Chapter 6, Item 22). The recommended doubling time for each is about three years, or a compound rate of growth of about 23% per year. We believe that a reasonable rate of growth should lie between these two estimates and could be based on Dr. Harvey Brooks' estimate of the rate of growth for university scientific research of 13–15% annually (National Academy of Sciences report, "Basic Research and National Goals,"[7]). Dr. Brooks based his estimate on an annual growth rate of 10% in the numbers of graduate students and an annual rate of increase of 5% in the cost per student in constant dollars.

In view of the basic nature of biophysical science and its additional importance in contributing trained biophysical scientists for research careers in other disciplines, we recommend that the rate of growth of biophysics should be greater than the proposed national average, by an additional 3–5% per year. Thus, on the basis of the Brooks' estimate the rate of growth of support in biophysical science should be 16–20% per year in constant dollars. This extra emphasis on biophysics is in accord with the "Wooldridge Report" concerning NIH Extramural Programs: "Increasing quantification of the biologic sciences requires increased participation of physical scientists and mathematicians in all aspects of NIH operations. The Institutes should take an active role to encourage this participation where appropriate." To be sure that the "Wooldridge Report" is implemented, the recommended annual rate of growth of 16–20% must apply not only to training in biophysics research but also to research grants which will enable the trained graduates in the biophysical sciences to carry on fruitful research after their training has been completed.[8]

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[5] *Biomedical Science and Its Administration.* A Study of the National Institutes of Health. The White House, February 1965. p. 83.

[6] A *National Program to Conquer Heart Disease, Cancer and Stroke,* A Report to the President, December, 1964.

[7] *Basic Research and National Goals.* A Report to the Committee on Science and Astronautics, U.S. House of Representatives by The National Academy of Sciences, 1965. p. 94.

[8] Incidentally, our recommendation is in reasonable agreement with the proposed rate of growth in chemistry as given in the National Academy of Sciences—National Research Council report "Chemistry: Opportunities and Needs" which recommends an annual growth rate in chemistry of 20% for three or four years to be followed by a period of 15% annual growth (page 22).

We are cognizant of the fact that such a rate of growth should not be maintained for an indefinite period but should gradually decrease as the rate of supply of trained biophysical scientists comes into balance with the needs of the country. We envisage therefore that at some point in a period of 10–20 years the rate of growth of biophysical sciences should approach the rate of increase of the Gross National Product. If, as we suppose, scientific progress continues to make an important contribution to our society, the rate of supply of scientists may be set somewhat higher than the rate of growth of the GNP but it seems important to recognize the need for an orderly transition to a somewhat slower rate of growth as we begin to make increasing progress toward our national scientific goals.

We recommend an annual review, at the highest level within the National Institutes of Health, of the long-range plans for biomedical research and its rate of growth.

The desirable rate of growth of biomedical research should be the subject of continual examination and evaluation and the proposed Policy and Planning Council ("Wooldridge Report," page 46) should make annual recommendations on this subject. If it appears necessary and desirable to establish a growth rate higher than the figure of 13–15% estimated by Dr. Brooks, the rate of growth in the biophysical sciences should also be increased so that it still remains 3–5% higher than the average in order to meet the national goals. The Policy and Planning Council should also be charged with the difficult task of deciding when the rate of growth of biomedical research should be brought in line with that of the GNP and of making long-range plans to ensure that the transition be smooth and easy. The achievement of a planned program requires continual attention to two important questions of fund allocation: division between the more basic and the more technological research projects, and division between the several disciplines. We recommend that the Policy and Planning Committee solicit advice on both these questions from the Institutes and establish priorities which should be reviewed annually.