the computer simulations with the protocols of human subjects.

Psychology has discovered an important new tool whose power appears to be commensurate with the complexity of the phenomena the science seeks to explain. As our skills in using this new tool develop, we may expect that the paralyzing conflict between the good problems in psychology and the good techniques will be greatly lessened (*12*).

References and Notes

1. A. Newell, J. C. Shaw, H. A. Simon, in *Self-Organizing Systems*, M. C. Yovits and S. Cameron, Eds. (Pergamon, New York, 1960), pp. 153–189.
2. For discussion of the comparison of the trace of slightly different versions of GPS with protocols, see A. Newell and H. A. Simon, in *Current Trends in Psychological Theory* (Univ. of Pittsburgh Press, Pittsburgh, 1961), pp. 152–179, and ——, *Proc. Conference on Learning Automata, Karlsruhe, Apr. 1961* (Oldenbourg, Munich, 1961).
3. A. Newel and H. A. Simon, *IRE Trans. on Inform. Theory* **IT-2**, No. 3, 61 (1956).
4. H. Gelernter, J. R. Hansen, D. W. Loveland, *Proc. Western Joint Computer Conf. 1960* (1960), pp. 143–150.
5. G. L. Goodwin, *Power* **102** (Apr. 1958).
6. L. A. Hiller and L. M. Isaacson, *Experimental Music* (McGraw-Hill, New York, 1959).
7. A. Newell, J. C. Shaw, H. A. Simon, *IBM J. Research and Develop.* **2**, 320 (1958).
8. A. L Samuel, *ibid.* **3**, 210 (1959); A. Newell, J. C. Shaw, H. A. Simon, *Proc. Western Joint Computer Conf. 1957* (1957), pp. 218–230.
9. J. Feldman, *Proc. Western Joint Computer Conf. 1961* (1961), pp. 133–144.
10. E. A. Feigenbaum, *Proc. Western Joint Computer Conf. 1961* (1961), pp. 121–132.
11. C. I. Hovland and E. B. Hunt, *ibid.* (1961).

12. We acknowledge our debt to J. C. Shaw, our co-worker in the research described here.

Medical Research: Past Support, Future Directions

Aims of the National Institutes of Health are surveyed as its annual budget passes the half-billion mark.

Dale R. Lindsay and Ernest M. Allen

The health status of the nation is a complex matter, involving many factors. Cancer, tuberculosis, heart disease, pneumonia and influenza, arthritis, blindness, deafness, mental illnesses, diabetes—these are only a few of the hundreds of diseases and disabilities that have long afflicted mankind and that still persist as greater or lesser health problems in this and other countries.

New diseases have appeared in the world from time to time, and the industrial age has brought with it environmental health problems not dreamed of by earlier generations. Left to themselves these influences, together with the greater opportunities for the spread of contagion in a crowded urban society, would have brought our national health level to a new low, beneath that of the preponderantly rural society of a century ago. Yet, as we are all aware, such have been the advances in the broad attack upon these influences that there has been a steady improvement in the health status of the nation.

The picture has not been one of uniform improvement on all fronts, as may be seen in the death rates for our two major killers, heart disease and cancer (Table 1). We find encouragement, on the other hand, in figures such as those in Table 2, for three other disease categories. Still other diseases have declined to so low a level of importance in the total health picture that they must be looked for only among the fine details. Typhoid fever, malaria, and smallpox, once scourges, have been tamed. The hookworm problem is steadily diminishing in importance in areas where hookworm was once so prevalent. Pellagra is almost a thing of the past.

Health Parameters

We may feel the need of an over-all measurement that expresses or reflects the nation's present health status and permits us to evaluate past and future change. One that is informative is the age-adjusted death rate in our population for deaths from all causes. It stands now at only 44 percent of the death rate at the beginning of the century and has gone down appreciably even in the past several years (Table 3).

Another over-all measurement, a different health parameter of the population, is the average life span, known technically as the "life expectancy at birth." It stands at the highest figure in our history, is among the highest in the world, and has risen noticeably in even so short a period as the past 8 or 9 years (Table 4).

Further information, of a different sort, dealing with the prevalence of *all* illnesses, not just those that have a fatal outcome, might be had from figures on the average number of days per person per year lost from work or other normal activity because of illness—the average days of "incapacity." No information from which to compute this additional parameter is available for the past decade, but we may anticipate that such data for coming years will be available in the future (*1*).

The death rate, average life span, and average days of incapacity are not, of course, the only informative parameters of the health of a population that one might desire. The summary data that are available and that are given here, however, do reflect the generally favorable trend observed in the past half century and more. They also bring to sharp focus a challenge: It is necessary that the trend, where favorable, be continued or even accelerated, and that every effort be made to reverse the present trend in the incidence and outcome of diseases, such as heart disease and cancer, which have not yet responded favorably.

To accept such a challenge, it is necessary to understand the factors responsible for the improvement in health

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Table 1. Age-adjusted death rates for the continental United States, exclusive of Alaska, for heart disease and cancer.

Year	Deaths per 100,000 population	
	Heart disease	Cancer and other malignancies*
1900	167	80
1950	300	126
1959	291	127

* This category includes leukemia.

that has taken place. One factor is surely the higher economic level of our society: A rising per capita income has made possible a larger investment in health measures, both by the individual and by philanthropic agencies and the state. We shall not attempt to evaluate the magnitude of the contribution of this factor. It may be large, and in the short view it may be even larger than that of the other major factor, research. In short, most or much of the improvement could conceivably be a "catching up," a putting to good use the research findings of the past.

Certain it is, however, that for the improvement to continue, research and ever more research will be necessary. Without it the upward progress in health would necessarily level off to a plateau.

The National Institutes of Health has played a significant part in the support of medical research for only a decade and a half, but its role seems destined to be of even greater significance in the decade to come. In view of the growing importance of NIH on the biomedical research scene, it seems fitting to present a brief account of the growth of research support provided through NIH in the past, of what has been achieved, and of what seems to lie ahead.

Historical Background

At the beginning of the century the part played by the federal government in the drama of medical research was small indeed. Philanthropic granting agencies and universities, with some participation by industry, together with private individuals, constituted the main sources of research support. The federal government's participation traces back only to 1887, when a one-room laboratory, a "laboratory of hygiene" devoted to bacteriological studies on returned seamen (studies of cholera, tuberculosis, typhoid fever, diphtheria, and so on), was established in the Staten Island Marine Hospital. In 1891 this laboratory was moved to Washington, and in 1905, with a greatly expanded research mission—that of investigating "infectious and contagious diseases and *matters pertaining to the public health*"—it moved into its new laboratory building at 25th and E Streets, adjoining the Naval Hospital. It had come to be known officially, in the meantime, as the "Hygienic Laboratory." The research areas into which it extended its activities further increased in number thereafter; cancer was included in 1922, and mental hygiene in 1930. In the latter year the laboratory, with its several divisions, was rechristened the National Institute of Health—a name which was changed in 1948 to the present National Institutes of Health.

It was not until 1938 that the federal medical research effort expanded beyond the confines of government-operated laboratories. The expansion was through grants-in-aid to universities and other private research institutions under the newly inaugurated "research grants program." In that fiscal year the effective appropriation was $91,000. In the next several years, ending with 1945, appropriations for research grants remained at or below this level, but in 1946 an "*expanded* research grants program" came into being, with $780,000 in funds. The next year (1947) the program experienced an increase that was spectacular for the time, to $3.4 million, and now, 14 years later (fiscal year 1961), it stands at $287 million. The "intramural" research effort, within the confines of the National Institutes of Health, grew in the same period from $2.3 million in fiscal year 1946 to $98.4 million in 1961.

The figures for the successive years may be seen in Table 5.

It is important to note that, in the same period, *non*federal support of medical and related biological research also underwent a very substantial increase (for example, from $60,000,000 in fiscal year 1947 to $333,000,000 in 1960). Clearly, the great expansion of federal support has by no means acted to dry up nonfederal funds; it is reasonable to believe, on the contrary, that the increased harvest of research accomplishments brought about by the federal outlay has actually stimulated support of medical research through voluntary channels. Certainly both federal and nonfederal support have risen, each at an unprecedented rate, in the last 15 years, and particularly in the last decade.

Research Achievements

What has been achieved with this unprecedented outlay of federal and private funds? In the first place, to name an intangible but important achievement, there has been a great expansion and intensification of public interest in medical and related biological research. New research findings, if they have news value, are likely to be reported to the general public by the science writers for our newspapers and other periodicals. The average citizen is, accordingly, better informed on health matters than ever before, more "research-minded," more aware of the hopes that research can offer, more insistent that we "get on" with the task of research toward beneficent ends. With this growth in alertness to the promise and importance of medical research has come a willingness to contribute to its support—a willingness to have a greater share of the tax dollar invested in medical research and a willingness to make additional contribution to this urgently necessary activity through nonfederal channels. This aroused interest and willingness to contribute must be regarded as a major achievement of the greatly expanded research effort that has come about, under federal leadership, in the last decade and a half, and particularly in the past 10 years.

Basic research. A second result of the developing research-mindedness of the American public is the greater public understanding of the essential part played by basic research in our effort to conquer disease. Basic research may be likened to the submerged part of an iceberg: It does not call attention to itself, but it provides indispensable support for all applied research directed toward the control or conquest of disease.

NIH-supported research. Although both federal and nonfederal funds for medical research are fundamentally from the same source, differing only in route, it may seem important to attempt to give "credit" to the National Institutes of Health (as to other federal agencies) for the research accomplishments resulting from its grants to universities and other research centers and from the research conducted within this great medical center itself. It is easy enough to enumerate some of the more important discoveries in the medical and related biological sciences that have been made in the past decade or so, and to list specifically some that have been made in the course of work supported by research grants from the

Table 2. Age-adjusted death rates for the continental United States, exclusive of Alaska, for three disease categories.

Year	Deaths per 100,000 population		
	Tuberculosis	Influenza, pneumonia*	Gastro-intestinal inflammatory disease†
1900	199	210	113
1950	15	24	4
1959	6	24	4

* Exclusive of pneumonia in the newborn.
† Exclusive of the newborn.

NIH. This is done elsewhere in this article. It is important, however, first to understand federal support as it has influenced the total body of medical research, regardless of the source of support.

Research expenditures by the National Institutes of Health in fiscal year 1950 represented approximately 18 percent of the total national outlay for medical research. For fiscal year 1960, the percentage stands at an estimated 40 percent, or double the earlier figure. An average of the two, expressed roughly as "one out of three," may be taken as representing the entire 10-year period. One out of every three dollars spent for medical research in the decade was spent via the NIH. Certainly during the latter part of the decade, it may be presumed, one out of every three research findings—big or little, basic or applied—came to light during work financed through NIH support.

But the other two out of three research findings were not isolated—quarantined as it were—from scientific contact with the one. On the contrary, each of these, and indeed every research finding, owes something to other findings that have preceded it. A recent quick count of the number of bibliographic references appended to each of five papers in ten representative journals in the medical sciences reveals that one scientific paper refers, on the average, to between 25 and 30 previously published papers. These papers have contributed either to the investigator's conception of the problem he has attacked, or to his method of attack, or to his interpretation of his findings, or to all three. His work, like the capstone of a pyramid, rests upon the work of others. He has seen findings reported in recent issues of journals, heard them reported at scientific meetings, and even learned about new findings in private conversation with fellow scientists in the same general field of interest.

In short, this "one recent research finding, out of every three," that may conservatively be attributed directly to NIH support has itself undoubtedly been an essential step leading toward the other two, or to *some* other two in the total body of advances in medical research. To disentangle the research achievements clearly creditable to NIH support from the achievements to which NIH support has contributed indirectly by making them possible as "a next step," is quite an artificial separation. To use a phrase from Scripture, "the little leaven leaveneth the whole lump" and cannot thereafter be extracted from it. It must be said that in recent years NIH-supported research has been an important factor, has played an inextricable part, in the general advance in knowledge and practice toward the control of disease, in every area in the total field of medicine and related biology.

The picture would be distorted if the presumably even greater influence *on* NIH-supported research arising from research supported by other agencies—60 percent of the national total, as estimated for 1960—were not also pointed out.

Number of projects supported. The influence of NIH-supported work has surely permeated the whole body of modern research in the medical and related biological sciences, but is it possible to sharpen the focus a bit? Can one be more specific about what the nation has got for the tax money channeled through the NIH? How many research projects have been supported? How many papers have been published? What of importance has been discovered?

The number of separate research "projects" given NIH support in each of the years in the past decade may be seen in Table 6, column 6. The average "dollar size" of a project (col. 2) can also be computed for each year, by dividing the total amount of funds granted by the number of projects. It is recognized, of course, that there is a wide spread in the annual dollar size of individual projects supported by the NIH. Some cost less than $1000 for 1 year; others cost more than 100 times as much. They also vary correspondingly in personnel and equipment, ranging from a single investigator with his microscope to half a dozen interdisciplinary teams, each working with complicated and costly facilities, in half a dozen scattered research centers.

Table 3. Age-adjusted death rates for the continental United States, exclusive of Alaska, for deaths from all causes.

Year	Deaths per 100,000 population
1900	1778
1950	840
1959	770

Table 4. Average life expectancy at birth (age-adjusted rates for the continental United States, exclusive of Alaska).

Year	Life expectancy at birth (yr)		
	Total population	Males	Females
1900	47.3	46.3	48.3
1950	68.2	65.6	71.1
1959	69.7	66.5	73.0

The number of NIH-supported research projects can be appreciated better when it is viewed as a component of the estimated total number of medical and related biological research projects in the nation (Table 6, col. 3). These estimates have been computed by dividing the estimated total medical research expenditure (*2*) for the nation by the "average dollar size" of an NIH-supported research project—that is, the average dollar outlay per year per project (col. 2). The estimates in columns 4 to 6 have been similarly computed. Underlying these computations is, of course, the assumption that the average dollar size of a project, in NIH experience, can be used as an estimate of the average for medical research in general (see Table 6, footnote *).

The NIH supported 10,700 projects in universities and other research institutions in 1960, out of a national total estimated at 38,500 projects.

Table 5. Funds for NIH-supported medical and related biological research for fiscal years 1946 through 1961.

Fiscal year	NIH-supported research ($, millions)		
	Extra-mural*	Intra-mural†	Totals
1946	.8	2.3	3.1
1947	3.4	5.0	8.4
1948	8.9	7.5	16.4
1949	10.9	10.3	21.2
1950	13.1	12.7	25.8
1951	15.6	14.8	30.4
1952	18.2	13.9	32.1
1953	20.3	17.9	38.2
1954	28.9	19.9	48.8
1955	33.9	24.9	58.8
1956	38.6	32.4	71.0
1957	80.6	44.6	125.2
1958	100.0	57.4	157.4
1959	140.7	68.9	209.6
1960	199.2	84.6	283.8
1961	286.9	98.4	385.3
Totals	1000.0	515.5	1515.5

* Grants. † Includes field investigations and administration of research and research grants.

Table 6. Average size of projects (in dollars) and number of medical and related biological research projects for fiscal years 1950 through 1960.

Fiscal year	Average* size of project ($)	Active medical research projects (No.)			
		Throughout the nation†	All nonfederal†	Federal (including NIH)†	NIH extramural research‡
1950	9,649	15,300	9,100	6,200	1,400
1951	10,601	15,400	8,500	6,900	1,500
1952	10,658	16,200	8,800	7,400	1,700
1953	10,261	19,800	10,400	9,400	2,000
1954	11,203	20,100	10,500	9,600	2,600
1955	11,379	21,100	10,700	10,400	3,000
1956	12,470	22,900	12,000	10,900	3,100
1957	14,209	28,000	14,900	13,100	5,700
1958	15,300	32,100	17,300	14,800	6,500
1959	16,584	35,400	17,900	17,500	8,500
1960	18,584	38,500	18,000	20,500	10,700

* "Average" means the average for all projects supported by NIH research grants. These averages were used as estimates of the national average in calculating entries in columns 4 to 6. For the separate institutes, averages for fiscal year 1960 were as follows: Arthritis and Metabolic Diseases, $16,200; Neurological Diseases and Blindness, $21,700; Cancer, $21,100; Dental Research, $13,500; Allergy and Infectious Diseases, $15,000; General Medical Sciences, $18,200; Heart, $19,300; Mental Health, $21,600. The NIH averages in column 2 may possibly be somewhat higher than averages for the nation. † Estimates, calculated by dividing the figures for total reported research outlay (not shown) by the amounts in column 2. Discrepancies are due to rounding of figures. ‡ NIH research grants program.

Number of papers. On publication of a paper from NIH-supported research, the author is asked to (and usually does) supply a reprint for the NIH files. These files are, unfortunately, incomplete prior to 1957; the count for 1957 and later years (believed to be 90-percent complete) is shown in Table 7.

A backward extrapolation of these figures is quite speculative but suggests that the number of papers from NIH-supported research for the year 1950 was in the neighborhood of 2000. The total for the 11 years ending with 1960 is conservatively estimated to be 50,000 or more.

Each paper reports from one to several research findings in its field.

There is reason to believe that the findings from NIH-supported research are of somewhat greater than average scientific importance, for, although the judgment of the mature and experienced investigator of scientific standing is, and should continue to be, sufficient certification of the importance—indeed, the necessity—of any research he proposes, every project supported by an NIH research grant has, nevertheless, been in a sense doubly certified as to its scientific importance and necessity (*3*). Each project awarded an NIH grant has been endorsed by a "jury" of from 10 to 20 distinguished scientists who have studied the proposal, and has been given further consideration by an advisory council of equally distinguished members and recommended by them to the surgeon general of the Public Health Service for grant-in-aid support.

It is reasonable to believe that research undertakings that have been so competently scrutinized and screened constitute, as a body, an aggregate research effort of superior worth and promise. Even if the results from NIH-supported research were not identifiable as such in the vast output of the nation's research laboratories and only the total forward march of research achievement could be perceived, it could still be said with assurance that most of the work coming out of the laboratories receiving NIH support (together with research supported by other agencies using similarly effective screening mechanisms) must be in or near the forefront of the procession.

Listed below are a few research findings from the thousands of significant advances in medicine and related biology that have been made in the past decade in the course of research supported by the NIH (*4*). It should be pointed out again that such findings are but capstones of "pyramids" of findings by many workers, supported by many agencies. These peak findings will, of course, be built in turn into the lower levels of other such pyramids, to be capped by further achievements.

Some Research Findings

Prednisone, a synthetic relative of the steroid cortisone, was found to be as effective as cortisone or hydrocortisone, or more so, for treating rheumatoid arthritis, and to cause less edema or none at all.

The folic acid antagonist methotrexate has been found to have pronounced beneficial effects in cases of choriocarcinoma, a variety of cancer.

With the albino hamster as the experimental animal, it has been shown that dental caries can be both infectious and transmissible. The organism is a streptococcus. A different study has shown that fluoride (1 part per million) in drinking water has a dramatic preventive action in children.

The hemadsorption viruses, members of the parainfluenza group, were isolated and shown to cause many of the acute respiratory infections in children, from afebrile infections to such conditions as croup and pneumonia.

It has been shown that giving cod-liver oil to pregnant rats reduces the incidence and severity of congenital anomalies caused by deficiency of vitamin E in their diet. A change in the balance of the remaining vitamins in the diet apparently compensates to some extent for deficiency of the single vitamin.

The adrenocorticotrophic hormone (ACTH), a protein hormone containing 23 amino acids, was synthesized from the natural amino acids. This is the largest protein molecule yet synthesized.

Convincing evidence that the onset of acute multiple sclerosis, in a case of the disease in man, resulted from injection of rabies vaccine (containing elements of nervous tissue) has strengthened the view that multiple sclerosis, as it ordinarily occurs, is an autoallergic disease representing an immunologic response to some unknown chemical constituent of the patient's own nervous tissue.

Raising the brain's concentration of gamma-aminobutyric acid (GABA), a normal constituent of the brain, has been found to give protection against convulsive seizures.

Scientists studying epilepsy were handicapped by their inability to reproduce it in any laboratory animal until it was found that, after a simple surgical operation in which alumina cream is applied to a very small area of the brain surface, the experimental animal for some months becomes an "epileptic," having typical epileptic attacks.

A viral agent associated with mouse leukemia has been found to acquire such potency in serial passage in tissue culture that it can produce *multiple* primary tumors in mice and sarcomas in hamsters and rats. This discovery strengthens the view that viruses may be at least one of the causes of cancer in man.

Chloroquine and pyrimethamine were

shown to be suppressive, and primaquine was shown to be curative, of malaria. These drugs have now been adopted for use in the U.S. military forces.

It has been shown that the placenta will, if necessary, deplete levels of vitamins B_{12}, B_6, C, and iron in the mother's blood in maintaining these nutrients at more nearly normal levels in the fetal blood stream.

It has been shown that forced oral (or intravenous) administration of large quantities of a solution of one teaspoon of table salt and one-half teaspoon of baking soda in a quart of water can serve in cases of burn shock as an emergency substitute for plasma. In another study it has been shown that, of individuals treated with balanced salt solution and individuals treated with whole blood, more of the former survive.

A living virus, the "tobacco mosaic virus," has been taken apart, into its skeleton of ribonucleic acid and the latter's protein envelope, and reconstituted. The ribonucleic acid is the primary source of the infectious activity of the virus. These findings will lead to a better understanding of the pathogenicity of viruses.

Two specific tests, each based on the bentonite flocculation procedure, now permit diagnosis, in a few minutes, of rheumatoid arthritis and lupus erythematosus.

Mapping of the gene locations in the chromosomes of the red bread mold *Neurospora* is continuing and will contribute information that will ultimately be useful in the effort to unravel the mystery of the action of deoxyribonucleic acid and ribonucleic acid as code-determinants of the hereditary structure and function of all organisms.

It has been found that galactosemia is due to the absence of the enzyme P-Gal transferase—a genetic defect. A quick test on the blood permits diagnosis and prompt institution of a galactose-free diet.

A culture medium of chemically defined composition has been developed that has made it possible to maintain cultures of cells from a variety of tissues (such as normal skin, bone, kidney, connective tissue, and cancers) indefinitely.

It has been shown that production of the fetal type of hemoglobin is favored by oxygen and glucose deficiencies.

A new drug, phenazocine, first conceived on the "drawing board" and then synthesized, has been found to be many times more potent than morphine in relieving pain.

Table 7. Number of reprints of papers on NIH-supported research (extra- and intramural) in the files of the National Institutes of Health.

Year	Number of papers
1957	5,230
1958	5,895
1959	8,364
1960	11,000

An erythropoietic factor is formed by goats exposed to a simulated altitude of 22,000 feet and is secreted in the milk. Injected into rats, it raises the blood hemoglobin and the reticulocyte count.

A new pathway for sugar metabolism, the "hexosemonophosphate shunt," has been discovered. It bypasses the citric acid cycle and contains several previously unknown sugars.

Evidence has been obtained that liver changes similar to those in carbon tetrachloride poisoning can be brought about by central stimulation of the sympathetic nervous system.

Two independent investigators have won Nobel prizes for nucleic acid synthesis—the one for discovering an enzyme that synthesizes deoxyribonucleic acid, the other for discovering an enzyme that synthesizes ribonucleic acid. These two nucleic acids code-control bodily structure and function, apparently throughout all animal and plant life.

A molded plastic replica of a normal mitral valve of the heart has been constructed and used successfully to replace a diseased valve in man.

This list could be greatly extended.

Research achievements summarized. We might summarize research achievements through NIH support as follows.

1) In 1950 the number of published papers from NIH-supported research projects appears to have been in the neighborhood of 2000 or 2500 (reliable figures are not available); in 1960 the number is reliably estimated at 11,000. The total number of such papers from (and including) 1950 through 1960 is conservatively estimated at 50,000.

2) In 1950 the number of active research projects receiving NIH support through its program of research grants to medical schools and other institutions conducting medical research amounted to 1400, out of a national total of medical research projects estimated at 15,000; in 1960 the number had grown to 10,700, out of a national total estimated at over 38,000.

There is every reason to believe that this NIH-supported research (and research supported by other granting agencies with similarly effective screening mechanisms) has, on the average, been of superior scientific merit and importance.

3) The number of research findings reported in papers published in the period 1950–60 that give credit to NIH for support cannot be estimated. At a minimum it would be expected to equal the number of research papers published in the period (estimated at 50,000) and might well be two or three times that number.

4) NIH-supported research has made an inextricable contribution to the total progress of medical science and its achievements in the last 10 or 15 years. The past 10 years' research supported by this and other granting agencies active in the medical and health research field has, without much doubt, played a part in the fall in death rate and the rise in life expectancy that have occurred even in the same decade. It is reasonable to expect that continued or expanded biomedical research in the next decade will have an increasingly important impact on the health of the nation.

Future Research Opportunities

Let us now look beyond the periphery of present biomedical knowledge and mention a few of the areas where it appears that intensive exploration would be rewarding.

It should be understood that no attempt at complete coverage of research opportunities will be made here, and no attempt to shape the pattern of the discussion into conformity with any pre-existing formulation, such as the balanced pattern of program interests of the several institutes of the NIH. An attempt will be made, however, to convey the restrained enthusiasm of many of the group of competent scientists who have left their laboratories in order to render a broader service to medical science through their office in the Division of Research Grants of NIH (*5*).

Instrumentation. The objectives of instrumentation and automation research have been succinctly stated as follows: "to measure (and record) more things, more accurately, and automatically."

It has long been said in science that the ability to measure some important quantity with greater precision by one more decimal place opens up a new era of advance in the scientific field. To be conservative, one might amend the saying to read "two more decimal places" —measurements 100 times more precise. The core of truth in the saying is that the progress of biological science is ultimately dependent upon development of ever more sensitive instruments and methods for making ever more precise measurement of an ever wider variety of things, and that an explosion of new research follows a new and important development in instrumentation. A modern example is the burst of research progress in cell biology that has resulted from invention of the electron microscope and development of the techniques of immuno- and microchemistry, the electron microscope making visible cell structures a thousand times more minute than those visible without it, and microchemical methods making possible more and more progress in the chemical analysis of these minute structures.

Instrumentation (including science technology in general) has been given first place in this survey of important and promising avenues of research effort because it stands at the doorway to progress in science.

Further advances in the sensitivity of instrument types now in use, development of new types of instruments, and further adaptation for biological use of instruments used in other areas may be expected in the next decade, and, with each development, an explosion of new research in the corresponding scientific area. Great advances are to be expected in the coming decade in the adaptation of computers to medical and related biological research. The use of electronic computers for analyzing the complexities of interrelated biological data is in its infancy. Efforts will surely be intensified to develop improved methods for storing and retrieving scientific data, and for analyzing and interpreting them. The further use of computers in the analysis of data from x-ray crystallography of proteins and nucleic acids may be cited as an example.

Quantification and evaluation of the information-input capacity of the various senses may be achieved. Progress may be expected in the development of computer analogs or models for the simpler brain functions. More instrumentation will undoubtedly be developed for continuous measurement and recording of some of the many variables undergoing simultaneous change in the body in response to stress or other change in conditions, or to disease or therapeutic measures, both for purposes of research and for diagnosis and observation in medical practice. The use of computers in the further development of mathematical biology and for further progress toward ultimate automatic translation of foreign scientific literature may be expected.

Prosthesis. Related to instrumentation and associated techniques is the area of prosthesis—a term referring here, in the broadest sense, to artificial substitutes for, or aids to, body parts and functions. Further investigation directed toward the following objectives may be expected: developing artificial heart valves; improving extracorporeal blood oxygenating and circulating units; perfecting techniques for maintaining some part of the body (for example, a cancerous extremity) under a separate circulation with a high concentration of some remedial agent; devising a means of aiding or replacing failing kidney function; improving dental filling and bonding materials; devising a substitute (possibly tactile) for lost vision or for a lost sense of equilibrium.

Tissue and organ transplants. Research may be expected to continue on the problem of the rejection of skin grafts and organ transplants (for example, kidney), which now occurs except in cases where the recipient and the donor of the transplant have near-to-identical genetic backgrounds. Blood and bone-marrow transfusions regardless of serological type may be an associated development, if and when the general problem of immunological rejection of foreign tissue is ever solved. The same process of rejection is, of course, altogether beneficent when the body combats the "foreign tissue" of an invading pathogenic organism.

Tissue culture of bone marrow for purposes of transfusion may be brought nearer in the next decade. "Tooth banks" and tooth transplants are a hoped-for possibility.

Associated with the objective of successfully making tissue and organ transplants is that of regenerating lost tissues. A breakthrough toward controlled and useful regeneration of lost tissues in mammalian forms is hardly to be expected in the next decade, but as a long-term goal it will surely be kept in view, as research is continued on suitable lower species.

Human ecology and environmental health. A vast terrain remains to be explored in the general research area of man and his environment, both animate and inanimate—the mutual balance of environmental factors, beneficent and harmful, as they affect health and disease, longevity, performance levels, and even evolution. Important in this field are also the health interactions between human populations and interactions of these with other populations of animal and plant life.

One of the most important problems in environmental health is protection against unwanted radiation effects. Research has been pressed in the past several years and will surely be intensified in the coming decade.

The problem of making desired food additives safe and of determining a safe tolerance level for adventitious additives (chiefly residues left in food from insecticidal crop sprays) has become increasingly more acute in recent years, as agricultural chemicals and various substances required in food processing and packaging have multiplied. A vast amount of research will be needed to make sure the public is protected. The continued search for better biological tests that are equivalent to lifetime exposure for man is a prime necessity in such efforts.

Closely related to the foregoing problems are the problems of pollution of air and water by substances harmful to health. "Smog" is only one among many such harmful agents. Of prime interest is the pollution of urban air from products of the motor age. Identification of such products and knowledge of their long-term biological effects, with development of suitable control measures, are objectives of pressing importance. The possibility that some of these products of incomplete combustion may be implicated in the steadily growing incidence of malignancy of the lower respiratory tract gives such research added importance. Progress can be hastened through accelerated research in instrumentation; the need for such acceleration indeed pervades all research areas.

The atom bomb is a potential environmental hazard that warrants more health-related research than appears to be in prospect.

Cancer. The search for the cause or causes of human cancer and for means of prevention and better means of therapy has been pressed in recent years to an extent that almost entitles this to be called a crash program. Crucial knowledge is slowly but surely being accumulated. Demonstration of the virus etiology of a variety of cancers (including leukemia) in certain laboratory animals has renewed our hope for an early breakthrough toward control of this dread disease and has already led to more intensified research in this direction. There is also growing, if not indeed conclusive, evidence that carcinogenic substances can reach the body through the inspired air—evidence that relates the cancer problem to the general problem of environmental health. Research in this direction is being pushed and will surely be increased in the coming decade.

Host-parasite relations. The area of research on host-parasite relations encompasses all the relationships between man (and other animal and plant hosts) and the beneficent, neutral, and harmful plant and animal parasites that infest and infect, including viruses, bacteria, protozoa, and other parasitic organisms. An extension of the parasite concept can, of course, bring the invasive cells of cancer into the same category. Research will continue on a broad front on the pathogenic parasitic organisms, on their nutritional requirements and metabolic processes, and on the evolution of pathogenic forms and the development of pathogenicity in forms that were previously inactive (in the carrier state) or harmless or even beneficent (for example, the colon bacillus). The interaction between host and parasite, in particular the effects of the parasite upon the host and the mechanism of these effects, will continue to engage the attention and effort of research workers, as will the continued development of control measures, including antibiotics and other chemotherapy. The development of parasite resistance to such therapy in the course of an infection—a heartbreaking event—and the perpetuation of such resistant strains thereafter to endanger the lives of others are twin problems that will call for intensified further research. The restraint upon one parasitic population that results from the presence of another also deserves more study.

This research area is obviously one of extraordinarily broad scope, including as it does all the infectious diseases. A vast amount of work has already been done, during nearly a century of research, but the area remains at or near the top of any list where priority is determined by pressing need or promising opportunity.

Tissue immune reactions. Closely related to the great research area just discussed is that of the reaction of the body to substances foreign to it—a reaction of either defense or neutralization or acceptance. The preponderance of research in the past has properly been directed toward strengthening the mechanisms for defense, for here lies the greatest need; but when the defense is against a skin graft or a transplanted kidney donated to an individual in dire need, the same beneficent mechanism can act blindly as a liability. The next decade should see an intensification of work in both directions—toward strengthening the body's defense mechanisms on the one hand and toward holding them in check on the other.

Inseparable from the objective of strengthening the body's natural defenses is that of adding new defense factors, chemically tailored to general or specific needs. Research toward this end holds continued promise of future rewards.

Antimetabolites, antibiotics, other chemotherapeutic agents. Although they have been referred to incidentally in the previous discussion, antimetabolites, antibiotics, and other chemotherapeutic agents deserve special mention. Antimetabolites are among the most promising of the agents being tested for anticancer action, and they also offer continued promise in the attack on invading disease organisms. The last several years have seen the testing of all manner of chemical compounds, many thousands of them, for possible anticancer activity. The next decade will see a continuation of such testing and of research toward the development of new antimetabolites and antibiotics and of other compounds for effective chemotherapy.

Heart, circulation, and blood. We may expect further advances yearly in heart surgery and prosthesis, in techniques of localized perfusion, in diagnosis and relief of vascular insufficiencies of various body areas, in the control of clotting, in understanding and controlling the processes in hematopoiesis, and in our knowledge and control of the basic causes of atherosclerosis.

Reproduction. The well-being of the new individual will continue to be the dominant practical objective in research on reproduction, where progress will be dependent upon a clearer understanding of the processes involved and the factors that influence them. Reduction in fetal wastage and deformity (biochemical as well as anatomical) will remain an important immediate objective. Overpopulation and associated hunger in some world areas will continue to stimulate interest in developing more effective measures of birth and population control.

The brain. The outlook for brain research in the next decade is one of continuing investigation with the oscillograph, the electroencephalograph, and other instruments; of localized short-term and long-term brain stimulation and the placing of minute brain lesions, precisely localized; of continued exploration of the biochemistry and the pharmacology of limited areas and of brain secretion of hormones; of deeper delving into the biophysics and biochemistry of excitation in studies on single neurons (and other types of cells); and of continued efforts to extend the limited analogies between brain activity and the function of computers (as a class) in information storage, organization, and retrieval. Both in the field of neurology and in that of mental health, advancement toward the control of disease will be promoted by such research.

Behavioral science, mental health. During the next 10 years we may expect to see more research in which attempts are made to relate mental phenomena to the underlying biochemistry, biophysics, and endocrinology of the brain; more study of the behavioral patterns in the lower animals; and further study of the factors affecting and determining the course of development of the child, enabling him to assume the responsibilities of the adult as a member of society.

Cross-cultural and other studies are needed to determine the influence on mental health of such factors as patterns of thought and behavior, systems of personal and social values, the structure of the family and other social groups, patterns of interaction in the family and community, levels of aspiration in relation to the attendant environmental and economic potentials, and hygienic practices of populations. Such research will promote control of mental disease and control of the development of such patterns of deviance from social norms as alcoholism, accident-proneness, and juvenile delinquency. Research in some of these areas is practically in its infancy.

Aging. Research directed toward discovery of the fundamental processes in aging will be pursued further by investigators experienced in the field of cell biology. It may be hoped that the biochemical, biophysical, and structural differences between the aged and the youthful cell, and the effects of these differences, will begin to be understood.

As for the diseases so prevalent among the aged—heart and vascular and collagen disease (including excessive fibrosis)—and the "natural process" of progressive shrinkage of the various functional cell populations of the body with advancing age, no dramatic "breakthrough" is in sight; but as the coming decade advances, the slow accumulation and piecing together of bits of knowledge gained through basic research will surely bring us nearer to an answer to the problems of aging.

Cell and molecular biology. Reference has been made to improvements in instrumentation that have permitted examination of finer structural detail and chemical analysis of more minute portions of material than was previously possible. The electron microscope and the developments in microchemistry and in x-ray crystallography, together with technical developments in other areas (for example, immunochemistry), have opened up for study the single cell and its constituent structures. Researches on cell morphology, physiology, biochemistry, biophysics, pharmacology, pathology, radiobiology, and genetics are in progress and will undoubtedly be greatly extended in the coming years.

More detailed study of disease processes may be expected, with further exploration of the precise architectural structure of molecules in disease states as contrasted with their structure in the state of health. Although the importance of the precise architecture of molecules in biological processes has long been appreciated, particularly in the fields of enzymology and immunology, molecular biology as a research field is still in its infancy. It will undoubtedly grow in stature in the next decade, as its newly conceived sibling, submolecular biology, just begins to stir.

Nucleic acids. If the research areas in the whole of medicine and related biology were represented as mountain peaks in a vast terrain yet to be fully explored, the Mount Everest in that little-explored country would surely be "Mount DNA." Deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) are the two nucleic acids that are found, singly or together, in the cellular units of all living organisms so far examined, from viruses, bacteria, and other plant forms through all animals forms up to and including man. The most challenging research in the future will be that directed toward the biosynthesis and function of these nucleic acids; for out of such studies will come the revolutionary answers to long-standing questions regarding the phenomena of genetic reproduction (replication) of cell structure and function and the biosynthesis of the proteins, the most important structural components of living systems. Possibly, too, from such studies will come the answers to questions regarding the fundamental nature of cell differentiation, the development in each individual of such different cell populations as those of nerve and liver from an original single cell—the fertilized ovum. New techniques in the study of the nucleic acids have been delevoped in the past 10 years, and it is certain that research on these compounds will be vigorously carried on for many years to come. This research is so basic that dividends can flow from it in almost any direction. One could well be in the direction of cancer control.

Genetics. Closely related to, even inseparable from, research on DNA and RNA is research on the gene population (the "genotype") in the original single cell from which a cell progeny is derived, whether this be a clone community of bacteria in a flask or a cell aggregate making up one human being. What genes are present in the parent cell, what factors determined their presence together, and what bodily attributes (including hereditary disease or susceptibility to disease) each gene or gene group controls—these are some of the challenging questions in genetics. New techniques for visualizing the entire complement of chromosomes in a single cell and identifying each by its peculiar characteristics now make possible a surge of new work on hereditary disease and susceptibility to disease. Control of the complement of genes with which each individual starts his existence is a visionary objective, even though probably unattainable as a goal.

The genetics of new pathogenic strains of organisms; of the first malignant cell to appear in an individual who develops cancer; of the development of resistance to chemotherapy in a viral, bacterial, or cancer cell population—these fields, too, present challenging problems on which more research is urgently needed.

Much of the promise of achievement yet to come from medical and related biological research rests upon the further development of interdisciplinary team work, now well under way. A more extensive development of great research centers for categorial and general research in the coming decade is a strong possibility.

Basic and applied research. The amount of applied research carried on from year to year in the coming decade should be in homeostatic equilibrium with the amount of (pre-existing) basic research, for each is dependent upon the other.

Applied research has as its objective some achievement that can be put to "practical" use in some way other than as a step toward further research. Basic research contributes new variables to science, quantitates them, identifies (and quantitates) new causal relationships between variables, and points out new spatial and temporal groupings of variables and new sequences in their changes in value.

The motivation and justification and the basis of evaluation are the same for applied research in general and for any one project in applied research: They are, respectively, the practical objective and the extent to which it is attained. For basic research, the motivation is scientific curiosity—an almost monastic dedication to the pursuit of learning. The justification (in the eyes of the onlooker, including the one who supplies the funds) is that the stream of applied research dries up unless it is fed by basic research. The merit of any one achievement in basic research is measured by the extent to which it clarifies pre-existing knowledge, contributes toward establishing a new generalization, or simply leads to new research.

The interdependence of applied and basic research has been pointed out. No matter what the practical objective of any applied research is, "spade work" (equated here with basic research), unless it has already been done, is found to be necessary. An enormous amount of basic research may yet have to be carried out before death rates from heart disease and cancer can be substantially improved. Thus, the need for applied research stimulates support of basic research, and the findings of basic research ultimately open the doors to more applied research. There is no reason to believe that this symbiosis will be in any way disturbed in the coming decade.

Notes

1. The data are being collected by the U.S. National Health Survey, which was begun in 1957.
2. This figure is not shown in Table 6 but can be obtained by multiplying entries in column 2 by those in column 3.
3. This can also be said, of course, of work supported by other agencies that have a similarly effective review mechanism.
4. "Research supported by the NIH" includes both grant-supported and intramural research.
5. Grateful acknowledgment is made here for the contribution of these scientists.