Scientific Basis for the Support of Biomedical Science

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Our project had only one goal: to demonstrate that objective, scientific techniques—instead of the present anecdotal approach—can be used to design and justify a national biomedical research policy.

Our interest in this project began in 1966 when President Lyndon Johnson said, "Presidents . . . need to show more interest in what the specific results of research are—in their lifetime, and in their administration. A great deal of *basic* research has been done . . . but I think the time has come to zero in on the targets—by trying to get our knowledge fully applied. . . . *We must make sure that no lifesaving discovery is locked up in the laboratory* [italics ours]."

The position of the Johnson Administration on basic research was bolstered by a preliminary report of a study, "Project Hindsight," commissioned by the Department of Defense and published in 1966 (*1*). A team of scientists and engineers analyzed retrospectively how 20 important military weapons came to be developed. Among these were weapons such as Polaris and Minuteman missiles, nuclear warheads, C-141 aircraft, the Mark 46 torpedo, and the M 102 Howitzer.

Some of the conclusions of that study were as follows. (i) The contributions of university research were minimal. (ii) Scientists contributed most effectively when their effort was mission-oriented. (iii) The lag between initial discovery and final application was shortest when the scientist worked in areas targeted by his sponsor.

The President's words and the Department of Defense's report popularized a new set of terms such as research in the service of man, strategy for the cure of disease, targeted research, mission-oriented research, disease-oriented research, programmatic research, relevant research, commission-initiated research, contract-supported research, and payoff research. These phrases had a great impact on Congress and on the Office of Management and Budget and led to a sharp upsurge of contract research and commission-initiated research supported by the National Institutes of Health (NIH).

Medical and other scientists countered with carefully prepared case reports that illustrated the important contributions of basic, fundamental, undirected, nontargeted research to advances in medicine, social sciences, and physics (*2*).

Since 1966 there has been a continuing debate whether the federal government would get more for its biomedical research dollars if they were used to support clinically oriented research or if they were used to support research that was not clinically oriented.

We believe that the Department of Defense's study suffered from two factors. (i) Only a preliminary report has been released (and that 9 years ago) and even it is not yet widely available. (ii) Some who have read it have transferred conclusions drawn from that study on development of military weapons directly to biomedical research. However, the reports of those who countered Project Hindsight also suffered from one or both of two problems. (i) Some presented single case reports and so were anecdotal or "for instance" arguments. (ii) The cases were selected by those who did the study and so were subject to their bias.

It is easy to select examples in which basic, undirected, nonclinical research led to dramatic advance in clinical medicine and equally easy to give examples in which either clinically oriented research or development was all-important. A classic example of the great importance of research completely unrelated to clinical medicine or surgery was that of Wilhelm Roentgen. While studying a basic problem in the physics of rays emitted from a Crookes' tube, he discovered x-rays that immediately became vital for precise diagnosis of many diseases and later for the treatment of some. A classic example of the importance of mission-oriented research was that of Louis Pasteur. Pasteur, originally trained as a chemist, was employed by the French government as an industrial troubleshooter. Among the problems assigned to him were the practical ones of how to keep wine from turning to vinegar, how to cure ailing silkworms, and how to save sheep dying of anthrax and chickens dying of cholera. The solution of these practical problems led Pasteur to discover bacteria and become the founder of modern bacteriology and the father of the germ theory of disease. A classic example of the importance to medicine of development (as opposed to research) was the mass production of penicillin in the United States in the early 1940's when it was required immediately for England's war effort and later for our own.

The anecdotal or "let me give you an example" approach provides fascinating after-dinner conversation and even interesting testimony before congressional appropriations committees. However, we believe that the time has come for the nation's biomedical research policy to be based on something more substantial than a preliminary analysis of weapons development by the Department of Defense and informal let-me-give-you-an-example arguments by concerned scientists, and that Congress and the Administration should require more than for-instances from proponents or opponents of any policy for the support of medical research. We believe that the design and the broad scope of our study avoid the weaknesses of previous studies and provide an example to show how long-term policies on support of biomedical research can be developed on an objective basis.

Scope of Our Study

Because the heart of our thesis is that the support of research should not be based on selected examples or anecdotes, it was mandatory that we study all of a broad field. We selected the field of cardiovascular and pulmonary diseases because these are responsible for more than half of all deaths in the United States each year and because we have some competence in evaluating research on the heart, blood vessels, and lungs, or know where to go for advice. To ensure that our study was concerned directly with the health of the nation and not with esoteric scientific discoveries, we directed our attention only to clinical advances since the early 1940's that have been

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Table 1. The top ten clinical advances in cardiovascular and pulmonary medicine and surgery in the last 30 years.

Cardiac surgery (including open-heart repair of congenital defects and replacement of diseased valves)
Vascular surgery (including repair or bypass of obstructions or other lesions in aorta, coronary, cerebral, renal, and limb arteries)
Drug treatment of hypertension
Medical treatment of coronary insufficiency (myocardial ischemia)
Cardiac resuscitation, defibrillation, "cardioversion" and pacing in patients with cardiac arrest, slow hearts, or serious arrhythmias
Oral diuretics (in treatment of patients with congestive heart failure or hypertension)
Intensive cardiovascular and respiratory care units (including those for postoperative care, coronary care, respiratory failure, and disorders of newborn)
Chemotherapy and antibiotics (including prevention of acute rheumatic fever and treatment of tuberculosis, pneumonias, and cardiovascular syphilis)
New diagnostic methods (for earlier and more accurate diagnosis of disease of cardiovascular and pulmonary-respiratory systems)
Prevention of poliomyelitis (especially of respiratory paralysis due to polio)

directly responsible for diagnosing, preventing, or curing cardiovascular or pulmonary disease; stopping its progression, decreasing suffering, or prolonging useful life.

To avoid our own bias, we asked 40 physicians to list the advances they considered to be the most important for their patients. We then divided their selections into a cardiovascular and a pulmonary list and sent the appropriate list to 40 to 50 specialists in each field, asking each to vote on the list and to add additional advances that they believed belonged on the list. Their votes selected the top ten advances (Table 1). With these as a starting point, we worked retrospectively to learn why and how they occurred.

With the help of 140 consultants (*3*), including 46 interviewed personally, we identified the essential bodies of knowledge that had to be developed before each of the ten clinical advances could reach its current state of achievement. To make clear what we mean by this, let us consider cardiac surgery.

When general anesthesia was first put to use in 1846, the practice of surgery exploded in many directions, except for thoracic surgery. Cardiac surgery did not take off until almost 100 years later, and John Gibbon did not perform the first successful operation on an open heart with complete cardiopulmonary bypass apparatus until 108 years after the first use of ether anesthesia. What held back cardiac surgery? What had to be known before a surgeon could predictably and successfully repair cardiac defects? First of all, the surgeon required precise preoperative diagnosis in every patient whose heart needed repair. That required selective angiocardiography which, in turn, required the earlier discovery of cardiac catheterization, which required the still earlier discovery of x-rays. But the surgeon also needed an artificial heart-lung apparatus (pump-oxygenator) to take over the function of the patient's heart and lungs while he stopped the patient's heart in order to open and repair it. For pumps, this required a design that would not damage blood; for oxygenators, this required basic knowledge of the exchange of O_2 and CO_2 between gas and blood. However, even a perfect pump-oxygenator would be useless if the blood in it clotted. Thus, the cardiac surgeon had to await the discovery and purification of a potent, nontoxic anticoagulant—heparin.

Table 2. Essential bodies of knowledge required for successful open-heart surgery.

Preoperative diagnosis of cardiac defects
Anatomic and clinical
Physiologic: electrocardiography, other noninvasive tests
Physiologic: cardiac catheterization
Radiologic: selective angiocardiography
Preoperative care and preparation
Blood groups and typing; blood preservation; blood banks
Nutrition
Assessment of cardiac, pulmonary, renal, hepatic, and brain function
Management of heart failure
Intraoperative management
Asepsis
Monitoring ECG, blood pressure, heart rate, EEG, and blood O_2, CO_2, and *p*H
Anesthesia and neuromuscular blocking agents
Hypothermia and survival of ischemic organs
Ventilation of open thorax
Anticoagulants
Pump-oxygenator
Elective cardiac arrest; defibrillation
Transfusions; fluid and electrolytes; acid-base balance
Surgical instruments and materials
Surgical techniques and operations
Postoperative care
Relief of pain
General principles of intensive care; recording and warning systems
Management of infection
Diagnosis and management of circulatory failure
Diagnosis and management of other postoperative complications
Wound healing

These are just a few examples; obviously Gibbon needed many more essential bodies of knowledge. Table 2 lists 25 that we believe he needed in 1954 before he could perform open-heart surgery with confidence in the result; we list all of these because some, such as antibiotics, are so commonplace in 1976 that we forget that even they once had to be discovered! For the ten advances, we identified 137 essential bodies of knowledge.

The knowledge essential for these advances has accumulated over decades or centuries from the lifetime work of many thousands of scientists. It was clearly impossible for us to read all of their publications to determine how and why the research of each was done. But, because we were determined to avoid the let-me-give-you-an-example approach, we did examine about 4000 published articles. Of these, we identified about 2500 specific scientific reports that were particularly important to the development of one or more of the 137 essential bodies of knowledge. We arranged these chronologically in 137 tables. From these, with the advice of consultants, we then selected more than 500 essential or key articles for careful study.

Why did we spend several years collecting and reading thousands of articles and arranging more than 2500 of these in 137 chronological tables before doing our final analysis? There were several reasons.

1) It was essential that we have tangible evidence that our selections came from painstaking, scholarly review and not from the imperfect memories of a group of scientists at a cocktail party.

2) The chronological lists facilitate analysis of lags between initial discovery and clinical application (to be reported elsewhere).

3) They emphasize to the reader that scientific advance requires far more work than that reported by the discoverer or by those who wrote key articles essential for his discovery. We believe that a major defect in education in science in high school and colleges is the perpetuation of the one person = one discovery myth (for example, Marconi = wireless; Edison = electric light) and that this is partly responsible for the anecdotal approach to national science policy. Without a long chronologic tabulation, such as the elec-

Table 3. Chronological events in the development of electrocardiography. The scientists' names that are printed in boldface type indicate key articles.

Year of discovery	Scientist	Event and publication
B.C.	Ancients	Early manifestations of electricity: electric fish, rubbed amber, lodestone, terrestrial lightning
1660	von Guericke	First electricity machine (friction of glass and hand) [*Experimenta Nova Magdeburgica* (Jansson, Amsterdam, 1672), book 4, p. 147]
1745	von Kleist	Charge from electricity machine stored in glass bottle and delivered as static electric shock [Letter to Dr. Lieberkühn, 4 November 1745; J. G. Krüger, *Geschichte der Erde* (Luderwaldischen, Halle, 1746)]
1745–1750	Musschenbroek	Electricity stored in Leyden jar; shocks killed small animals [*Introductio ad Philosophiam Naturalem* (Luchtmans, Leyden, 1762), pp. 477–1132]
1752	**Franklin**	Kite and key used to charge Leyden jar from lightning; identity of lightning and electricity proved [*Philos. Trans. R. Soc. London* **47**, 565 (1751–1752)]
1756–1757	Caldani	Nerve and muscle excited by discharge from Leyden jar [*Institutiones Physiologicae* (Pezzana, Venice, 1786)]
1780	Galvani	Stimulation of nerve by Leyden jar and "electricity machine" caused identical muscle contraction [*Bononiensi Scientiarum et Artium Instituto Atque Academia Commentarii* **7**, 363 (1791)]
1786	**Galvani**	Concept of animal electricity [*Bononiensi Scientiarum et Artium Instituto Atque Academia Commentarii* **7**, 363 (1791)]
1791	**Galvani**	Contraction of heart muscle produced by discharge from electric eel; contraction of muscle caused by injury current [*Dell'uso e dell'attività dell'arco conduttóre nelle contrazioni dei muscoli* (Tommaso d'Aquino, Bologna, 1794)]
1800	Volta	Electricity generated by dissimilar metals; voltaic pile or battery [*Philos. Trans. R. Soc. London Part 2* **90**, 403 (1800)]
1839	Purkinje	Purkinje's fibers in the cardiac ventricles [*De Musculari Cordis Structura* (Friedlaender, Bratislava, 1839)]
1842	**Matteucci**	Muscle contracts if its nerve is laid across another contracting muscle [see Dumas, *C. R. Acad. Sci.* **15**, 797 (1842)]
1843	DuBois-Reymond	Action current in nerve as well as muscle [*Untersuchungen über Thierische Elektricität* (Reimer, Berlin, 1848–49)]
1852	Stannius	Ligatures demonstrating specific conduction paths in heart [*Arch. Anat. Physiol. Wiss. Med.* p. 85 (1852)]
1856	Kölliker and Müller	Frog muscle contraction used as indicator of cardiac currents [*Verh. Phys.-Med. Ges. Würzberg* **6**, 428 (1856)]
1875	Lippmann	Use of capillary electrometer [*Ann. Chim. Phys. Ser. 5* **5**, 494 (1875)]
1876	Marey	Refractory period in early cardiac systole [*Physiol. Exp. Trav. Lab. Marey* **2**, 63 (1876)]
1878	Engelmann	Studied electrical excitation of isolated frog heart [*Pflügers Arch.* **17**, 68 (1878)]
1879–1880	**Burdon-Sanderson and Page**	First ECG in intact animals (frogs) [*J. Physiol.* **2**, 384 (1879–80)]
1883	Gaskell	Sequence of contraction from sinus venosus to atria to ventricles [*J. Physiol.* **4**, 43 (1883)]
1887	**Waller**	First human ECG using Lippmann's capillary electrometer [*J. Physiol.* **8**, 229 (1887)]
1887	McWilliam	Noted fibrillary contractions of heart [*J. Physiol.* **8**, 296 (1887)]
1893	**His**	Atrioventricular bundle [*Arbeit. Med. Klin. Leipzig.* **14**, 14 (1893)]
1893	Kent	Atrioventricular bundle [*J. Physiol.* **14**, 233 (1893)]
1897	Ader	Thread or string galvanometer [*C. R. Acad. Sci.* **124**, 1440 (1897)]
1903	**Einthoven**	Sensitive string galvanometer for measuring human ECG; telemetry of ECG signals [*Pflügers Arch.* **99**, 472 (1903)]
1906	Tawara	Atrioventricular node [*Das Reizleitungssystem des Säugethierherzens* (Fischer, Jena, 1906)]
1907	Keith and Flack	Sinoatrial node, mammals [*J. Anat. Physiol.* **41**, 172 (1907)]
1908	Mackenzie	Polygraph, venous pulse and arrhythmias [*Diseases of the Heart* (Frowde, London, 1908)]
1909–1920	**Lewis**	ECG and arrhythmias in man (numerous articles in *Heart*, a magazine he founded)
1913	Einthoven, Fahr, de Waart	Equilateral triangle theory of ECG [*Arch. Ges. Physiol.* **150**, 275 (1913)]
1914	Garrey	Mechanisms of flutter and fibrillation; "circus" movements [*Am. J. Physiol.* **33**, 397 (1914)]
1915	Lewis and Rothschild	Excitation wave in dog heart [*Philos. Trans. R. Soc. London Ser. B* **206**, 181 (1915)]
1918	Smith	ECG changes after ligating a branch of coronary artery in dogs [*Arch. Int. Med.* **22**, 8 (1918)]
1926	Rothberger	Arrhythmias in man [in *Handbuch der Normalen und Pathologischen Physiologie* (Springer, Berlin, 1926), vol. 7]
1927	Wenckebach and Winterberg	Arrhythmias in man [*Die Unregelmässige Herztätigkeit* (Engelmann, Leipzig, 1927)]
1930	**Wilson**	Laws of distribution of potential differences in solid conductors; modern theory of ECG [*Am. Heart J.* **5**, 599 (1930)]

Table 3 (continued).

Year of discovery	Scientist	Event and publication
1939	Hodgkin and Huxley	Transmembrane action potential recorded in giant axone of squid [*Nature (London)* **144**, 710 (1939)]
1946 1949	Graham and Gerard Ling and Gerard	First measurement of transmembrane potential in skeletal muscle with intracellular microelectrodes [*J. Cell. Comp. Physiol.* **28**, 99 (1946); *ibid.* **34**, 383 (1949)]
1949	Coraboeuf and Weidmann	Intracellular electrode to record mammalian cardiac potentials [*C. R. Seances Soc. Biol. Paris* **143**, 1329 (1949)]
1951	**Draper and Weidmann**	Intracellular electrode used to measure transmembrane potentials of heart muscle cells [*J. Physiol.* **115**, 74 (1951)]
1958	Alanís, González, López	Electrical activity of bundle of His [*J. Physiol.* **142**, 127 (1958)]
1960	Giraud, Peuch, Latour	Electrical activity of bundle of His in man [*Bull. Acad. Natl. Med. Paris* **144**, 363 (1960)]
1967–1968	**Scherlag** *et al.*	Recording from bundle of His by cardiac catheter in man [*J. Appl. Physiol.* **22**, 584 (1967); *ibid.* **25**, 425 (1968)]
1967	Watson, Emslie-Smith, Lowe	Recording from bundle of His in patient undergoing cardiac catheterization [*Am. Heart J.* **74**, 66 (1967)]

trocardiography (ECG) list in Table 3, some might consider that Einthoven in 1903 invented the ECG in its 1976 form, without help from those who preceded or followed him. Chronological tables provide specific evidence for policy-makers that scientists earlier and later than the discoverer have always been essential to each discovery and its full development. A defect in tables is that they can convey only a bit of the message, because even a long list includes only a small fraction of the good, original research that helped to move us away from complete ignorance toward full knowledge.

Definition of a Key Article

1) It had an important effect on the direction of subsequent research and development, which, in turn, proved to be important for clinical advance in one or more of the ten clinical advances under study.

2) It reported new data, new ways of looking at old data, a new concept or hypothesis, a new method, new drug, new apparatus, or a new technique that either was essential for full development of one or more of the clinical advances (or necessary bodies of knowledge) or greatly accelerated it. The key article might report basic laboratory investigation, clinical investigation, development of apparatus or essential components, synthesis of data and ideas of others, or wholly theoretical work.

3) A study is not a key study (even if it won the Nobel Prize for its author) if it has not yet served directly or indirectly as a step toward solving one of the ten clinical advances.

4) An article is a key article if it described the final step in the clinical advance, even though it was an inevitable step requiring no unusual imagination, creativity, or special competence (for example, first person to report on a new drug in humans even though basic work on animals had been done and results in humans were largely predictable) (*4*).

Selection and Analysis of Key Articles

Because these key articles formed the basis of our analysis, we devoted considerable thought to their selection. We realized that bias in selecting them could invalidate our study and that their careful review by consultants was essential. At the same time, experience with pilot studies showed us that scientists are rarely unanimous in voting that Jones's discovery is more important than Smith's. Sometimes this is because of justified differences in judgment; sometimes it is because there is no one article that can be singled out from many in a steady advance with many equal contributors. We solved this problem for the purposes of this study (though not for election of individual scientists to a "Hall of Fame") by first selecting key articles in 42 of our tables and then sending the same tables (with no clue to our choices) to reviewers for their independent selection. We then analyzed the articles that we had selected to determine the goal of the investigators and repeated the same process for the articles selected by our reviewers. Although there was not complete agreement on the selection of individual key articles, there was almost exact agreement on the type of articles selected. Thus the percentage of key articles reporting research that was not clinically oriented was almost identical in their selections and in ours (Table 4). Because our interest was in determining the type of research reported in key articles (for example, clinically oriented research or that which was not clinically oriented) rather than in identifying specific scientists and their reports, we believe that the agreement on type, based on a sample of more than 50 percent of our key articles, justifies our extending it to the whole group (*5*).

Once the key articles were selected, we re-read and analyzed each article to determine the answers to the following questions. (i) How many key studies were clinically oriented? How many were not directed toward the solution of a clinical problem? (ii) How many key articles reported basic research? Other kinds of research? Development or engineering?

Was the Key Research Clinically Oriented?

To eliminate uncertainty about our definitions, in this section we avoid classifying research as clinical investigation, basic research, fundamental studies, directed or undirected research, or targeted or nontargeted research. Instead, we use only two terms; (i) clinically oriented research, and (ii) research that was not clinically oriented.

We define research as clinically oriented, even if it was performed entirely on animals, tissues, cells, or subcellular particles, if the author mentions even briefly an interest in diagnosis, treatment, or prevention of a clinical disorder or in explaining the basic mechanisms of a sign or symptom of the disease itself. Thus the Nobel Prize–winning research of Enders, Weller, and Robbins on extraneural culture of poliovirus in vitro was classified as clinically oriented because the team expressed an interest in multiplication of poliovirus outside the ner-

vous system (for example, in the patient's gastrointestinal tract).

We define research as not clinically oriented if the authors neither state nor suggest any direct or indirect bearing that their research might have on a clinical disorder of humans, even though their work later helped to clarify some aspect of it. An article can be classified as not clinically oriented even if the research is done on a human (for example, Oliver's administration of an adrenal extract, later known as epinephrine, to his son in 1895 to see whether it would narrow the diameter of his radial artery).

Each article was classified as one or the other without consideration of earlier or later work of the same investigator and without being influenced by later stories (written or verbal) of "Why I did my research." The results of classifying 529 key articles into these two categories are shown in Table 5.

These data strongly support our contention that those concerned with preserving or changing national biomedical science policy should disregard anecdotal "evidence" no matter how convincingly the case is presented. Table 5 shows that someone looking for evidence to defend any position on the support of research can get it by choosing the right clinical advance as his example or his for-instance. If one picks vascular surgery or antibiotics or poliomyelitis, one can "prove" that clinically oriented research deserves major support; if one selects hypertension or oral diuretics or new diagnostic tests, one can "prove" that research that is not clinically oriented deserves major support.

The most important figure in Table 5 is that, for cardiovascular and pulmonary advances as a whole, 41 percent of all work judged to be essential or crucial for later clinical advances was not clinically oriented at the time of the research; 41 percent of the investigators, when they did their work, expressed no interest in a clinical problem—their goal was knowledge for the sake of knowledge. These data indicate clearly that planning for future clinical advances must include generous support for innovative and imaginative research that bears no discernible relation to a clinical problem at the time of peer review. Because of many unknown factors (for example, ratio of clinical as compared to nonclinical scientists who do not produce key articles to those who do; relative costs of supporting one type of scientist versus the other), we cannot translate "generous support" into a percentage of NIH's budget for extramural programs. Nor can we transfer conclusions from a study of cardiovascular and pulmonary research to other research fields, such as cancer research. But the conclusion seems inescapable that programs to identify and then to provide long-term support for creative individuals or groups (judged more likely than others to produce key research) should be expanded.

Table 4. Goal of authors of key articles as selected by reviewers and by us from the same 42 tables.

Key articles selected by	Number of articles	Goal was not clinically oriented	Goal was clinically oriented	Percent of total not clinically oriented
Reviewers	494*	189*	305*	38.3
Us	267	101	166	37.8

*Total number of key articles selected by reviewers is higher than number selected by us because (i) the reviewers on the average selected 8.4 key articles per table and we selected on the average only 6.7 for these 42 tables; and (ii) we sent some tables to more than one reviewer.

Was the Key Research Basic or Not?

Earlier, we avoided using the term basic research. We must now use it and define what we mean by it. We classify research as basic when the investigator, in addition to observing, describing, or measuring, attempts to determine the mechanisms responsible for the observed effects; with our definition, basic research can be on healthy or sick people, on animals, tissues, cells, or subcellular components. Our definition differs from the layman's (and some scientists') concept that research is more and more basic when the unit investigated is smaller and smaller; further, it allows that work on small units, such as cells, need not be basic if it is purely descriptive. It steers clear of whether the research was initiated by the investigator or by a commission, whether it was undirected or directed, whether supported by grant or by contract, because who initiated, directed, or supported the research has nothing to do with whether it is basic.

We analyzed each key article to determine how each investigator carried out his research and put each article in one or more of six categories.

1) Basic research unrelated to the solution of a clinical problem.

2) Basic research related to the solution of a clinical problem.

The clinical relationship was obvious when the investigator studied basic mechanisms of disease in patients; when it was not obvious, we depended on the investigator's statement, no matter how brief, that he initiated his research to gain further insights to the diagnosis, treatment, or prevention of human disease.

Two examples will clarify the difference between categories 1 and 2. When Landsteiner discovered human blood groups in 1900 he was investigating a basic problem in immunology and had no thought of the importance of his discovery to the transfusion of blood; this was clearly basic research unrelated at the time to the solution of a clinical problem (category 1). When Landsteiner, in 1909, found that a nonbacterial material (a virus) caused poliomyelitis in monkeys,

Table 5. Goal of authors of 529 key articles that later were judged to be essential for a clinical advance.

Clinical advance	Clinically oriented	Not clinically oriented	Total	Percent of total not clinically oriented
Cardiac surgery	53	35	88	39.8
Vascular surgery	40	8	48	16.7
Hypertension	35	44	79	55.7
Coronary insufficiency	44	21	65	32.3
Cardiac resuscitation	24	16	40	40.0
Oral diuretics	19	24	43	55.8
Intensive care	*	*	*	*
Antibiotics	40	13	53	24.5
New diagnostic methods	41	53	94	56.4
Poliomyelitis	16	3	19	15.8
Total	312	217	529	41.0

*A key article is assigned to only one advance even though it may have been essential to more than one. Because practically every key article in intensive care was also essential to other advances, these articles were assigned elsewhere (for example, to cardiac or vascular surgery, coronary insufficiency, resuscitation, or antibiotics).

this again was basic research but, since it was clearly related to a clinical problem, it fits category 2.

3) Studies not concerned with basic biological, chemical, or physical mechanisms.

These include purely descriptive studies (for example, description of a new disease, such as Stokes-Adams disease, without an investigation of the mechanism); an important observation that initially required no research (inhalation of ether causes anesthesia); a new procedure that required no research (cardiac catheterization); a new operation on humans that first required only perfecting surgical techniques in animals; and clinical tests of a new diuretic, antibiotic, or antihypertensive drug in humans without measurements designed to determine its mechanism of action.

4) Review and critical analysis of published work and synthesis of new concepts (without new experimental data).

5) Developmental work or engineering to create, improve, or perfect apparatus or a technique for research use.

6) Developmental work or engineering to create, improve, or perfect apparatus or a technique for use in diagnosis or care of patients.

The difference between categories 5 and 6 can be clarified by an example. Bayliss and Müller developed a roller-pump in 1929 to solve a problem in basic cardiac physiology; we classify this under category 5 even though later, as the DeBakey pump, it had widespread clinical use. The Drinker respirator (iron lung), developed for clinical use, we classify under category 6.

The results of classifying 529 key articles into these six categories are shown in Table 6. Note that of 567 entries, 209 are in category 1 and 141 in category 2; the total of studies in basic research, either unrelated or related to a clinical problem, was 350, or 61.7 percent of the total number of entries. Other types of clinically oriented studies (some inevitable once the basic research was done) (*4*) accounted for 21.2 percent of the total; development and engineering (much of it inevitable once the basic research was done) (*4*) accounted for 15.3 percent; synthesis accounted for less than 2 percent. Basic research therefore was responsible for almost three times as many key articles as other types of research and almost twice as many as nonbasic research and development combined.

Objectivity of Our Study

Research on the process of discovery is unusually difficult in that the data come from judgments and decisions and not from physical measurements. Further, no matter how many consultants participate in the judgments and no matter how distinguished each is, to be a consultant each must be an expert in his field of knowledge (we cannot ask clergy, lawyers, or ethicists to determine which were the key advances leading to the prevention of poliomyelitis), and as such, each is likely to have some bias.

In the case of our study, its objectivity is strengthened by the fact that, although the data and conclusions emphasize the importance of nonclinically oriented research and of basic research for clinical advance, only 26 percent of our consultants and only 24 percent of advisers on key articles were basic scientists (*3, 5*).

In the long run, data and conclusions from any single study should stand, fall, or be modified not by anecdotes or gut reactions, but by confirmation or refutation by better studies with improved design and more objective methods. We believe that a $2 billion industry might well put more of its annual budget into research on improving its main product, which in this case is discovery and its application.

Summary and Conclusions

There has been much expert testimony before congressional committees and much national debate on the relative value of targeted in contrast to nontargeted and of applied in contrast to basic biomedical research. Most of it has been based on anecdotal evidence and little or none on an objective analysis of research in broad fields of medicine and surgery. This is understandable because for-instances are easy to come by, whereas research on research is unusually difficult and time consuming. Because we believe that national biomedical science policy should be based on research on the nature of discovery and its application, we have devoted several years to analyzing how and why lifesaving advances have come about in cardiovascular and pulmonary diseases. The advances that we studied were open-heart surgery, blood vessel surgery, treatment of hypertension, management of coronary artery disease, prevention of poliomyelitis, chemotherapy of tuberculosis and acute rheumatic fever, cardiac resuscitation and cardiac pacemakers, oral diuretics (for treatment of high blood pressure or of congestive heart failure), intensive care units, and new diagnostic methods. We screened more than 4000 scientific articles published in these fields, selected 2500 of these for further

Table 6. Types of research reported in 529 key articles.

Type	Basic: not clinically oriented	Basic: clinically oriented	Not basic	Review and synthesis	Development: research	Development: clinical	Total
Cardiac surgery	34	23	19	0	3	11	90
Vascular surgery	9	7	14	3	0	21	54
Hypertension	42	16	21	2	0	0	81
Coronary insufficiency	21	20	22	1	1	3	68
Cardiac resuscitation	16	11	9	0	0	6	42
Oral diuretics	23	13	6	1	0	0	43
Intensive care	*	*	*	*	*	*	*
Antibiotics	12	18	21	1	0	2	54
New diagnostic methods	49	21	5	2	17	22	116
Poliomyelitis	3	12	3	0	1	0	19
Total	209	141	120	10	22	65	567†
Percent of total	36.8	24.9	21.2	1.8	3.9	11.4	

*Because practically every key article in intensive care was also essential to other advances, these articles were assigned elsewhere (for example, to cardiac or vascular surgery, coronary insufficiency, resuscitation, or antibiotics). †The total number of entries in the six categories (567) exceeds the total in Table 5 (529) by 38 entries. This is because some key articles fit into more than one category here, particularly when articles reporting development of new apparatus also reported research using it; no article in Table 5 was classified more than once.

consideration, and then analyzed 529 of those that we (and 140 consultants) considered to be essential for the clinical advances.

Our analysis showed the following. (i) Of 529 key articles, 41 percent of all work judged to be essential for later clinical advance was not clinically oriented at the time it was done; the scientists responsible for these key articles sought knowledge for the sake of knowledge. (ii) Of the 529 articles, 61.7 percent described basic research (defined as research to determine mechanisms by which living organisms—including humans—function, or mechanisms by which drugs act); 21.2 percent reported other types of research; 15.3 percent were concerned with development of new apparatus, techniques, operations, or procedures; and 1.8 percent were review articles or reported synthesis of the data of others. Our data show that clinical advance requires different types of research and development and not one to the exclusion of another. Thus the problem is not either-or, but a question of how much support to one type and how much to another. Our data compel us to conclude (i) that a generous portion of the nation's biomedical research dollars should be used to identify and then to provide long-term support for creative scientists whose main goal is to learn how living organisms function, without regard to the immediate relation of their research to specific human diseases, and (ii) that basic research, as we have defined it, pays off in terms of key discoveries almost twice as handsomely as other types of research and development combined.

We believe that much more research needs to be done on the nature of research and its application so that data from objective studies can be applied to all aspects of biomedical research. Because the very nature of research on research, particularly if it is prospective rather than retrospective, requires long periods of time, we recommend that an independent, highly competent group be established with ample, long-term support to conduct and support retrospective and prospective research on the nature of scientific discovery, to analyze the causes of long and short lags between discovery and clinical application and to suggest and test means of decreasing long lags, and to evaluate present and proposed mechanisms for the support of biomedical research and development.

References and Notes

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3. Of these, 70 were clinicians, 37 were basic medical scientists, and 33 were engineers, science administrators (in industry, government, or universities), or science writers.
4. Some consultants did not designate such contributions as key articles. We did, however, because we knew of a number of instances in which the final step was "inevitable" but no one seemed willing to take it (for example, vascular surgery was inevitable by 1910 but was not applied until 1939).
5. Bias could also enter into our selection of reviewers of tables. Thirty-two reviewers were physicians, surgeons, or medical or surgical specialists; 10 were basic medical scientists. All were highly knowledgeable in the field that they reviewed.

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Photochemistry of the Polluted Troposphere

SO_x is now included with NO_x and HC in homogeneous and heterogeneous atmospheric chemistry.

Barbara J. Finlayson and James N. Pitts, Jr.

Photochemical smog was only recognized about three decades ago in Los Angeles, although "London-type" sulfurous smog has been known for at least eight centuries. However, air pollution is not a new phenomenon in southern California. In 1542, heavy haze caused Juan Rodriquez Cabrillo to name San Pedro Bay the "Bay of Smokes," and, as early as 1868, eye irritation was recorded in Los Angeles (*1*).

Since the first recognition that photochemical oxidant (Ox) (*2*) is produced by action of solar ultraviolet (UV) [290 $\lesssim$ wavelength (λ) $\lesssim$ 430 nm] light on mixtures of reactive hydrocarbons (HC) and oxides of nitrogen (NO_x) (*3*)

$$NO_x + HC + \text{solar UV} \rightarrow O_3 + CH_3C(O)OONO_2 \text{ (PAN)} + NO_2 + \ldots \quad (1)$$

where PAN is peroxyacetyl nitrate, its frequency and global distribution have increased dramatically. Thus, under appropriate conditions of emissions, meteorology, and topography, it constitutes a serious problem in many major urban areas of the world; furthermore, its impact can extend hundreds of kilometers downwind.

One goal of current air pollution research is the generation of accurate urban airshed models capable of predicting the impact on air quality of spatial and temporal changes in the quantity and composition of primary pollutants (*4*) under various meteorological conditions. Such models, although complex, are essential for the evaluation of cost-effective pollutant control strategies and transportation, land-use, and growth alternatives. They are also of increasing importance in the development of efficient energy options that minimize adverse effects on public health, as in the allocation of natural gas and low-sulfur fuels, the location of coal-fired power plants, or the use of alternate fuels such as methanol.

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