CAN THE IMPACT OF BASIC BIOMEDICAL RESEARCH BE MEASURED?: A CASE STUDY APPROACH

August 1993

Prepared by

Daniel J. Raiten, Ph.D.
Stanley M. Berman, M.A.
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LIFE SCIENCES RESEARCH OFFICE
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FOREWORD

The Life Sciences Research Office (LSRO), Federation of American Societies for Experimental Biology (FASEB), provides scientific assessments of topics in the biomedical sciences. Reports are based upon literature reviews, analyses of pertinent data, and the scientific opinions of knowledgeable investigators engaged in work in specific areas of biology and medicine.

This report was prepared for the Federation Board in accordance with a motion approved by the Board on April 5, 1992. This report was prepared by Daniel J. Raiten, Ph.D., Senior Staff Scientist, LSRO and Stanley M. Berman, M.A., Senior Staff Consultant, LSRO. The authors acknowledge the support and guidance of the following individuals: Samuel C. Silverstein, M.D., Department of Physiology and Cell Biophysics, Columbia University, College of Physicians and Surgeons; Alexander Lawton, M.D., Department of Pediatrics, Vanderbilt University, School of Medicine; Ronald Kostoff, Director, Technical Assessment, Office of Naval Research; and Cesar Milstein, MRC, Laboratory of Molecular Biology, Cambridge, UK.

The final report was reviewed and approved by the LSRO Advisory Committee (which consists of representatives of each constituent society of FASEB) under authority delegated by the FASEB Board. Upon completion of these review procedures, the report was approved and transmitted to the Federation Board by the Executive Director, FASEB.

While this is a report of the Federation of American Societies for Experimental Biology, it does not necessarily reflect the opinion of the individual members of the FASEB constituent societies.

September 17, 1992
Date

Kenneth D. Fisher, Ph.D.
Director
Life Sciences Research Office
EXECUTIVE SUMMARY

Since World War II, investments in biomedical R&D have been widely accepted as the source of great societal benefits. However, an expanding public debate on funding and management of Federal biomedical research reflects increasing concern over the state of the biomedical research enterprise, and the cost, quantity, quality, character, impacts, and utility of its outputs. Our ability to define and analyze these concerns is limited. This paper provides a framework by which some of the questions may be addressed.

Economic cost-benefit analysis may be a useful technique to address a core question in the continuing debate about the role of the Federal government in financing biomedical research; that is, do the benefits of basic biomedical research justify the costs? While there is an extensive literature on economic analysis of both commercial and public investments, there is little that would be helpful in assessing basic non-mission directed investigator-initiated biomedical research.

A review of the extant literature revealed that efforts to analyze investments in biomedical research have taken two forms: macro-analyses of the impact of spending on public health or economic growth, and cost-benefit analyses (micro-analyses) of specific clinical applications. The analytical frameworks employed in the past have been narrowly focused on applied research and development (when using the micro approach), and aggregative and inconclusive (when using the macro approach). Both approaches fall short in their ability to identify the contribution of basic research to health or economic goals. Consequently, a proposed framework for conducting analyses of the costs, benefits, and impacts of basic biomedical research is presented.

The approach used in this study was an integration of cost-benefit analysis with historical tracing of important scientific developments leading up to a specific research discovery, the methodology for producing monoclonal antibodies (MAb). The historical tracing, beginning with the early developments in immunology and culminating in the hybridoma technology described by Köhler and Milstein in 1975, provides corroboration of the length of the innovation process. The tracing also provides further evidence of the inextricable and unpredictable role of non-directed, investigator-initiated fundamental research in the subsequent evolution of new technology.

The economic analysis provides insights into the extent of the industry which has developed since 1975. Using cost data of the five-year period associated with the MAb work of Köhler and Milstein (estimated to be originally about $330K) and current ($1.9B in 1991) and projected ($4B in 1996) estimates of the extent of the MAb enterprise, a substantial return on investment is demonstrated. In a case-study of a single application of MAb technology, using data supplied by the National Institutes of Health (NIH), the benefit to cost ratio for the initial investment in the development of a screening test for HIV contamination of the blood supply is estimated to be 19:1.

This study establishes the utility of the combination of historical tracing, documents the important role of investigator-initiated research, and cost-benefit analysis to account for the return on the public's investment. Future studies will continue to utilize this approach to document the essential role of basic investigator-initiated research in the health and growth of society.
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I. INTRODUCTION

Beveridge in 1951 stated, "Research is one of those highly complex and subtle activities that remain quite unformulated in the minds of those who practice it. This is probably why most scientists think it is not possible to give any formal instructions on how to do research (Beveridge, 1951)." This was true then and is probably true to some extent now; however, the days in which scientists can remain in their laboratories and expect unquestioned support for their efforts are gone. The biomedical research community must compete for increasingly constrained resources. In addition, as pointed out by Congressman George Brown, Chairman of the Congressional Committee on Science, Space and Technology (Brown, 1992), the scientific community must confront the realities of living in, and interacting with, the elements of a pluralistic society in order to effectively maintain its stature as an "ennobling" force in human culture. The scientific community must be accountable and realistic in its requests for funding. Consequently, there must be effective and convincing examples that can be used by those advocating the continued funding of investigator-initiated non-mission oriented basic research.

In general, efforts to perform analyses of the investment into medical research have taken two forms: macro-analyses of the impact of spending policy on public health or industrial expansion and cost-benefit analyses of clinical applications such as interferon treatment of acute lymphoma. In both cases, the analyses are focused on quantifiable outcomes of research application or effects. But both approaches fall short in their ability to identify the contribution of the basic research that led to the applied research impetus and ultimately to the public health outcomes. Yet, in most cases, the seminal basic research drives the entire process that ultimately leads to economic growth and enhanced delivery of health care.

The conflict between "applied" and "basic" research is perhaps best summed up by the parable recounted by Kornberg (1991) in which a surgeon, while jogging around a lake, spots someone drowning. He dove in, pulled out and resuscitated the victim. The surgeon thereupon continued his jog until confronted with another victim. The scenario was repeated and the surgeon wearily continued his journey. He was soon confronted with several drowning people. While surveying the scene, he spotted a biochemist contemplating the situation. The surgeon's attempts to enlist the active participation of the biochemist in the rescue were met with a slow response to which the surgeon asked, "Why aren't you doing something?" The biochemist replied, "I am doing something, I'm trying to figure out who's throwing all these people in the lake."

The interpretation of this story will be influenced by one's perspective; however, the relevant message is that basic and applied research are not mutually exclusive. As noted by Kornberg (1991), "... the war on disease must be fought on several fronts. Some must contribute their special skills to the distressed individual while others must try to gain the broad knowledge base necessary to outwit both present and future enemies."

Charles Kidd, former chief of the Office of Research Planning at NIH, wrote in 1959 of two contrasting definitions of basic research: a) investigator centered, focusing on the investigator's motives and intentions and the freedom with which each works, and b) substance centered, focusing on the research product -- its breadth of significance and generalizability rather than the investigator's freedom to pursue whatever he/she desires to know and understand (Kidd, 1959). The conflict between these two definitions is at the core of the debate about funding of biomedical research. In times of fiscal austerity it becomes increasingly harder to defend the former in the face of rising expectations about the latter.
Perhaps within the context of rising societal expectations about health care, the definition of basic research offered by Comroe and Dripps (1976) may be more palatable. They suggested that research is basic "when the investigator, in addition to observing, describing, and measuring, attempts to determine mechanisms responsible for the observed effects ... basic research can be on healthy or sick people, on animals, tissues, cells or subcellular components." The implication is that the research be directed in some way towards an enhanced understanding of an aspect of human biology with some ultimate practical application no matter how indirect or remote. The onus is thus on the investigator(s) making that link to justify funding.

The ability of scientists to defend their position as recipients of the public's trust and support must include an accounting of how that support has been utilized. Many of the critical developments in biomedical application have evolved from a convergence of basic research on ideas in several disciplines culminating at a discrete point.

In an examination of recent trends in biomedical research and application, it became apparent that one of the most successful endeavors that followed such a pattern has been the burgeoning biotechnology industry. A significant component of this field is the exploitation of monoclonal antibodies (MAb) in research, development of new therapeutics, and as components of new diagnostic tests. The following historical tracing of the development of MAb methodology serves as a case study of how the process of basic science leads to the development of a new technology that can be applied towards meeting the public's perceived needs, i.e., enhanced physical and economic health.
II. MONOCLONAL ANTIBODIES: A SUCCESS STORY

The human immune system has an almost limitless ability to protect the body from potentially harmful foreign bodies such as viruses and bacteria. The immune system produces antibodies in response to antigens. Antibodies recognize different proteins, polysaccharides, or other structures of the antigen as well as distinct determinants within these structures. The immune response includes production of a wide variety of antibodies all of which react with some component of the antigen. Consequently, the serum of any individual will contain a vast array of antibodies all of which may be responding to the same antigen. The different species of antibodies within a given sample of sera cannot be separated from each other and, therefore, isolation or purification of a particular antibody is impossible. In addition to the technical problem of separation and production of particular antibodies, the fundamental theoretical question facing immunologists in the early 1970's was best expressed by Cesar Milstein (1984) in his acceptance speech for the 1984 Nobel Prize; "There are millions of different chemical structures that the animal has never seen and yet which it is able to recognize in a specific manner. How is this achieved?"

In 1974 Georges Köhler arrived in Cesar Milstein's laboratory with the intention of studying the genetic basis of antibody diversity. They soon decided that access to a readily available source of known antibody was needed. The technology for generating monoclonal immunoglobulin molecules had been known for some time. In fact, Milstein had generated lines of tumor cells (myelomas) producing monoclonal immunoglobulins. Unfortunately, these cell lines from malignant tumors of plasma cells produced antibody molecules of unknown specificity. What they needed was the methodology to create an immortalized line of specific MAbs. The solution of the problem and the advent of hybridoma technology resulted in a revolution in immunology, both in terms of an enhanced ability to study aspects of the immune response and a myriad of clinical uses including diagnosis and treatment of diseases that have plagued humanity.

Köhler and Milstein's (1975) discovery, which culminated in the award of the 1984 Nobel Prize and the burgeoning hybridoma/monoclonal industry, has been well documented. What has not been well recognized are those theories and technologies deriving from basic research that led to this discovery. The ability of these two scientists to solve this problem was a consequence of the convergence of basic research on several theories and development of technologies that had evolved from the investigations of several generations of immunologists and basic scientists working independently to understand the body's response to foreign antigens. Some of the seminal contributions that led to the hybridoma technology are listed in Table 1. An appreciation of the development of hybridoma technology provides a case study of the process and essential nature of basic biomedical research.

Silverstein (1989) noted that modern immunology began about 1876 with Pasteur's and Koch's "germ theory" of disease which in turn led to the advent of immunization for the treatment of infectious diseases. This period was followed by the discovery of numerous infectious agents that were subsequently conquered by immunization. However, while the elucidation of the role of microorganisms in disease and a greater appreciation of the immune process were important first steps, these discoveries led to many more questions about this intricate process.
Table 1. Selected Seminal Events Leading to the Development of MAb.

<table>
<thead>
<tr>
<th>Event</th>
<th>Description</th>
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<tr>
<td>Pasteur and Koch (in Silverstein, 1989; 6)</td>
<td>Period of &quot;modern immunology&quot; began with the conceptualization of the &quot;germ theory&quot; of disease.</td>
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<tr>
<td>von Behring and Kitasato (1890) and Erlich (1891)</td>
<td>Development of the theory of humoral immunity (antigen-antibody interactions).</td>
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<td>Wright and Douglas (1903)</td>
<td>Their characterization of opsonins, defined as serum components that interact with antigen to enhance antibody action, was an attempt at unification of theories of humoral and cellular immunity.</td>
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<td>Erlich (1900)</td>
<td>His &quot;side chain theory&quot; was an attempt to provide a conceptual framework for the understanding of the antigen-antibody interaction that combined elements of theories about cellular and humoral immunity. It was also the first postulation of the existence of cellular receptors for antibodies.</td>
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<tr>
<td>Kabat (1939)</td>
<td>Delineated the physical and chemical properties of antibodies which led eventually to the determination of antibody structure and diversity.</td>
</tr>
<tr>
<td>Tiselius and Kabat (1939)</td>
<td>Tiselius and Kabat developed the processes of ultracentrifugation and electrophoresis which were refined by Grabar and Williams for immunological application.</td>
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<td>Grabar and Williams (1955)</td>
<td></td>
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<tr>
<td>Gutman et al. (1941)</td>
<td>As part of Kabat's research group, demonstrated the homogeneity of myeloma proteins.</td>
</tr>
<tr>
<td>Landsteiner and Wiener (1940); Landsteiner (1947)</td>
<td>Among an impressive body of work in immunology were his demonstration of the specificity of antibodies and identification of blood group types.</td>
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<td>Jerne (1955)</td>
<td>His &quot;selective theory of antibody production&quot; proposed that the information for producing antibodies of different specificities is present in the host before it is exposed to a given antigen. This theory represented a sharp departure from prevailing opinion which held that the antigen served as a template on which antibodies were formed.</td>
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<tr>
<td>Potter (1957); reviewed by Potter (1972)</td>
<td>In following the earlier realization that myelomas produced homogeneous proteins, Potter demonstrated that plasma cell tumors (myelomas) could be induced in mice. The immunoglobulin secreted by each cell line was distinct with its own characteristic isoelectric point, binding uniformity, and biochemical properties.</td>
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<tr>
<td>Nossal and Lederberg (1958)</td>
<td>Observed that cultured antibody-producing cells produced only one antibody.</td>
</tr>
<tr>
<td>Porter (1959)</td>
<td>Seminal work on the structural determinants of antibodies.</td>
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<tr>
<td>Edelman and Gally (1962)</td>
<td>Discovered the so-called &quot;Bence-Jones proteins&quot;, representing the light and heavy chains of immunoglobulins.</td>
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<tr>
<td>Name (Year)</td>
<td>Description</td>
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<tr>
<td>Littlefield (1964)</td>
<td>Developed a method (the use of the so-called HAT medium) which when used to grow hybrid cells results in the survival of only fused cells containing both the desired antibody-producing cells (mouse spleen cells containing the necessary enzyme) and myeloma cells. This methodology proved to be a key step in Köhler and Milstein’s fusion process.</td>
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<tr>
<td>Horibata and Harris (1970)</td>
<td>Were the first to transplant and adapt the tumors to continuous culture and in vitro growth.</td>
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<tr>
<td>Askonas et al. (1970)</td>
<td>Produced “monoclonal antibodies” by taking spleen cells from humans and injecting them along with an antigen into immunoincompetent mice which resulted in the proliferation of the spleen cells in vivo.</td>
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<td>Coffino et al. (1971)</td>
<td>Fused myeloma cells with other cells not of the B-cell lineage, such as fibroblasts or epithelial cells, and found that this type of fusion results in extinction of immunoglobulin production.</td>
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<tr>
<td>Schwaber and Cohen (1973)</td>
<td>By fusing mouse lymphoma cells with human peripheral blood cells, these researchers demonstrated that fusion of malignant cells with normal cells could produce products of the normal cell.</td>
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<td>Cotton and Milstein (1973)</td>
<td>Demonstrated that when two myelomas were fused, immunoglobulines from each parental cell were expressed.</td>
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<tr>
<td>Benner et al. (1974)</td>
<td>Described the optimal time for harvesting the greatest number of antibody-forming spleen cells following immunization.</td>
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<td>Köhler and Milstein (1975)</td>
<td>Through the process of fusion and the use of the HAT media, established the methodology for producing immortalized cell lines capable of production of specific or monoclonal antibodies.</td>
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This period of discovery following Pasteur, Koch, and the early "germ fighters" was followed by one of clinical application and enhancement of diagnostic acumen but little progress in terms of a theoretical understanding of the immune process. In fact, the focus on the mission of eradication of diseases led to the period of about 50 years (1910-1960) termed by some as the "dark ages of immunology" (Silverstein, 1989), so-called because of a relative dearth of new immunological applications. The term immunology was not coined to describe the discrete discipline until 1911 (Gay, 1911).

The gap in the evolution of new ideas in the field of immunology was due, as with other scientific disciplines, to an adherence to established paradigms and a reluctance to acknowledge new ideas (Talmadge, 1986). The acceptance of a revolutionary new scientific concept is a long process which involves the reshaping of existing paradigms. As discussed by Kuhn (1970), scientists are trained and invested in preexisting paradigms or dogma. The process by which the community begins to acknowledge and eventually accept a new paradigm is often turbulent. Talmadge (1986) discussed this process as it relates to several new concepts in immunology.

However, the dark ages of immunology (Silverstein, 1989) were not a time of stagnation with regard to the development of new knowledge about antibodies and the immune process. In retrospect, it was a time of entrenchment in which theories were developed about the nature of the antibody-antigen interaction. An example of the resistance to new ideas is found in the response of the scientific community to the side-chain theory of Erlich (1900). This work provided a conceptual framework for the understanding of the antigen-antibody interaction that combined elements of theories about cellular (phagocytosis) (Metchnikoff, 1905) and humoral (antibody-antigen interaction) (Erlich, 1891; von Behring, E. and Kitasato, 1890) immunity, as well as an early appreciation of the existence and importance of cellular receptors. While a few researchers continued in the effort to expand on this theory, e.g., the unification of theories of cellular and humoral immunity by Wright and Douglas (1903), Erlich’s side chain theory was largely rejected by the majority of researchers, who continued to focus on the two prevailing doctrines about the nature of the immune response. Talmadge refers to this time (1910-1940) as the period of serology as most of the attention was focused on serum antibodies. Little attention was paid to theories about antibody formation (Silverstein, 1989).

The chemical or humoral nature of the antigen-antibody relationship continued to generate great interest during this time. For example, Landsteiner demonstrated the exquisite specificity of antibodies and blood group types (Landsteiner, 1947; Landsteiner and Wiener, 1940). Kabat’s work, delineating the physical and chemical properties of antibodies (Kabat, 1939), led eventually to the determination of antibody structure and diversity. An ancillary benefit of a collaboration between Kabat and Tiselius was the development and application of key technologies, e.g., ultracentrifugation and electrophoresis (Tiselius and Kabat, 1939) which were essential for continued evolution of immunological research. Grabar and Williams (1955) subsequently refined the electrophoretic process for immunological application. Another critical observation by Kabat’s research group was the demonstration of the homogeneity of myeloma proteins (Gutman, et al., 1941). This work provided a critical element that led to insights about the monoclonality of myelomas and eventually their utilization in hybridoma technology.

Other work being done during this period included the discoveries by Porter (1959) of structural determinants of antibodies and Edelman (Edelman and Gally, 1962) of Bence-Jones proteins, subsequently designated K and A, representing the light and heavy chains of immunoglobulins. The latter discovery led eventually to the ability to determine the amino acid sequence of immunoglobulins. Porter and Edelman shared the 1972 Nobel Prize for their discoveries which in effect confirmed the theories of Erlich. These breakthroughs then provided a scientific underpinning for the development of theories about the polyclonal or heterogeneous nature of the antibodies produced for a given antigen.
An important theoretical step in the understanding of how antibodies are produced was provided by Jerne’s selective theory of antibody production (Jerne, 1955). Jerne proposed that the information for producing antibodies of different specificities is present in the host before it is exposed to a given antigen. His contention was that there was a randomly diversified pool of immunoglobulins. Upon exposure to an antigen there would be some that would fit. This antigen/globulin complex would be transported to an antibody-producing cell which would then produce specific antibodies. As pointed out by Uhr (1984), this theory was a sharp departure from prevailing opinion which held that antigen served as a template on which antibodies were formed. The skepticism about Jerne’s theory was based on the observation that an animal can produce a multitude of antibodies upon exposure to an antigen, and it therefore seemed unreasonable, in the absence of a clear understanding of the genetics of antibody production, that so much information could be contained in the immune system.

The "clonal selection theory" of Burnet (1959), which gave support and clarity to Jerne’s theory, states that each cell makes only one antibody structure. In effect, Burnet substituted randomly diversified cells for Jerne’s randomly diversified globulins and postulated that antigen selection stimulates the cells to proliferate clonally and to differentiate into Ig-secreting plasma cells. As described by Yelton and Scharff (1981), Burnet’s theory stated that each antibody-forming cell is designed to produce one type of antibody that can potentially react with one or perhaps at most several structurally similar antigen determinants. Each antigen has several different determinants; each of which may associate with different antibodies derived from many cell clones. The result of this relationship is that exposure or immunization to an antigen results in a polyclonal response and the resulting production of sera containing many antibodies. These concepts brought Erlich’s side chain theory into the context of modern biology.

Subsequent research supported the clonal selection theory. Nossal and Lederberg (1958) observed that cultured antibody-producing cells produced only one antibody, and Raff et al. (1973) confirmed that individual B-lymphocytes had surface receptors of a single unique specificity for an antigen.

There was an eventual recognition that the normal immune response is polyclonal and represents the sum of a large number of expanded clones, all reactive with a particular antigen. The immune response to most antigens is so polyclonal as to preclude isolation of individual components. The contribution of individual clones of cells may be electrophoretically detected as a closely spaced family of bands called a clonotype. The sum of clonotypes in a serum defines the spectrotype of response to a given antigen. The clonotype pattern is highly characteristic of any MAb and is a practical and useful way of establishing the purity of a monoclonal preparation (Reisner and Wick, 1988).

The clonal selection theory provided the basis for the development of MAb produced from single cell lines. According to Reisner and Wick (1988), the key concept was the realization that spontaneously occurring multiple myeloma, and closely related plasmacytomas that occur either by induction or are spontaneously developed in rodents, are neoplastic, monoclonally derived proliferations that arise in cells differentiated to secrete immunoglobulins. In other words, since malignant transformation has a clonal origin (derived from a single cell), one myeloma produced one type of immunoglobulin.

In 1962, Potter demonstrated that plasma cell tumors (myelomas) could be induced in mice (Potter, 1972). The immunoglobulin secreted by each cell line was distinct with its own characteristic isoelectric point, binding uniformity, and biochemical properties. Some of these immunoglobulins had antibody activity with specificities similar to that found in immune sera. The development of these cell lines was an essential step in the evolution of hybridoma technology. In fact, Milstein and coworkers did use cells from Potter’s original myeloma lines (Milstein, 1980). While these myeloma proteins are in a sense MAb, they have two critical limitations: there is no way to know what antigen they are specific for, and there is no way to generate a myeloma that produces antibodies to a specific antigen (Milstein, 1980).
Much of the work being done during this time (1962-1975) focused on the nature of the structural determinants of the antigens and antibodies. Milstein and colleagues were interested in the characterization of mutations occurring in myeloma proteins produced in culture. Their work was paralleled by similar efforts by other investigators (Heylon and Scharff, 1981), who were also cloning and genetically manipulating myeloma cell lines. Because the myeloma proteins did not have specific antibody activity, what these investigators needed was the ability to produce and "immortalize" a cell culture that could produce a single antibody and thereby serve as a tool to study the molecular biology and genetics of the antibody.

An important step in this process was accomplished by Horibata and Harris (1970), who were the first to transplant and adapt the tumors to continuous culture and in vitro growth. The production of monoclonal antibodies was accomplished by Askonas et al. (1970), who took spleen cells from humans and injected them along with an antigen into immunocompetent mice which resulted in the proliferation of the spleen cells in vivo. Parenthetically, a key contribution to myeloma and subsequently hybridoma technology was made by Benner et al. (1974), who described the optimal time for harvesting the greatest number of antibody-forming spleen cells following immunization. Eventually, an essentially monoclonal antibody preparation of predefined specificity was possible. Unfortunately, the capacity to purify or immortalize these cell lines remained an elusive goal.

The derivation of truly immortal cell lines was achieved by cell fusion. Curiously, while Köhler and Milstein are usually credited with this discovery, several investigators had already accomplished cell fusion. Coffino et al. (1971) fused myeloma cells with other cells not of the B-cell lineage such as fibroblasts or epithelial cells and found that this type of fusion results in extinction of immunoglobulin production. Schwaber and Cohen (1973) fused mouse lymphoma cells with human peripheral blood cells and created hybrid lines which expressed both human and murine immunoglobulins and thereby demonstrated that fusion of malignant cells with normal cells could produce products of the normal cell. In their landmark paper, Köhler and Milstein (1975) demonstrated the production of hybrid cell lines that were capable of permanent growth, possessed the synthetic and secretory capacity of plasmacytomas, and contained the genetic information to define a specific antibody.

Köhler had come to Milstein's lab as a postdoctoral fellow. Their initial goal was to create immortalized antibody-forming cells by fusion with a myeloma line to study the genetic basis of antibody diversity. The technology for fusion had been developed in several laboratories previously. As mentioned, Milstein already had developed several myeloma lines in his own research. Cotton and Milstein (1973) had preceded the hybridoma breakthrough with a demonstration that when two myelomas were fused, immunoglobulins from each parental cell were expressed.

Köhler and Milstein's novel idea was to use available technology, e.g., Potter's myelomas and the ability to fuse cells, to immortalize the antibody-forming cell which would ordinarily live only a few days in culture, by fusing it with the myeloma cell line which can divide indefinitely in culture. The tumor cell would thereby endow the new cell, called a hybridoma, with the long-term capacity for survival. Köhler's contribution was in devising how to recover only fused cells producing the specific antibody. This was accomplished with the use of a method developed by Littlefield (1964) in which a mutant myeloma line was used that was deficient in a specific enzyme, hypoxanthine phosphoribosyltransferase. In the absence of this enzyme, myeloma cells die in the presence of a mixture of hypoxanthine, aminopterin, and thymidine (a combination referred to as HAT). When hybrid cells are grown in the HAT medium, only fused cells containing both the desired antibody-producing cells (mouse spleen cells containing the necessary enzyme) and myeloma cells would survive.

This fusion process was inefficient, resulting in relatively few hybrid cells. However, through a selection process involving killing of unfused myeloma cells (via the HAT medium) and the
spontaneous death of the spleen cells, only viable hybrid cells survived. In the early stages of this technology, the hybridomas were easily derived but produced a mixture of hybrid molecules consisting of combinations of heavy and light chains from both the myeloma and the normal cells. The ability to obtain the desired cell lines capable of producing antibodies that could recognize the specific desired antigens was not as easily accomplished. In order to avoid some of the problems associated with the use of antibody-producing myelomas, non-producing lines suitable for fusion were developed (Shulman et al., 1978) and are now commonly used.

The use of MAb technology has increased dramatically in the last 15 years. Milstein (1986) described the progression of acceptance of the original methodology noting that after a slow start reflected by few references or original papers, by 1980, there were numerous papers describing new hybridomas and applications of monoclonal technology to divergent fields of biomedicine.

Along with their use as research and clinical tools, the most wide spread use of MAb is as a diagnostic aid for numerous conditions and diseases. Among the current uses for monoclonals are blood typing, diagnosis of AIDS (via the CD4 cell count), transplantation technology (tissue matching), pregnancy testing, and testing for several viral and bacterial diseases of significant public health consequence including influenza, measles, malaria, herpes, and toxoplasmosis.

The impact of MAb on public health has far exceeded even the greatest expectations of the basic researchers who developed this method. The development of MAb is only one of many examples of how basic investigator-initiated research works to society’s benefit both economically and socially. As a consequence of the simple quest for a tool to advance our fundamental knowledge about how the immune system worked, a whole new and ever-expanding industry evolved thereby giving credence to the description of basic science as "... a voyage of discovery, sometimes reaching the expected objective, but often revealing unanticipated new information that leads, in turn, to new voyages" (Carnegie Commission on Science, Technology and Government, 1992).

The next sections will include an overview of the economic impact of hybridoma technology and a case-study analysis of the economic impact of one of the diagnostic uses of MAb. The examination of only one of the myriad of uses for monoclonals is, as was the choice of MAb, an attempt to provide an appreciation of the widespread impact of basic research. Moreover, the selection of only one application of hybridoma technology was a logistical decision and is not intended to diminish the ubiquitous domestic and international nature of the contribution of MAb to health care and economic growth. Furthermore, while the focus will be on economic impact, this approach is not intended to imply that science responds to societal needs only in terms of economic benefit. It is an attempt to document the potential that basic non-mission-oriented research has for changing not only the way the world is viewed but how to deal with its challenges today and in the future.
III. COST-BENEFIT ANALYSIS

A. OVERVIEW

Cost-benefit analysis consists of identification, description, quantification, and analysis of the resources devoted to or invested in a structured activity or project and the outcomes or benefits derived thereof. Quantification is sought in monetary terms where possible. The benefit-cost ratio (the endpoint of such an analysis) can provide a single quantitative measure of returns for public sector investments and is analogous to similar measures of returns on private commercial investments. The intent of the analysis is to determine if an investment yields a positive return (a ratio greater than 1.0), thereby allowing for comparisons between different investments and providing data upon which decisions about resource allocation might be made.

B. ANALYZING INVESTMENTS IN BASIC RESEARCH

In 1986, a wide-ranging review of efforts to measure the returns on investments in research, including cost-benefit analysis, bibliometric analysis, and government and industry approaches was published by the Office of Technology Assessment (OTA) (1986). OTA concluded that each approach had shortcomings and measuring the returns was not practical. Referring specifically to economic analysis, the OTA report stated:

"Economists have shown a strong positive correlation between research and development (R&D) spending and economic growth. They have estimated private returns in excess of 20 percent per year and social returns in excess of 40 percent on private sector R&D expenditures. They have not been able to show comparable returns, and at times been unable to show any returns, on Federal R&D expenditures, except for some applied research programs in agriculture, aeronautics, and energy designed to improve industrial productivity."

A review of other attempts at cost-benefit analyses, conducted both before and since the OTA report, supports the OTA view that economic studies, including cost-benefit analyses had not been useful for evaluating basic research as an investment for the following reasons:

(1) The majority of cost-benefit analyses dealing with research have focused on applied research rather than basic research and did not relate applied research and development, as well as resulting technologies back to the underlying basic research.

(2) Attempts at relating economic growth to research at the macro-economic level typically employed correlation/regression analyses which were not conclusive.

Despite the limitations in previous attempts and the inherent problems in performing economic analyses of basic research, there have been several important efforts which are worth noting.

Mushkin (1979) conducted a study of biomedical research in which correlation/regression techniques were used to relate mortality and morbidity (the dependent variables) to four factors: economic, societal, environmental, and provider characteristics. NIH (1990) conducted a series of cost-benefit analyses of discoveries which resulted in cost savings in health care. These latter studies, however, dealt solely with applied research and made no attempt to identify or describe the background basic research that made these discoveries possible. Moreover, in estimating research costs, the costs of the research conducted or supported by organizations other than NIH were not included.
Using data collected in a survey of the R&D management of 76 companies in 7 manufacturing industries and information from secondary sources, Mansfield (1991) estimated the dollar value of research performed in academic institutions. He found that there was a synergism between industrial application research and academic basic research to the extent that without the latter the former could not proceed or at least would proceed more slowly.

The predominant methods used to evaluate research projects and programs including historical tracings, bibliometrics, peer-review, and cost-benefit analysis have been reviewed by Kostoff (1992) in an attempt to determine the best method for the selection of fundable projects. With regard to cost-benefit analysis, Kostoff echoed the reservations of others in noting its limited accuracy due to the quality of both the cost and benefit data. He attributed these limitations to the unpredictability of the research process and the difficulty in the selection of appropriate time frames. His analysis ultimately suggested the establishment of a network model to evaluate existing and proposed research projects within the context of economic analysis. The model Kostoff proposed covers the different types of basic research impacts and incorporates the impacts of that research on other basic research and on applied research and development.

Other efforts at research analysis include Fudenberg (1983), who provided a description of the benefits and costs of basic biomedical research using several examples from the National Institutes of Allergy and Infectious Diseases. His discussion outlined the complex process of technological advancement, especially through a look at recombinant DNA. The utility of this report is limited by its narrow scope and the basis of the estimations of costs and benefits. Despite these limitations, Fudenberg has related the costs of government supported research to the fiscal impacts of the research, many of which may be viewed as savings to the Federal government.

Weisbrod (1971) analyzed the costs and benefits of the development of the polio vaccine and pointed out the intimate relationship between research and application. Since the work of Salk and Sabin leading to the vaccine was directed towards the solution of a specific public problem, the focus of this analysis is more correctly viewed in terms of the returns of applied- or mission-oriented research.

C. PROBLEMS AND ISSUES PECULIAR TO BASIC RESEARCH

As noted by Kostoff (1992), undirected investigator-initiated, or non-mission-oriented research presents special problems for analysis. The outputs or benefits of basic research are unpredictable in advance, diffuse, and obtained, to a great extent, from future applications, even though the research activity generated benefits along the way. In the case study being presented here, it is important to realize that Köhler and Milstein were seeking a method necessary to advance their research objectives, not to develop a multifaceted billion dollar industrial enterprise.

Costs are equally diffuse and difficult to trace. The costs of the discoveries leading to production of MAb, while acknowledged, are shared costs, and the benefits of these seminal events stand on their own merits.

An additional confounding factor is the substantial amount of time from basic research discovery to applied research and/or application. The National Science Foundation's (NSF) TRACES studies (Illinois Institute of Technology Research Institute, 1968; Battelle, 1973) found that the average time between conception and demonstration of an innovation was nine years. Moreover, TRACES also noted that the number of seminal non-mission events peaked between two and three decades prior to an innovation; a pattern that also occurred in the development of MAb. The U.S. Department of Defense's (DOD) (1969) Project Hindsight found that developments from directed basic research emerged in systems development about nine years following their conception, while developments from
undirected basic research took twenty or more years. The NSF and DOD studies and others indicate that the flow from basic research to applied research to development to commercialization of new technologies is complex and may be multidirectional and interactive.

The nature of basic research, therefore, dictates that analyses of its impacts span the process from basic research through use of the derived technologies. Furthermore, ex ante cost-benefit analysis does not adequately address the process and contributions of basic research. Significant tracing efforts will be required to estimate both cost and benefit components.

An additional consideration in the economic analysis of basic research is the presence of a high degree of technical and market risk in non-directed investigator-initiated research, i.e., the decision-maker does not know whether the product or any product will be generated or whether there will be any demand for the output. This could be a critical consideration for the prospective investor, but it is of much less importance for the retrospective analyses of research investment.

Moreover, results of economic analyses are highly dependent upon the time frame within which they are performed. Kostoff (1992) observed by selecting 1980 instead of 1934 as the point of departure for the analysis of the fusion-fission hybrid reactor and ignoring previous expenditures (sunk costs), different results were obtained. Similarly, the endpoint in an analysis will determine the extent to which the future stream of benefits will be documented, a particularly relevant factor for basic research whose outcomes often project far into the future.

A final consideration in such analyses is the choice of interest rates. Whether the interest rate is used directly as a criterion for decisions, or it is used in calculating net present values, its choice will have an impact on the relative attractiveness of prospective investments or the estimated returns on past expenditures.
IV. A PRELIMINARY COST-BENEFIT FRAMEWORK AND ANALYSIS

A. THE MONOCLONAL ANTIBODY INDUSTRY

Among the uses for MAb are pharmaceutical applications, components of diagnostic devices, and research. Other uses include food technology, agriculture, veterinary medicine, and bioremediation applications. As a consequence of this diversity of use, data and statistics on MAb are difficult to obtain and discourage the definition of MAb production as a distinct industry in various government industrial monitoring programs. MAb are often considered a part of the biotechnology industry which is similarly diverse and has likewise not been classified as a distinct industry. Estimates of the MAb industry's size for 1991 range from about $329 million to about $1.9 billion (Anonymous, 1992; Market Intelligence, Inc., 1992; Theta Corporation, 1992). According to The Biotechnology Directory 1992 (1991), there are 191 companies throughout the United States identified as sources of MAb products.

According to Market Intelligence (1992), total MAb product revenues were $329.0 million in 1991. Of this total, $27.5 million are for veterinary diagnostics, $35.0 million for contract MAb revenues, $31.2 million for ovulation prediction, and $195.3 million for pregnancy diagnostic products. Total revenues are projected to reach $3 billion by 1998.

A survey by Theta Corporation (1992) concluded that MAb markets reached $1.9 billion in 1991 and are projected to reach nearly $4 billion in 1996. The derivation of this estimate did not include veterinary, agriculture, or bioremediation applications. The research market for 1991 was estimated at $125 million and is projected to grow slowly. The diagnostics segment represents the bulk of the current MAb industry, with a total of $1.8 billion in 1991, and is projected to grow significantly in the future. The therapeutic market segment was estimated to be only $30 million, but relatively rapid growth is forecast.

The 1991 diagnostics market was divided into five categories in the Theta Corporation study (1992): non-sexually and sexually transmitted diseases, bloodbank testing, drug abuse detection, and reproduction. Estimated market sizes for these areas are $255 million, $245 million, $840 million, $200 million, and $217 million, respectively.

B. CASE STUDY: TESTING FOR HIV PRESENCE IN BLOOD SUPPLIES

Given constraints on data availability and time, this case study uses a simple and conventional methodology to provide a preliminary and partial evaluation of the costs and benefits of basic biomedical research. To do a complete analysis of the entire MAb industry using the micro-approach would require a series of these types of analyses, touching on all the segments of the MAb enterprise. The approach and data for the previously mentioned NIH report on biomedical innovations (National Institutes of Health, 1990) were described by Schuttinga in an internal NIH document "Guidelines for the Preparation of Cost-Savings Examples" (Schuttinga, 1992) and in a case study of HIV testing by the National Cancer Institute (NCI) (1989). The guidelines and the case study served as the basic inputs for this analysis and were supplemented with additional material as appropriate, e.g., rough estimates of such secondary benefits as expanded output and employment.
C. BACKGROUND: HIV TESTING OF THE BLOOD SUPPLY

Since the first report of transfusion-related HIV infection in 1982 (Anonymous, 1985), there has been a concerted effort at screening the blood supply for contamination with the HIV (Zuck, 1992). Routine laboratory screening of all donated blood was initiated in 1985. The first generation of tests for blood screening was licensed by the Food and Drug Administration (FDA) in 1985. The prototype enzyme linked immunosorbent assay (ELISA) test for detection of HIV antibodies was developed at the NCI. In order to expedite the development of the tests, private companies were selected to do the refinements necessary to make the test publicly available. The five companies selected, Abbott Laboratories, Electro-Nucleonics, Inc., Du Pont, Litton Bionetics, and Travenol/Genentech Diagnostics received FDA approval for clinical trials in the fall of 1985. The first two companies to receive licenses to sell screening tests were Abbott Laboratories and Electro-Nucleonics, Inc. (Anonymous, 1985).

The ELISA tests have become the benchmark procedures for detection of HIV antibodies (Anonymous, 1985). The assay most commonly involves exposure of a blood sample to immobilized, disrupted, inactivated HIV virus. The antigen-antibody complex is then exposed to a medium containing an enzyme-linked, anti-human antibody, often goat anti-human Ig. Upon addition of the enzyme's substrate to the mixture, a characteristic, easily detectable, colorimetric reaction can be readily quantified spectrophotometrically. The principle is that if the blood sample contains antibodies to the HIV virus, these antibodies will bind the immobilized antigen and, after removal of blood, serve as the target for the enzyme-labeled animal antibody to human immunoglobulin, resulting in a positive test. When originally developed, MAb were used to bind HIV proteins (antigens) to the beads in the first step of the ELISA assay. Since 1988, ELISA tests used in screening human blood have relied on HIV proteins produced in bacteria by recombinant DNA technology. The principles of the testing procedures are the same; the current generation ELISA tests use viral proteins produced in bacteria for reasons related to costs of production. The advantages of the ELISA assays are their relative simplicity, low cost (they require little or no expensive equipment), and adaptability to mass screening and automation (Burke, 1989). In addition to the ELISA test, MAb are used in the quantitative measurement of the CD4 count which is the primary diagnostic criterion for diagnosis of AIDS (Burke, 1989).

Currently, the primary test for blood screening, the ELISA test, is manufactured by several companies: Abbott, ORTHO, Genetic Systems, Organon Teknika, Olympus, and Cellular Products. One manufacturer, Abbott Laboratories, probably accounts for well over 50 percent of marketplace sales.

D. PRIMARY COSTS AND BENEFITS

For this case study, the benefits are measured in terms of: (1) income losses avoided from lower production as a result of lost days of work and lost production or work due to accelerated mortality; and (2) the reduction in medical care costs which would otherwise be incurred as a result of blood supply transmission of the HIV and the subsequent development of AIDS.

NIH (National Institutes of Health, 1990; National Cancer Institute, 1989) conducted an analysis of cost savings resulting from its R&D efforts to develop a test of blood supplies for the HIV. A study by Scitovsky and Rice (1987) was undertaken for the Centers for Disease Control (CDC) to estimate the economic costs of HIV/AIDS. The Scitovsky and Rice study, along with an analysis performed by Hellinger (1990), was used to confirm the validity of the NIH estimates.

The NIH study (National Institutes of Health, 1990; National Cancer Institute, 1989) estimated direct medical treatment cost-savings and "indirect cost-savings" (avoided losses in earnings) but did not include R&D or other costs incurred by private firms in developing and marketing the HIV test kits,
blood bank capital equipment, facility renovation costs, donor counseling, donor notification, computer reprogramming to defer donors, or confirmatory testing. The Scitovsky and Rice (1987) study had a different objective than the NIH study in that it looked at all the economic costs of HIV/AIDS in the United States. While it did not focus on benefits (avoided costs), it did make similar estimates, including lifetime earnings and earnings-loss estimates.

The NIH estimated costs for testing a unit of blood are $2.44 for Red Cross blood banks and $2.79 for other smaller blood banks (National Institutes of Health, 1990; National Cancer Institute, 1989). Scitovsky and Rice (1987) estimated that the ELISA test costs are in the range of $5 to $10. NIH estimated the total annual cost of blood supply testing at about $34.5 million (National Institutes of Health, 1990; National Cancer Institute, 1989). Applying an average of the Scitovsky and Rice unit-cost estimates ($7.50) results in a comparative total of about $98.7 million in testing costs (Scitovsky and Rice, 1987). The reason(s) for this disparity in testing costs is unclear.

NIH, based on an assumed lifetime health care cost of $75,000, estimated a direct medical treatment cost-savings of $33.3 million for a one-year cohort. Scitovsky and Rice (1987) estimated personal 1985 health care costs of $630 million for a population of 18,720. Scitovsky and Rice (1987) did not calculate lifetime health care costs; however, their numbers seem to imply lifetime health care costs of the same order of magnitude as the NIH estimates.

Hellinger (1990) made three estimates of lifetime medical care costs, $60,006, $75,009, and $90,008, which varied according to the assumed average survival times of 12, 15, and 18 months, respectively. Regarding earnings losses, Hellinger (1990) made no earnings estimates, while NIH estimated the value of lifetime earnings saved for the one-year cohort at $64.9 million (National Institutes of Health, 1990; National Cancer Institute, 1989). Scitovsky and Rice (1987) estimated the earnings saved for both morbidity and mortality as $3.9 billion (1985 dollars using a 4 percent discount rate) for the population of 18,720. The Scitovsky and Rice estimate (1987) on a per individual basis ($207,639) is roughly triple the NIH average ($72,835) (Burke, 1988; National Institutes of Health, 1990). This difference is due to two factors: (1) use of a different discount rate (NIH - 6 percent, Scitovsky and Rice - 4 percent); (2) inclusion of earnings losses from morbidity by Scitovsky and Rice; and perhaps (3) a lower rate of development of AIDS from HIV exposure assumed by NIH.

The work of Köhler and Milstein took place in a five-year period (1971-1976) and involved a small staff of research assistants, doctoral candidates, and post-doctoral appointees. The total cost, including staff, associated research expenses and overhead, was modest -- under £200,000 (Milstein, 1993). To make the data comparable for analytical purposes, we have converted the Köhler-Milstein research costs from pounds to dollars, adjusted for inflation, calculated their net present value, and allocated to the HIV test about 1.8 percent on the basis of its share of the 1991 MAAb market (Federal Reserve Board 1971-1976; Milstein, 1993; National Institutes of Health, 1990). In 1988 dollars, the HIV test's share of the MAAb research costs is estimated at $40,000 as shown in Table 2.

The costs of R&D by manufacturers of the HIV test kits are implicit in the costs of the kits as used to offset the benefits shown in Table 2. This assumes full cost-recovery and a return to the kits' vendors.
Table 2. Summary of Costs and Benefits (in 1988 $\text{'s}).

<table>
<thead>
<tr>
<th>INVESTMENT COSTS:</th>
<th>ESTIMATES$^{1,2}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Köhler &amp; Milstein</td>
<td>- $40,000$</td>
</tr>
<tr>
<td>NIH R&amp;D</td>
<td>- $6,692,000</td>
</tr>
<tr>
<td>Company R&amp;D</td>
<td>N.A.$^4$</td>
</tr>
<tr>
<td>TOTAL</td>
<td>- $6,732,000</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>BENEFITS:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary</td>
<td></td>
</tr>
<tr>
<td>Earning Losses Avoided</td>
<td>$64,896,000</td>
</tr>
<tr>
<td>Health Care Savings</td>
<td>$33,278,000</td>
</tr>
<tr>
<td>HIV Test Costs (offset)</td>
<td>- $34,470,000</td>
</tr>
<tr>
<td>Subtotal Net Primary Benefits</td>
<td>$63,704,000</td>
</tr>
<tr>
<td>Secondary Benefits</td>
<td>$69,805,000</td>
</tr>
<tr>
<td>TOTAL BENEFITS</td>
<td>$133,509,000</td>
</tr>
</tbody>
</table>

| Primary Benefit-Cost Ratio: | 9.46:1 |
| Total Benefit-Cost Ratio:   | 19.83:1 |

1 Cost values are shown as negative values, benefits as positive values.
2 Primary estimates are estimates developed by NIH; secondary benefits are based on a multiplier supplied the U.S. Department of Commerce and applied to test costs.
3 The estimated costs over a five-year period are $2.2 million in 1988 dollars -- original data was converted from British pounds to dollars, and adjusted for inflation using the NIH Biomedical R&D Price Index (BRDPI), and net present value was calculated using a 6 percent interest rate. These costs are allocated to the HIV test on the basis of market share, approximately 1.8 percent. This has an insignificant impact on the benefit-cost ratio.
4 The R&D costs of private companies can reasonably be assumed to be implicit in the costs of the test kits which are shown as an offset to the benefits.
E. SECONDARY BENEFITS

In addition to the primary benefits described and estimated above, secondary benefits are induced by the manufacture and use of the products (the ELISA tests). These secondary benefits consist of the output and employment of supporting manufacturing and services, such as transportation, vendors of supplies, etc.

The U.S. Department of Commerce prepares estimates of the "final demand multiplier" for a large number of industrial groups. These multipliers are used in analyses such as this to provide an estimate of the impacts on the general economy. The relevant industry multiplier applies to final consumption which, in this case, is the utilization of MAb in the testing of the blood supply. It is appropriate to apply the final demand multiplier only to the testing phase because this multiplier is designed to estimate the impacts on the rest of the economy, including suppliers of inputs to testing, i.e., manufacturers of disposables and test kits, etc.

The industry group for which a multiplier is available that approximates the testing industry is Research and Testing Laboratories, Standard Industry Classification Codes, 7391, 7392, 7397 (U.S. Department of Commerce, 1989). The multiplier for this group is estimated at 3.0251. This means that for every $1.00 of increased final demand for the industry, $2.0251 will be generated elsewhere in the economy. Applying this multiplier to the NIH estimated cost of testing, $34.5 million (Burke, 1989; National Institutes of Health, 1990), yields an estimated $69.8 million in output generated elsewhere in the economy. Direct and indirect employment associated with the research and testing laboratories can be estimated at 1,420 (41.2 employees per $1.0 million in final demand).

Recognizing its limitations, this presentation has provided evidence of a significant return to the economy of but one application of MAb technology. Clearly, an expanded analysis of the entire MAb enterprise would document a significantly greater impact. The development of MAb exemplifies the fundamental quest for basic knowledge about human biology and its interaction with the environment. The benefits that accrue from such a quest are both tangible in terms of clinical applications and intangible in terms of new knowledge gained, the benefits of which cannot be predicted or quantified.

One may argue about the relative importance of these contributions to society, but there is little doubt that such quests must continue. The discussion of how to support such quests must start with the view of basic research as a "pluralistic and de-centralized process" (Carnegie Commission on Science, Technology and Government, 1992) and must also give due consideration to the critical concerns raised in recent public debate about the health of the scientific enterprise (Brown, 1992).
V. COST-BENEFIT ANALYSIS: ISSUES AND SUGGESTIONS FOR FURTHER ANALYSIS

There are several issues associated with cost-benefit analyses, many of which are technical in nature (e.g., the discount rate used), while others have greater significance related to our ability to effectively address science’s capacity to meet the needs of society. The latter includes the following issues or concerns:

1. The benefit-cost ratio attempts to provide a single and common measure by which investments can be compared in making decisions. However, it is impractical as a sole indicator for decision-making on prospective basic research projects because there is a lack of predictable outcomes. Moreover, effective decision-making requires a fuller public appreciation of resource requirements, potential impacts/benefits, and the mechanisms of basic and applied research, development, and innovation. Focusing on a single ratio tends to divert attention from important details necessary for a more global understanding of the research enterprise.

2. Secondary benefits are often omitted from cost-benefit studies. In some contexts, this may be justifiable. However, the impacts of R&D on the broader economy and society do need to be identified, described, quantified, and analyzed to the extent feasible. This will also contribute to better public appreciation of R&D and the nature of the R&D process.

3. The factors influencing the realization of benefits by society are rarely, if ever, touched upon within the context of cost-benefit analyses. They are beyond the scope of a cost-benefit analysis but highly germane to addressing public policy questions related to support for and benefits from basic research. In the public policy context, it is not enough to ask or answer the question: "Are the benefits worth the costs?"; one must also ask and attempt to answer the related questions: "How do we get more for our investment?" or "What factors are inhibiting commercial development and use of research results?" The impacts of tax policies, capital availability, intellectual property rights, technological transfer, and several other factors need to be considered.

By and large, the analytical frameworks employed in the past have been narrowly focused, i.e., on applied R&D (when using the micro approach), and aggregative and inconclusive (when using the macro approach). In essence, most previous analyses have taken a snapshot with a narrow angle camera lens. The requisite tracing, quantification, and analysis of research investments must be both backward and forward to capture the background or supporting research and the benefits which ultimately flow from the basic research.

This preliminary and partial analysis of MAb identified some of the features of a broader analytical framework. With regard to the impact of a single application of MAb, HIV testing of the blood supply, the key features included: tracing the investment from basic research through application; and identification and description of (quantifying where possible) all impacts, both primary and secondary. Future expanded evaluations should include an analysis of the factors that may influence both the evolution of new research developments and the realization of their benefits.


Zuck, T.F. 1992. The case of Arthur Ashe: that was then, this is now. J. NIH Res. 4(7):99-101.