

# Presidential Address to the American Society for Clinical Investigation, Baltimore, Maryland, 30 April, 1994

## Cross-fertilization among Fields: A Seminal Event in the Progress of Biomedical Research

Jay A. Berzofsky

*Molecular Immunogenetics and Vaccine Research Section, Metabolism Branch, National Cancer Institute, National Institutes of Health, Bethesda, Maryland 20892*

The theme of this presidential address is the importance of cross-fertilization in biomedical research, and the role of this meeting in facilitating such cross-fertilization. We are now finishing the first full day of a completely reorganized Clinical Research Meeting. The changes should be apparent to all. The TriSociety Council has dramatically revised the meeting to counter a trend of declining attendance and abstract submissions (Fig. 1). Attendance has fluctuated over the past decade and a half, but last year's attendance of 2690 was down 34% from the peak year of 1986. Equally distressing is the steady decline in abstract submissions at the uncannily constant rate of about 200/yr for the 5 years from 1989–1993 (Fig. 2). This may reflect a trend toward presenting one's best abstracts at subspecialty meetings rather than at a general meeting such as this one, or it may reflect dissatisfaction with the abstract presentation sessions. To counter these trends, the TriSociety Council felt that a dramatic change in the meeting was necessary (1). The format being tested this year is the result (Fig. 3). The leveling off of abstract submissions this year may indicate interest in this new format. We hope the interest will be sustained.

One major change is in the way abstracts are presented. For several years, participants have shown a preference for invited talks. However, one important function of these meetings has been to provide a forum for young investigators. To satisfy both needs, we have converted to a format in which all oral presentations will be by invited speakers and all abstracts will be presented in poster discussion workshops. We have invited well-known experts in each field to make "professor's rounds" on the posters, and then to chair a discussion workshop immediately following the poster viewing. Lively discussions led by a well-known expert should entice greater participation.

More fundamentally than this structural change, we hope to move this meeting away from a compendium of concurrent subspecialty meetings and toward the real niche it should occupy, to provide a single place where one can hear the most exciting new developments in all of medicine. To accomplish this, every morning, we have planned a two-hour set of "Year-in-Medicine" sessions, in which one will be able to hear the four or five most exciting breakthroughs in each subspecialty, chosen with input from the subspecialty societies. In addition, because important themes in research do not always correspond to traditional subspecialties, we have planned 12 theme symposia,

on topics that will vary from year to year, each given by outstanding speakers in their area. We have been lucky to obtain a truly stellar cast of chairpersons and speakers for 1994 to inaugurate this new format. Thus, we hope that these dramatic changes will signal a new era for the Clinical Research Meetings.

To attempt this revitalization of these meetings, we have had to rethink their real underlying purpose. To the extent that we all must teach, do research, and care for patients, it is important for everyone involved in academic medicine to keep up with the major new developments throughout medicine. We all recognize this, but demands of keeping up in just one subspecialty have made the job increasingly difficult. The unique functions that should be served by this meeting are to provide a place where one can learn of the important new developments selected and distilled from the huge mass of research that no one can realistically assimilate, and to bring together investigators from the full breadth of internal medicine and biomedical research to cross-fertilize ideas in what is becoming an increasingly complex web of interrelationships among disciplines. Countering the trend of increasing specialization becomes more essential as developments in biomedical research lead to a new integration of disciplines. The most exciting scientific breakthroughs cut across the traditional boundaries. Indeed, the most innovative research frequently arises from cross-fertilization between fields. The breakthroughs often depend on seeing links among multiple fields. This is the theme on which I would like to elaborate.

Often, the major breakthroughs come when someone enters the field from another discipline, and introduces a key concept or new experimental technique that makes possible a quantum leap, or a 90° turn in the field. As pointed out by Thomas Kuhn in his book, *The Structure of Scientific Revolutions* (2), "Almost always the men who achieve these fundamental inventions of a new paradigm have been either very young or very new to the field whose paradigm they change." A clinical or basic discovery in one field may have important impact in a very different field, basic or clinical. Thus, cross-fertilization among diverse fields is key to new birth of ideas in each field, and can create a type of hybrid vigor that sustains further advances. To make these concepts clearer, I would like to illustrate them with a few examples that come to mind. Because of my own experience in immunology, I will lean heavily on examples from that field.

One classic example of a scientific revolution discussed by Kuhn is based on Leonard Nash's analysis of "The origins of Dalton's chemical atomic theory" (3). In the first years of the 19th century, chemists were still far from understanding the way in which atoms and molecules combine to form other molecules, and did not always distinguish clearly a chemical compound from a physical mixture. Dalton, however, was not a

---

Address correspondence to Jay A. Berzofsky, M.D., Ph.D., Molecular Immunogenetics and Vaccine Research Section, Metabolism Branch, National Cancer Institute, Building 10, Room 6B-12, National Institutes of Health, Bethesda, MD 20892.

Received for publication 25 May 1994.

---

The Journal of Clinical Investigation, Inc.  
Volume 94, September 1994, 911–918

## Clinical Research Meeting Attendance 1980-93

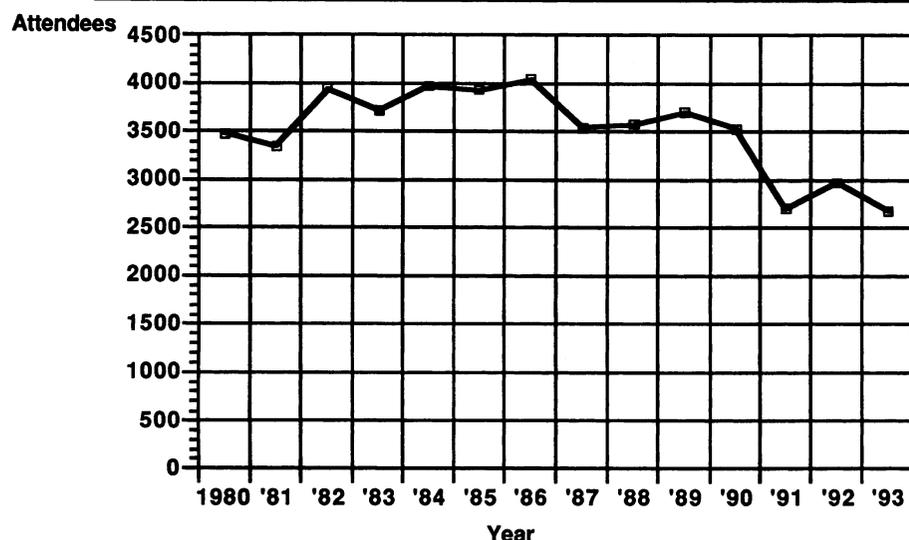


Figure 1. Attendance at the Clinical Research Meetings between 1980 and 1993. Shown are the total number of registrants at each annual meeting. All meetings shown were in Washington DC, except 1981 in San Francisco, 1987 in San Diego, 1991 in Seattle, and 1992 in Baltimore. Attendance at the current 1994 meeting increased by almost 100, to 2786 (not shown). Data were collected by Slack, Inc., for the TriSociety Council of the three societies organizing the meeting, the Association of American Physicians (AAP), the American Society for Clinical Investigation (ASCI), and the American Federation for Clinical Research (AFCR).

chemist influenced by current chemical thinking, but rather a meteorologist, with some background in physics, who was trying to understand how gases were absorbed by water (2). In the process, he came to the realization that if one could determine the weights of the atomic particles involved in chemical reactions, one could understand how these combined into compounds and that these would always combine in simple whole-number ratios. Thus, the revolution that led to our current understanding of chemical reactions came from a meteorologist who was attuned to developments in physics.

To look further for examples of cross-fertilization in scientific discoveries widely acknowledged to be critical in our own time and field, I thought it would be interesting to see how frequently the discoveries leading to Nobel prizes in the category called Medicine or Physiology depended on cross-fertilization (4). A number of such prizes awarded since 1960 could be connected in genealogical trees that shed light on these cross-

fertilizations. Of necessity for clarity and the limits of time, these trees are oversimplified, and I apologize for the omission of many important contributions not mentioned. Also, although I will not discuss it explicitly, we should not lose sight of the fact that many of these Nobel laureates were trained as physicians, and their medical experience contributed to the discoveries.

### Immunology Nobel prizes: partial genealogical tree

A number of interesting examples (4) can be gleaned from a partial genealogical tree of Nobel prizes since 1960 on immunological discoveries (Fig. 4). Niels Jerne was a physicist by training. The development of his widely used plaque assay for antibody-forming cells could be traced back to the virologist's phage plaque assay. Jerne contributed many important theories

## Clinical Research Meeting Abstract Submissions

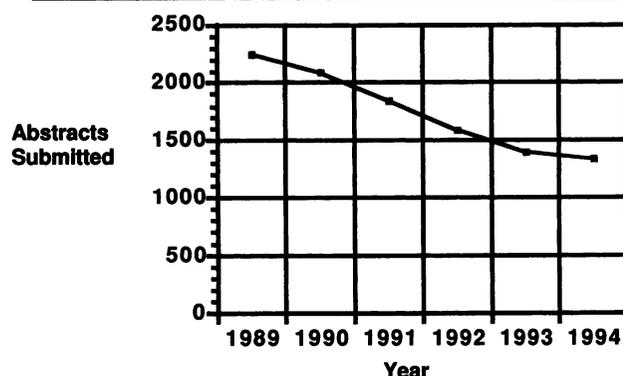


Figure 2. Abstract submissions to the Clinical Research Meetings from 1989 to 1994. Data were collected by Slack, Inc., for the TriSociety Council of the AAP, ASCI, and AFCR.

## New Meeting Format

Friday	Saturday	Sunday	Monday
	Year in Medicine	Year in Medicine	Year in Medicine
	Theme Symposia	AAP Plenary Session	AFCR Plenary Session
		Meet-the-Investigator	Meet-the-Investigator
	Poster Discussion Workshops	Theme Symposia	Theme Symposia
Poster Discussion Workshops	ASCI Plenary Session	Poster Discussion Workshops	Poster Discussion Workshops

Figure 3. The new format of the Clinical Research Meeting. Blocks show time slots for each type of session, most of which are new, as described in the text.

## Immunology Nobel Prizes: Partial Genealogy

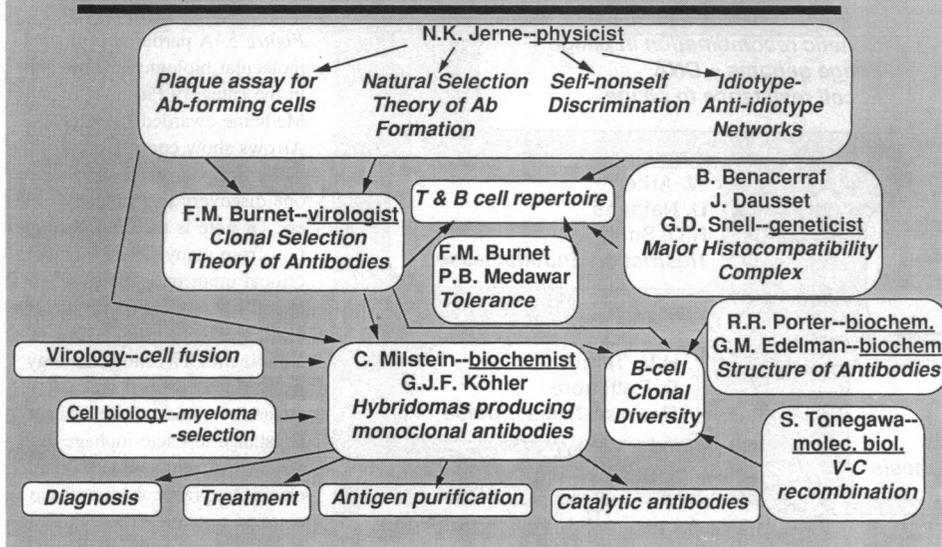


Figure 4. A partial genealogy of immunological Nobel prizes in the category Physiology or Medicine awarded since 1960. Arrows show connections in which ideas or approaches from one discovery contributed to others. Of note is the prevalence of cross-fertilization from many fields, including physics, genetics, molecular biology, biochemistry, cell biology, and virology.

to immunology. However, one of Jerne's earliest theories was a Natural Selection Theory of Antibody Formation that strongly influenced Macfarlane Burnet in forming his clonal selection theory of antibody producing cells. Burnet was a virologist by profession and made important discoveries in virology, but the concepts for which he is best remembered today are both in immunology. He shared the 1960 Nobel Prize with Peter Medawar for the discovery of acquired immunological tolerance, and his clonal selection theory became the basis for understanding how the immune system can have the capability of recognizing a diverse universe of antigens and yet counter with a very discrete response when challenged with a particular antigen. Burnet's thinking about clones of cells and their selection was influenced by his experience with viral foci. Furthermore, one proof of the clonal selection theory came from the use of a plaque assay developed by Jerne for antibody-forming cells, based on viral plaque assays.

The clonal selection theory, the discovery of immunological tolerance, and Jerne's ideas on self-nonself discrimination all contributed to our understanding of the factors shaping the T and B cell repertoire. Another very critical component in understanding the T cell repertoire was the discovery of the genetics and immunological function of the Major Histocompatibility Complex of transplantation antigens, such as HLA in humans and H-2 in the mouse, by George Snell, a geneticist more than an immunologist, Jean Dausset, and Baruj Benacerraf, who shared the Nobel Prize in 1980. Thus, classical genetics played a profound role in the development of modern immunology.

The structural basis for antibody diversity was the existence of separate variable domains of the heavy and light chains, that combined to form an antigen-binding site, as described by biochemists Rodney Porter and Gerald Edelman, who shared the Nobel prize in 1972. The genetic basis for generation of such a diversity of B lymphocyte clones, each producing different antibodies, was the combinatorial joining of genes for multiple variable regions with an antibody constant region first demon-

strated by basic molecular biologist Susumu Tonegawa, for which he won the 1987 prize.<sup>1</sup> This work also foreshadowed parallel concepts of genetic recombination in T lymphocyte receptor genes. Thus, much of modern immunology depends on interrelated discoveries in molecular biology and biochemistry.

Now, Cesar Milstein was a biochemist with a background in enzymology who was interested in structure-function relationships in antibodies. Using a myeloma cell line<sup>2</sup> and a selection method developed by cell biologists, and a method of fusing cells borrowed from virology, Milstein and Georges Köhler developed a way to fuse antibody-producing B lymphocytes with a drug-marked myeloma cell to create a hybridoma sharing the characteristics of both cell parents. Cloned hybridomas produced monoclonal antibodies that have been invaluable in purification of other molecules, and in the diagnosis and treatment of disease. Indeed, monoclonal antibodies have been a cornerstone of the biotechnology revolution. For their work, Köhler and Milstein shared the 1984 prize with Niels Jerne. Interestingly, monoclonal antibodies have more recently completed the circle back to enzymology, by the development of catalytic antibodies as pioneered by Richard Lerner, P. G. Schultz, and others (5).

### Molecular biology Nobel prizes: partial genealogical tree

A similar genealogical tree can be shown for Nobel prizes (4) in molecular biology (Fig. 5). First, it is surprising how much

1. Susumu Tonegawa, Philip Leder, and Leroy Hood all shared the 1987 Lasker Award for demonstrating and analyzing the combinatorial joining of variable and constant region gene segments in all three loci of immunoglobulin genes, heavy chain, kappa chain, and lambda chain, and for discovering other gene segments involved in this combinatorial process that contribute to the generation of diversity, such as D and J region genes.

2. The myeloma cell lines used were developed by cell biologist Michael Potter, who shared the 1984 Lasker Award with Köhler and Milstein for this work.

## Molecular Biology Nobel Prizes: Partial Genealogy

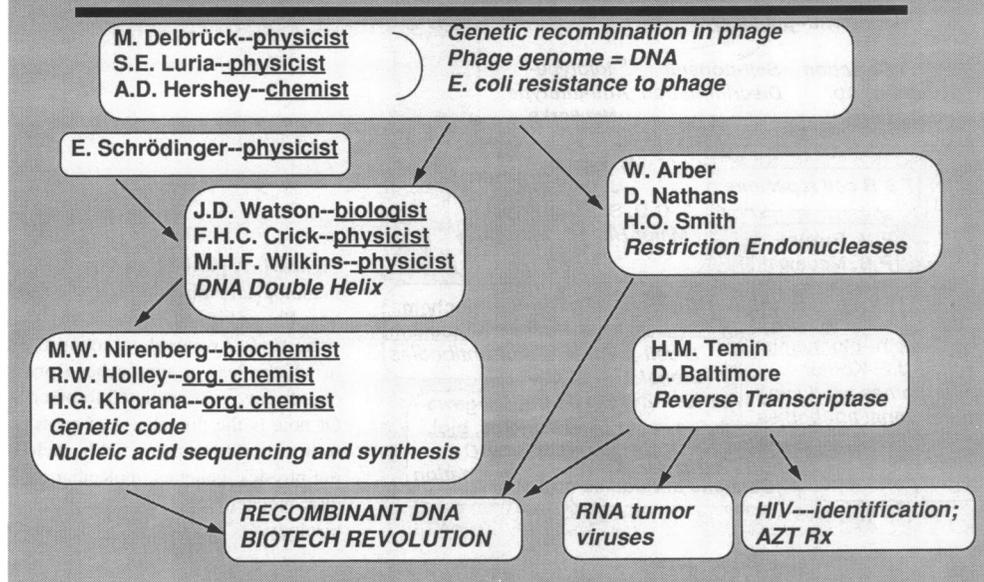


Figure 5. A partial genealogy of molecular biological Nobel prizes in the category Physiology or Medicine awarded since 1960. Arrows show connections in which ideas or approaches from one discovery contributed to others. Of note is the cross-fertilization from many fields, including critical input from physics, biochemistry, organic chemistry, bacteriology, and virology. The recombinant DNA biotechnology revolution depended on basic discoveries in areas such as bacterial resistance to bacteriophage and RNA virus replication, whose enormous practical importance in creating a whole new technology could not have been readily anticipated when these studies were undertaken.

the early foundations of molecular biology were laid by physicists. Max Delbrück was a physicist who trained with Max Born, Wolfgang Pauli, and Niels Bohr, themselves all three Nobel prize winners in physics. Delbrück used bacteriophage as an ideal simple model to study the ability of radiation to induce genetic mutations. Together with co-Nobelists Salvador Luria, another physicist, and Alfred Hershey, a chemist, he founded the Phage Group that initiated many major discoveries.

Jim Watson was a Ph.D. student of Luria's, whose thesis was on irradiated phage. To address the structure of DNA, he teamed up with Francis Crick, a physicist doing x-ray diffraction, which was still largely the realm of physicists and physical chemists. Both Watson and Crick were also heavily influenced by a book by Erwin Schrödinger, the father of quantum mechanics, entitled *What is Life?* They also depended on the x-ray diffraction studies of another physicist, Maurice Wilkins. As is now well known, this combination led to the discovery of the double helix and the base-pairing strategy by which DNA encodes a copy of itself. The subsequent solution of the genetic code by Nirenberg, Holley, and Khorana depended heavily on input from chemistry.

Second, problems in basic microbiology led to critical discoveries that initiated the biotechnology revolution. Luria also found that *E. coli* developed mutations affecting resistance to particular phage, and postulated that the resistance was due to enzymes that preferentially degraded the DNA of the phage but not the bacteria's own DNA. This was the basis for the later discovery and use of restriction endonucleases by Arber, Nathans, and Smith, which was one of the cornerstones on which the whole molecular biology revolution depends, allowing for DNA mapping, and the cloning and engineering of genes.

Similarly, the discovery of reverse transcriptase by Howard Temin, whose recent untimely death is mourned, and David Baltimore was aimed at learning how RNA tumor viruses replicated, not at developing a universal tool. Yet, this discovery,

allowing cDNA to be made from messenger RNA, turned out to be another major cornerstone on which recombinant DNA technology was built. Thus, the biotechnology revolution developed from basic discoveries in microbiology on how bacteria defended themselves against bacteriophage, and on how RNA tumor viruses worked. The discovery of reverse transcriptase was also critical in isolating and understanding the AIDS virus, HIV, which is also a retrovirus, and in developing the first somewhat successful drug for its treatment, AZT, which is an inhibitor of reverse transcriptase. These examples also make a strong case for the importance of undirected research (6).

### Interface between immunology and endocrinology

Another set of examples of cross-fertilization comes from the multiple interfaces that have developed between immunology and endocrinology (Fig. 6). One such interface comes from the parallels between immunological receptors and hormone receptors. Indeed, the spectrum of receptors involved in immunology and endocrinology blur into a continuum when one goes from antibodies and T cell receptors at the immunological end to hormone receptors at the endocrine end, with cytokine and growth factor receptors in between. Where is the line between cytokines and growth factors, or between growth factors and hormones? Moreover, the parallels and crosstalk between pathways in signal transduction imply that each field can learn considerably from the other.

The second interface comes from the findings that many endocrine diseases have autoimmune etiology. Obvious examples include type-I diabetes mellitus, Graves' disease, and Hashimoto's thyroiditis, premature ovarian failure, autoimmune hypophysitis, and Schmidt's syndrome. Prevention and treatment of these diseases must involve an interplay between immunological and endocrinological approaches.

A third interface arose from the development of the radioimmunoassay. Rosalyn Yalow, a physicist by training, was inter-

## Immunology-Endocrinology Interface

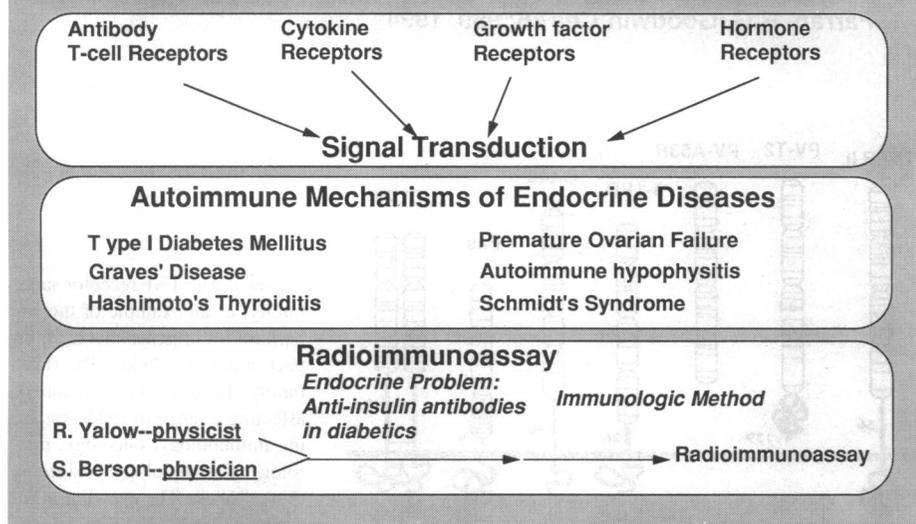


Figure 6. Interfaces between immunology and endocrinology. (*Upper box*) The continuum of receptors and the parallels and cross-talk in their paths of signal transduction; (*middle box*) examples of the many endocrine diseases with autoimmune mechanisms of pathogenesis; (*lower box*) the role of antibodies to insulin in diabetes, and the application of immunological approaches to an endocrine problem, carried out by a physicist, leading to the development of the radioimmunoassay.

ested in using radioisotopes as tracers. Together with Solomon Berson, a physician, she studied an endocrine problem, and discovered a delayed clearance of labeled insulin from the blood of diabetics due to the presence of anti-insulin antibodies. They realized that the ability of unlabeled insulin to compete with labeled insulin for binding to these antibodies would allow a very sensitive test for the level of insulin in an unknown sample. Rosalyn Yalow was awarded the Nobel prize in 1977 for this work (4). Radioimmunoassay and related techniques have since replaced bioassays as the primary techniques for measuring levels not only of most hormones, but also of molecules important to many other fields.

### Superfamilies of genes

Another important level on which the new biology is bringing different fields together is the discovery of superfamilies of genes with members that play roles in diverse organ systems and diseases. A good example is the TNF receptor superfamily (7) (Fig. 7). TNF receptors themselves are important in areas from immunology and oncology to septic shock. CD40 is central in B cell activation. Nerve growth factor receptor plays a role in neurology. Fas and its ligand, which trigger programmed cell death, may be central molecules in immune tolerance and rheumatological diseases, as defects in these genes are responsible for the lupus-like diseases of two mutant strains of mice. Interestingly, two molecules in this superfamily, PV-T2 and PV-A53R, are gene products of pox viruses, such as myxoma virus and smallpox. The T2 gene has been shown to contribute significantly to virulence of myxoma virus, possibly by acting as an inhibitor of TNF. Thus, this family is important in infectious disease as well. The pox virus example is particularly illustrative of the way in which understanding the role of one member of a superfamily can shed important light on the function of other members of the superfamily of interest to a different discipline.

### Cross-fertilization in my own research

Finally, to show that cross-fertilization plays an important role in the careers of many of us in biomedical research, not just

Nobel prize winners, I would like to illustrate a few examples from my personal experience (Fig. 8). My work as an immunologist has been greatly aided by a number of collaborations with fantastic immunologist colleagues at NIH, including Ron Germain, Richard Hodes, David Margulies, Ron Schwartz, Sue Sharrow, Alan Sher, Al Singer, and Warren Strober, as well as David Sachs and Gene Shearer mentioned later. However, I did not start out as an immunologist, and my work has been greatly influenced by interactions with researchers in many fields outside immunology.

As a student working with Frank Westheimer, and in my Ph.D. thesis research with Bernard Horecker, Jack Peisach, and Bill Blumberg, I developed a keen interest in structure and function in proteins (Fig. 8). I came to the NIH as a postdoc to work on protein folding with Alan Schechter and Chris Anfinsen, from whom I also learned peptide synthesis. However, a collaboration with the immunologist David Sachs on immune response genes in the major histocompatibility complex (MHC)<sup>3</sup> got me so excited about immunology that I started applying the approaches of protein and peptide chemistry to immunology. The immediate result was our observation of the epitope specificity of *Ir* genes (8). These studies on *Ir* genes then played into my earlier interest in protein structure-function relationships from biochemistry, and led to the more recent work of my lab on structure-function relationships for MHC molecule presentation of peptides to T lymphocytes (9). A key collaboration with protein biochemist Frank Gurd was essential in these investigations. These studies, in turn, led to a collabora-

3. David Sachs initially used an immunological approach, conformation-specific antibodies, to study a biochemical problem, the conformational equilibrium of staphylococcal nuclease in solution, with Alan Schechter and Chris Anfinsen. Later, at the time I arrived, he had reversed the roles of the molecules studied, and used staphylococcal nuclease as a simple model protein antigen to study an immunological problem, the mechanism by which antigen-specific MHC-linked *Ir* genes controlled antibody responses to a defined protein antigen.

# The TNF Receptor Superfamily

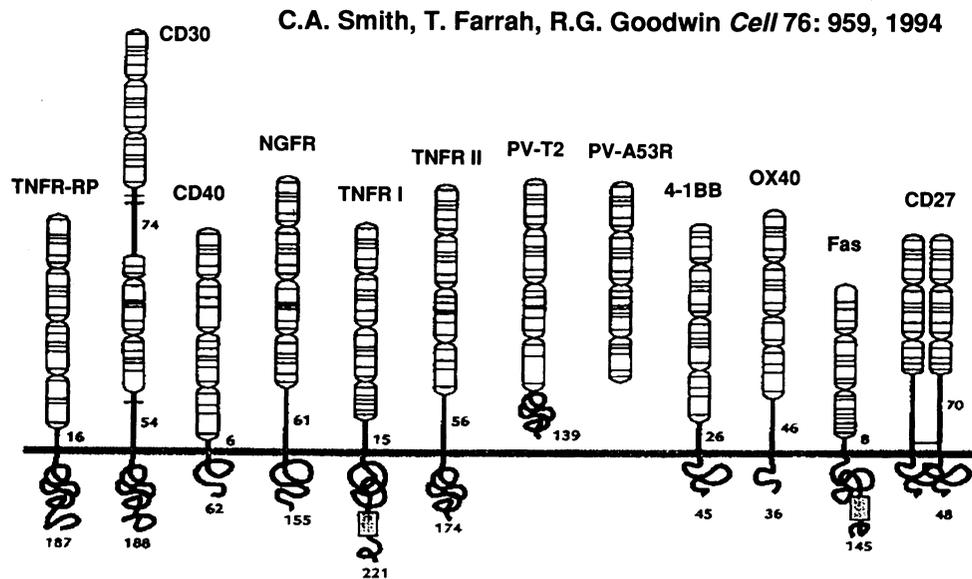


Figure 7. The TNF receptor superfamily, as an example of the superfamilies of genes that have impact in multiple fields. The superfamily shown contains members affecting a range of fields, including immunology, oncology, neurology, rheumatology, and infectious disease. The drawing is reproduced from reference 7 with permission of the authors and the copyright holder, Cell Press.

tion with a mathematical biologist, Charles DeLisi, to try to develop computer algorithms to search for T cell epitopes in protein sequences (10). This interaction was a key stepping stone in embarking on attempts to develop peptide vaccines to induce T cell immunity.

In a second example, around 1985, I was giving a talk at another general meeting, FASEB, on T cell immunology and epitope mapping, that was attended by Lou Miller, a parasitologist. Lou and I had never met even though he headed the malaria research group in an adjacent building at NIH. We had to go

to a meeting like this to learn of each other's existence. This chance meeting led to a longstanding and very productive collaboration between Lou's group and ours on malaria immunology and vaccines (10, 11).

Similar timely encounters with virologist Bob Gallo and his co-workers at a Cold Spring Harbor meeting, although I had never met them previously at NIH, facilitated the rapid application of our peptide approaches to the immunology of AIDS, and to the development of peptide vaccines for AIDS that are now being prepared for human trials (9, 10, 12). Our work on

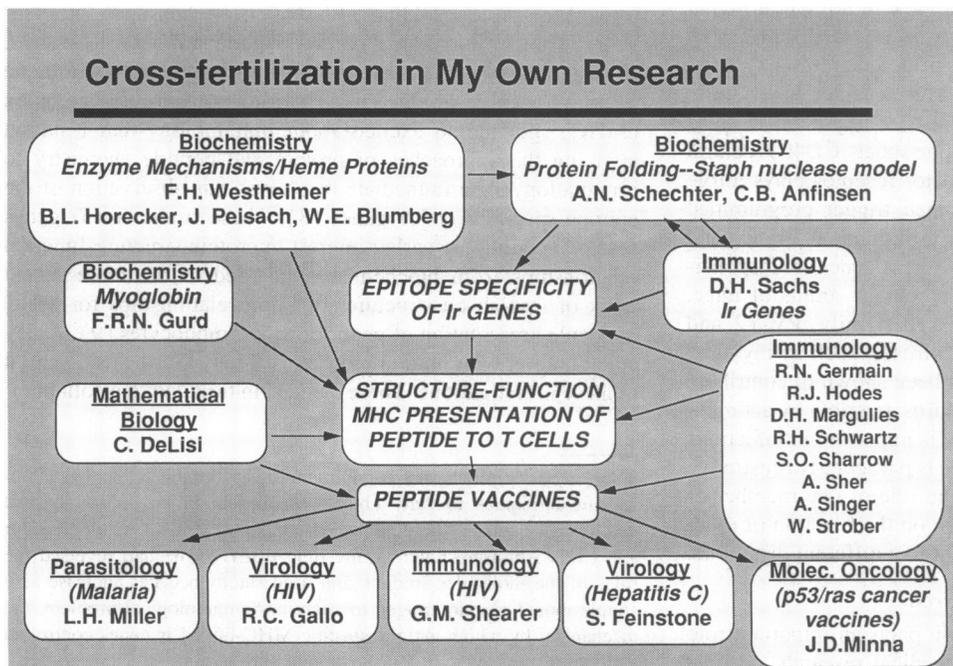


Figure 8. Examples of cross-fertilization in the author's own research career to date. Critical inputs from basic protein and peptide biochemistry and mathematical biology, as well as immunology, were essential to the basic research studies in immunology, that led to approaches to develop peptide vaccines. These vaccine approaches were then developed through encounters leading to cross-fertilization from parasitology, virology, and molecular oncology, which took the author from pure chemistry to immunology and vaccines, and from the bench top back to the bedside. Immunologists shown at right are limited to ones at the NIH with whom the author has published collaborative studies, although input from many others has been invaluable. Otherwise, the emphasis is on cross-fertilization from non-immunological fields.

HIV was also greatly facilitated by a very productive collaboration with immunologist Gene Shearer. Indeed, the whole field of HIV research has greatly benefited from cross-fertilization from many disciplines. Similarly, a collaboration with another virologist, Steve Feinstone, introduced us to hepatitis C.

Another major turn in our research came from cross-fertilization with the field of cancer etiology. After the discovery of cellular oncogenes by Bishop and Varmus, for which they shared the Nobel prize in 1989, the discovery that mutations in oncogenes such as ras or in tumor suppressor genes such as p53 can lead to a malignant phenotype was made by several groups whose goal was to understand the molecular basis of cancer, not to make vaccines. However, discussing this with John Minna, one of the pioneers in the study of p53 mutations in lung cancer, we realized that these mutations might be built-in targets for cytotoxic T lymphocytes that provide immune surveillance against expression of abnormal proteins inside the cell, regardless of whether they are expressed intact on the cell surface. We reasoned that even if the tumor itself could avoid inducing an immune response, if we could use a peptide vaccine to specifically elicit cytotoxic T cells that uniquely recognized the mutant oncoprotein sequence and not the wild type, we might be able to cause immune rejection of the tumor. In mouse models, we indeed found that specific cytotoxic T cells raised by immunization with a synthetic peptide could kill tumor cells expressing mutant p53 (13). I am happy to report that, with much support from Sam Broder and Tom Waldmann, we have just started our first clinical trial to treat cancer patients by mutant peptide immunization. The trial is a collaborative effort with molecular oncologists in John Minna's department in Dallas and with the NCI-Navy Medical Oncology Branch at NIH. Related approaches are also being attempted in other labs. Yet none of this would have occurred were it not for the cross-fertilization between studies of the molecular etiology of cancer and studies of the molecular basis of immune recognition. Thus, it was a series of accidental, as well as sometimes sought after, cross-fertilizations with many truly delightful collaborators that has taken me on this odyssey from pure chemistry to immunology and vaccines, and from the bench top back to the bedside.

Now to return to the original question, the problem we all face in achieving the type of cross-fertilization that could contribute to our research is mirrored by the problems of this meeting. The declining interest in a general meeting such as this or the FASEB meeting is symptomatic of the trend toward overspecialization in every field. The volume of literature is too enormous, and the pace of developments too fast, for an individual scientist or clinician to be able to keep up in all areas of his or her own narrow specialty, let alone in other disciplines. Although this centrifugal trend is difficult to counter as the pace of scientific advance accelerates, it should be viewed as dangerous. If one reads and hears only advances in one's own specialty, then one gradually loses interest in other areas, no matter how fascinating they were once found. Because each new result builds on earlier ones, the longer one is out of touch with a field, the more difficult it is to make sense of new developments in that field. Making matters worse, to extrapolate from C.P. Snow (14), each area develops its unique jargon, creating a language barrier to outsiders that represents not only a problem with language, but also a problem with the nested levels of concepts built into each of these terms. These barriers further discourage reading and attending seminars outside one's own

narrow specialty, and contribute to a vicious cycle in which one becomes increasingly cut off from the rest of biomedical research.

Those caught in this vortex not only lose the joy of learning the beautiful and elegant work being done in other fields, and the ability to teach effectively in the medical school and house-staff training setting, but also suffer a major handicap in their own research. This insidious process that handicaps one's originality comes from the fact that many fields develop along a set of expectations that create blinders to new directions.

From the above examples alone, it should be clear that an antidote is needed for this centrifugal fragmentation of biomedical science. This is the niche in which the Clinical Research Meeting finds itself, and the reorganization was designed to accomplish this goal. If we come here just to hear what is new in our own narrow fields, then we may as well cancel these meetings here and now, because the Clinical Research Meetings will never be able to provide the breadth and depth of coverage of any single field that the subspecialty meetings do. That is not the purpose of these meetings. However, no field can progress in a vacuum. What I hear at these meetings that excites me the most are the talks outside my own field, that give me new ideas and new ways of thinking about things. The primary purpose of these meetings is to translate and transmit new and exciting ideas from one field to another, to allow us all to rejuvenate our thinking. Thus, we hope that this restructuring and rejuvenation of the meetings will make the Clinical Research Meetings the primary place that all biomedical researchers will come to reinvigorate themselves and to glean fresh ideas to apply to their own research problems. If we succeed, then perhaps these meetings will help to break the vicious cycle and become a new upward force that will accelerate the pace of advances, by facilitating cross-fertilization.

In closing, I would like to say that it has been a great privilege to serve as your President for the past year. I would like to thank all of you for giving me that opportunity and honor. It has also been an enormous pleasure to be able to work with all the very bright, talented, creative, and enthusiastic people on the Council and Society committees over the past five years that I have been an officer. I would like to thank all of them for their tireless efforts for the Society, as well as all the help they have given me over these years. I would also like to thank Tom Waldmann, the head of our Branch at the NCI, for all of his encouragement and advice during this time. It will feel strange to be off the Council after five years, but I look forward to continuing to participate in the Society and in these Clinical Research Meetings, which, in their new format, should play an increasingly important role in fomenting innovative biomedical research in the years ahead.

## Acknowledgments

I thank Max Berzofsky, Sharon Berzofsky, William Chin, David Margulies, Bruce Scharshmidt, Alfred Singer, M. Charles Smith, Louis Staudt, Warren Strober, Ajit Varki, Thomas A. Waldmann, and Hans Wigzell for very helpful suggestions in preparing this address.

## References

1. Weissler, J. C., L. E. Rosenberg, and J. A. Berzofsky. 1994. The spring meetings: back to the future. *J. Clin. Invest.* 93:457-458.

2. Kuhn, T. S. 1962. *The Structure of Scientific Revolutions*. University of Chicago Press, Chicago.
3. Nash, L. K. 1956. The origin of Dalton's chemical atomic theory. *Isis*. 47:101-116.
4. Fox, D. M., M. Meldrum, and I. Rezak. 1990. Nobel laureates in medicine or physiology: a biographical dictionary. Garland Publishing Inc, New York and London.
5. Lerner, R. A., S. J. Benkovic, and P. G. Schultz. 1991. At the crossroads of chemistry and immunology: catalytic antibodies. *Science (Wash. DC)*. 252:659-667.
6. Comroe, J. H., Jr., and R. D. Dripps. 1976. Scientific basis for the support of biomedical science. *Science (Wash. DC)*. 192:105-111.
7. Smith, C. A., T. Farrah, and R. G. Goodwin. 1994. The TNF receptor superfamily of cellular and viral proteins: activation, costimulation, and death. *Cell*. 76:959-962.
8. Berzofsky, J. A. 1987. Ir genes: antigen-specific genetic regulation of the immune response. In *The Antigens*. M. Sela, editor. Academic Press, New York. 1-146.
9. Berzofsky, J. A. 1991. Antigenic peptide interaction with MHC molecules: implications for the design of artificial vaccines. *Semin. Immunology* 3:203-216.
10. Berzofsky, J. A., K. B. Cease, J. L. Cornette, J. L. Spouge, H. Margalit, I. J. Berkower, M. F. Good, L. H. Miller, and C. DeLisi. 1987. Protein antigenic structures recognized by T cells: Potential applications to vaccine design. *Immunol. Rev.* 98:9-52.
11. Good, M. F., J. A. Berzofsky, and L. H. Miller. 1988. The T-cell response to the malaria circumsporozoite protein: an immunological approach to vaccine development. *Annu. Rev. Immunol.* 6:663-688.
12. Cease, K. B., and J. A. Berzofsky. 1994. Towards a vaccine for AIDS: the emergence of immunobiology-based vaccine development. *Annu. Rev. Immunol.* 12:923-989.
13. Yanuck, M., D. P. Carbone, C. D. Pendleton, T. Tsukui, S. F. Winter, J. D. Minna, and J. A. Berzofsky. 1993. A mutant p53 tumor suppressor protein is a target for peptide-induced CD8<sup>+</sup> cytotoxic T cells. *Cancer Res.* 53:3257-3261.
14. Snow, C. P. 1959. *The two cultures and the scientific revolution*. Cambridge University Press, New York.