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Research Article

Clinical Investigation and the Clinical Investigator: The Past, Present, and Future

Presidential Address Delivered Before the 75th Annual Meeting of the American Society for Clinical Investigation, Washington, DC, 5 May 1984

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The first official meeting of the American Society for Clinical Investigation (ASCI) occurred on May 10, 1909, at the New Willard Hotel in Washington, DC (1). 10 papers were presented (Table I). Some of the papers covered areas of considerable importance, whereas others turned out to be of only transient interest. Nearly 50% of the membership or, if you will, 15 of the 31 members of the Society were present for this first meeting. The society was off and running, and today, we celebrate its 75th Anniversary.

By whom and why was the society formed? What has been the importance of the society over the subsequent 75 years? What does the future hold? These are the questions which I will address.

At a meeting of the American Medical Association held in Atlantic City in June of 1907, a small group of men stopped on the boardwalk to talk and were soon joined by Dr. Samuel J. Meltzer of New York. Dr. Meltzer was 57 at the time of this meeting. He was a Russian-born, European-educated practitioner of medicine and a well-known experimental physiologist at the Columbia College of Physicians and Surgeons. Just three years earlier, he had become Head of the Department of Physiology and Pharmacology at the Rockefeller Institute of Medical Research, which was newly established. As the group on the boardwalk conversed, the topic soon turned to medical meetings. The story goes that Dr. Meltzer introduced the concept that there was a pressing need for a forum where physicians actively engaged in clinical investigation could meet and present their work. Later that evening, he met in his hotel room at the Traymore with a small group of clinical investigators who were to become the organizing committee of our society (Table II). All of the other individuals involved were considerably younger than Dr. Meltzer but, virtually without exception, each was on his way to becoming a major leader of academic medicine in the United States.

Dr. Henry Christian, who was educated at Johns Hopkins and Boston City Hospital, had just become the Hershey Professor of the Theory and Practice of Physic and, at the age of 32, the "Boy Dean" of the Harvard Medical School. Dr. Warfield Longcope, a Johns Hopkins-trained pathologist was Director of the Ayer Clinical Laboratory at the Pennsylvania Hospital at the time. Later, he would become Bard Professor of Medicine at the Columbia College of Physicians and Surgeons in New York and, afterwards, Professor of Medicine and Physician-in-Chief at Johns Hopkins Hospital. Dr. David Edsall had trained and was currently on the faculty at the University of Pennsylvania. Later in his career, he served as the Jackson Professor of Medicine at Harvard and Chief of the East Medical Services at the Massachusetts General Hospital and, after that, the Dean of the Harvard Faculty of Medicine. Dr. Wilder Tileston, then a trainee at the Massachusetts General Hospital, was later appointed to the faculty at Yale. Dr. Joseph Pratt, a Johns Hopkins graduate and member of the staff at the Massachusetts General Hospital, was destined to become a founder, as well as Physician-in-Chief, of the New England Medical Center. Finally, Dr. Rufus Cole, a physician who had trained at the University of Michigan and Johns Hopkins, had just been named the first Director of the new hospital of the Rockefeller Institute for Medical Research.

Apparently, considerable progress was made that evening at the Traymore, and a second meeting was held in Boston several weeks later. At that time, the original organizing committee of seven was increased by the inclusion of Dr. Joseph Capps, who was a Harvard-trained physician on the faculty at Chicago's Rush Medical College, and Dr. A. W. Hewlett, a physician who had been trained at Johns Hopkins and was then a Professor of Internal Medicine at The University of Michigan.

At the second meeting, subcommittees were appointed to draft a constitution, to select members, and, indeed, to launch the society. On May 11, 1908, the ASCI was formally constituted as the "American Society for the Advancement of Clinical Investigation" and our first annual meeting was held the following year in conjunction with the Association of American Physicians (AAP). This early history of the ASCI is reviewed extensively in an article by Ellen Brainard, which was published in *The Journal of Clinical Investigation* (*JCI*) in 1959 at the time of our 50th anniversary (2).

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Table I. American Society for the Advancement of Clinical Investigation: First Annual Meeting Held in Washington, DC, 10 May 1909

Blood pressure in tuberculosis	S. J. Meltzer, New York
A modification of the Riva-Rocci method of determining blood pressure for use on the dog	T. C. Janeway, New York
The effect of compression of the superior mesenteric artery upon the systemic blood pressure	W. T. Longcope, Philadelphia
Note on the blood-pressure changes following reduction of the renal arterial circulation	T. C. Janeway, New York
Miliary tuberculosis of the skin	W. Tileston, New Haven
The sensory system and the sensory symptoms of the facial nerve	J. R. Hunt, New York
Studies in experimental anemia	J. H. Pratt, Boston
The reaction of atrophy of the pancreas to diabetes	J. H. Pratt, Boston
Some further observations of experimental nephritis	H. A. Christian, Boston
Respiration by distention of the lungs through a continuous stream of air	S. J. Meltzer and J. Auer, New York

Why was the ASCI formed? Some of the early history suggests that the ASCI represented a "revolt" from the already well-established AAP because the latter society had become "very conservative and somewhat dull, unaware of the tremendous advances being made in medicine" (2). While insurrection may be an overstatement, most historians do agree that the AAP and virtually all of the other professional societies in American medicine at that time were primarily oriented to clinical practice. The formation of the ASCI was an attempt to develop an organization for the clinician who had a strong professional interest in true experimental medicine. The society was to be composed of physician faculty who wanted clinical research to be recognized as an integral part of their academic responsibilities. In other words, the distinguished Professor of Medicine should be noted as such not only because of his superior clinical abilities, but also because of his important research contributions. The standards for membership were to be set at a high level with an emphasis on continuing scholarship within the discipline.

Table II. Founding Members of the ASCI

J. Capps	Chicago, IL
H. A. Christian	Boston, MA
R. Cole	Baltimore, MD
D. L. Edsall	Philadelphia, PA
A. W. Hewlett	Ann Arbor, MI
W. T. Longcope	Philadelphia, PA
S. J. Meltzer	New York, NY
J. H. Pratt	Boston, MA
W. Tileston	Boston, MA

The small group of founders understood the importance of attracting the best students and trainees to a career in clinical research. They appreciated the need to have research space designated for clinical investigation as well as the time available to use it. Since, in most cases, clinical research of that era was being conducted in the proverbial basement using personal funds from private practice, the need for external funding for clinical research was also clearly recognized. In effect, grants were required to support their investigation. Up to this time, with rare exception, the usual practice was to award individuals at the end of their careers for work that they had done rather than to fund them prospectively for work they wished to do.

In Dr. Meltzer's initial Presidential Address entitled "The Science of Clinical Medicine: What It Ought To Be and the Men To Uphold It," he emphasized the importance of the scientific basis of medicine. This was quite a different approach than had characterized academic medicine previously. Indeed, Dr. Meltzer felt the need for change so strongly that, in this inaugural address, he even encouraged the establishment of Departments of Clinical Science which would be separate from Departments of Medicine (3). At any rate, he certainly recognized the importance of studies on the pathophysiology of disease by physician investigators as essential elements in the future progress of medical science. His fervent support of clinical investigation, as contrasted with clinical practice, is perhaps best illustrated by a brief quote in his original Presidential Address: "Beware of practice. It is a bewitching graveyard in which many a brain has been buried alive with no other compensation than a gilded tombstone" (3). It is important to remind you that Dr. Meltzer was speaking in a world which had not yet recognized the value of clinical research.

Suffice it to say, the society was formed. Very rapidly it became known as the "Young Turks," apparently because the crusading spirit of the youthful society members who came to be identified with the "real young Turks" who, in 1908, startled the world with a revolt against Sultan Abdul Hamid II, deposed him the following year, and, with nationalistic fervor, set about to establish a constitutional regime and institute sweeping reforms in the decrepit Ottoman Empire. It seems that someone drew the parallel between these Turkish

revolutionaries and their counterparts in American medicine, and the name stuck.

Over the years that followed, the organization gradually evolved to its current form. The name was abbreviated. An absolute limitation on the number of members was eventually changed to recognize only those under age 45 as "active members." In 1924 our journal was established. The nature and content of our meetings were gradually expanded, and the current relationship to our sister organizations evolved slowly. From time to time, our society has suffered growth pains and periodic reexaminations of its role and spectrum of activity, a tradition which continues today.

The society's real impact is perhaps best reflected in the dramatic growth of clinical investigation as a discipline which has occurred since its formation in 1909. Some historians have suggested that the monumental revolution which the United States has experienced in clinical investigation and, to a great extent, in the practice of medicine has been heavily influenced by the formation of the society, the formulation and promulgation of its ideals, and the accomplishments of its membership. Could it be that the society's unchanging insistence on excellence from the time of its creation to the present day is the reason for its putative influence on the ascent of clinical investigation?

A major contribution of the ASCI since 1924 has, of course, been its sponsorship of the *JCI*. The *JCI* has persisted as the premiere journal in the field of clinical investigation and continues to define, on a regular basis, what is meant by clinical research at its finest. The high standards of the *JCI* are well recognized by essentially all biological scientists as well as by clinicians. Consider how important this high standard is to individuals in our discipline, who run the risk of being viewed as weaker scientists by the more basic investigator and as weaker clinicans by the practitioner. I will say no more about the *JCI;* its reputation and its stature within clinical investigation speak for themselves. I do believe, however, that the society owes a special debt of gratitude to the editors of the *JCI* since its inception, who are listed in Table III. These individuals have assured this high standard over the years.

In addition to the journal, surely, the ASCI has accomplished its original goal of providing a forum for the presentation and discussion of some of the most significant and exciting new advances in clinical investigation. As I looked through the plenary programs of the society over the past quarter of a century with the help of our current Subspecialty Chairs, the vast progress in medicine during this period was readily apparent. It was easy to identify, in retrospect, papers of lasting value. At least three papers were identifiable with a subsequent Nobel Prize and important trends in the nature of clinical investigation were clearly delineated. In addition, there were a substantial number of highly controversial studies and, unfortunately, also some which were later to be discredited. Finally, there were still other studies of considerable potential which have yet to be fully appreciated. While the quality of most of the oral and poster presentations is excellent, perhaps more importantly, the audience is predictably vigorous and demanding. To quote from an earlier Presidential Address by Dr. Good, "It is accepted behavior of the group, i.e., the audience, to demand that achievements be challenged ruthlessly, destroyed if possible, and accepted only tentatively with a brief word of caution if the ground is held" (4). This critical review, which is expected by all of us as we prepare our own presentations and those of our colleagues with extensive review and repeated rehearsals, contributes substantially to the excellence of the work presented.

Table III. Editors of JCI: 1924–Present

G. C. Robinson	1924–1926
J. H. Austin	1926–1935
J. R. Paul	1935–1935
R. West	1935–1941
J. L. Gamble	1941–1947
E. B. Ferris, Jr.	1947–1952
S. E. Bradley	1952–1957
P. K. Bondy	1957–1962
A. S. Relman	1962–1967
P. A. Marks	1967–1971
D. S. Goodman	1971–1972
J. D. Wilson	1972–1977
P. W. Majerus	1977–1981
S. Kornfeld	1981–1982
T. P. Stossel	1982–present

Most of what I've just noted about the contribution of the ASCI to clinical investigation could be said equally well for the AAP and for the American Federation for Clinical Research (AFCR). It is clearly impossible to dissect out the individual contributions which these three societies have made to the progress of clinical investigation during this century. The ASCI, however, is different from each of our two sister societies. First, we, as the AFCR, but unlike the AAP, have an age limitation which ensures that the ASCI is forever young. Whatever the age of scientific senescence or investigative climacteric, most members of the ASCI will have achieved emeritus status prior to its onset. The ASCI, as well as the AAP, differ from the AFCR in that the former two organizations set a limitation on their membership in an attempt to achieve high standards. Finally, as noted earlier, the ASCI publishes the *JCI*. Thus, with its journal, its age limitation, and its attempt to set high standards for membership, the ASCI is unique.

Perhaps it is this unique character of the ASCI which has so strongly influenced the development of clinical investigation by providing a model and an achievable goal of excellence for the individual clinical investigator. This is surely not to say that all excellent clinical investigators in the United States are members of this society. The society clearly makes mistakes, particularly of omission, in its choice of members and it will

always do so. On the other hand, election to the society often serves as a milestone in the career of the clinical investigator, by demonstrating that the newly elected member has met a high standard which is widely recognized. Indeed, the selection of leaders throughout the major medical research institutions in the United States often begins by a careful review and analysis of our membership roster for "Young Turks" who might be appropriate for the opening in question. Success of an academic program in an institution is sometimes even measured by the number of faculty who are members of the society. We do set an important standard in American medicine. In addition, I would submit that Samuel Meltzer and his colleagues have achieved a level of success with the society which it seems likely far exceeded their original goals.

To symbolize the members of the ASCI over the past 75 years of the existence of the society, we have chosen to recognize the previous Presidents of the ASCI who are still living. The previous Presidents of the society who are living at this time are listed in Table IV.

I shift now to the future of the society and, indeed, the future of the clinical investigator. While the founders of our society were most concerned with the creation and preservation of clinical investigation as a discipline, we must now concern ourselves with the promulgation and preservation of the clinical investigator. I predict that progress in clinical research over the next 25 years will dwarf that of the previous 75 years which I have been discussing. The great bulk of discoveries and breakthroughs in medicine over the past 75 years have come from young clinical investigators. While we may recognize the name of a senior scientist on many of the classic works of our time, I would submit that much of the creativity, hard work, persistence, and perhaps faith have come from a younger collaborator who may have been a junior faculty member, a fellow, or even perhaps a student. It follows, I believe, that it is not just the present membership of the ASCI who will make the vast majority of these discoveries in the next quarter of a century, but those who have yet to become Young Turks will be critical to this progress. In other words, it is not solely the big name nor the recognizable face who will be responsible for the major developments between now and the Centennial Celebration of this society in the year 2009. Rather, many of you who are now trainees or perhaps new faculty just starting your first real job will make many of the significant contributions although most of us don't recognize you . . . yet.

Table IV. Living Previous Presidents of ASCI

I. Starr	1940	G. W. Liddle	1967
W. B. Castle	1941	R. A. Good	1968
W. Dock	1942	A. S. Relman	1969
E. M. Landis	1943	L. H. Smith, Jr.	1970
W. W. Spink	1949	H. R. Holman	1971
T. H. Ham	1950	P. A. Marks	1972
E. A. Stead, Jr.	1953	N. S. Bricker	1973
A. M. Harvey	1956	E. Braunwald	1974
S. E. Bradley	1957	L. E. Earley	1975
R. V. Ebert	1958	J. S. Fordtran	1977
J. A. Luetscher, Jr.	1959	J. D. Wilson	1978
R. W. Berliner	1960	K. L. Melmon	1979
C. A. Finch	1961	J. Roth	1980
I. M. London	1964	W. E. Paul	1981
A. Leaf	1965	P. W. Majerus	1982
D. W. Seldin	1966	L. M. Sherwood	1983

Biomedical science has never been more exciting than it is today, and the future of the clinical investigator has never been more promising. We are beginning to enter a phase in which the immense power of molecular genetics will be applicable to clinical medicine with potential perhaps beyond our fondest dreams. Indeed, there may be other fields with which I am less familiar which are just as promising. Perhaps not since the founding of this society have we so badly needed to train and retain the brightest young stars in American medicine to translate basic biomedical investigation to the bedside. Has there ever been such a great opportunity for the creative, well-trained, and highly motivated clinical investigator?

Despite the enormous opportunity which exists, the young clinical investigator is still a vanishing species. I personally believe, however, that many of the factors leading to the decline in the attractiveness of a career in clinical investigation which began in the late 60's have reversed. We are now beginning to see increasing attention to the concerns of the young clinical investigator from the Federal Government as well as from others. Spectacular technological progress is allowing us to generate more scientific information from patients and patient material despite appropriate societal restrictions on many types of patient-related clinical research. Specialty and subspecialty boards seem to be increasingly aware of the importance of making time available for investigators to do research during their formal clinical training programs. Funds to support individuals making the transition from trainee to accomplished clinical investigator are becoming more readily available. The allure of private clinical practice is waning as competition, federal regulations, and third-party control become an increasing part of it. At the same time, the science itself is becoming more and more attractive.

On the other hand, the challenges for the clinical investigator are quite different today than they were for Samuel Meltzer and his colleagues. The very success of medical science has transformed the clinical investigator. Rather than dedicating himself to conducting controlled clinical observations and experimental medicine, the contemporary physician scientist must be able to master and apply concepts and techniques in molecular and cellular biology to answer the questions of interest. Thus, there is a domain of learning for this individual which is quite remote from the practice of medicine. One might argue that for the last several decades we have even seen a qualitative break in the spectrum of science of direct relevance to the clinical investigator. No longer does our

scientific discipline necessarily fit on a continuum from the bench to the bedside. In effect, sophisticated science has forced a discontinuum and, hence, a dichotomy with which the young clinical investigator must deal. While this gap is becoming increasingly difficult to bridge, we must continue to do so.

In a recent issue of *Clinical Research* (5), Dr. Bob Lefkowitz published an essay on the occasion of his receipt of the prestigious Lita Annenberg Hazen Award. In this essay, he reflected on his own career in science and medicine and he provided advice to the novice investigator. With regard to the latter, he highlighted four points: (*a*) the selection of a research mentor, (*b*) the importance of not attempting to build an investigative career on a method or technique, (*c*) the ability to say no, and (*d*) the maintenance of a balanced perspective. To this, I would also add the importance of complete honesty and that special extra effort which is often the difference between excellence and mediocrity.

I too would now like to focus on those of you who are just at this moment either considering or beginning your research careers. As the next 25 years unfold, those of us who are currently members of the ASCI will observe your progress with great pride. We will recognize your faces, learn your names, perhaps try to recruit you to bring additional status and fame to our institutions, and, I suspect, view you with a bit of envy. It is to you whom I will direct several comments and suggestions.

Obtain the best research training available in your field of interest. It is important that the proper philosophy of research pervade the laboratory you chose. In his Presidential Address over 20 years ago, Dr. Henry Kunkel spoke on the importance of a training program which emphasizes a philosophy that includes, and I quote from his address, "the scientific disciplines of thought, intellectual integrity, the sanctity of the written word and even the ethics of research work" (6).

There are several points related to timing that I judge to be important. First, at the outset, give yourself adequate time to be productive in the research laboratory. After a few months in the laboratory, it is the rare individual indeed who feels productive or satisfied with his or her accomplishments. It is more typical for the well-trained young clinician, accustomed to the immediate gratification associated with caring for acutely ill patients, to be frustrated at the discovery that the first six months in the lab seem to have led nowhere. Optimally, you should try not to make any irreversible decisions until you have given the laboratory at least one year, preferably more, of your dedicated time and effort. That "eureka experience" will occur at some point, making many months of seemingly wasted effort all worthwhile. Give it a fair trial.

In addition, you will need to make the effort and spend the time equivalent to a Ph.D. experience in order to maximize the likelihood of success in your research career. I am not suggesting that a Ph.D. degree is necessary in addition to an M.D. degree, but I do suggest that you dedicate two to four years to your fundamental area of interest with effective guidance and an absolute minimum of distraction.

Overall, you will need five to seven years of very protected time when combining your period of research training with your most critical early faculty years. Work with your Division Chief and/or Department Chairman to set priorities and keep these in mind as you allocate your time. As emphasized by Dr. Lefkowitz, learn to say no when appropriate. Fortunately, this track is becoming increasingly practical and available, thanks to the National Institutes of Health with its newly organized Physician Scientist Award Program, and similar programs offered by several other prestigious and forward-looking organizations. Without this strong research training and protected time, your likelihood of success as a clinical investigator will be considerably reduced.

Despite the importance of the teacher-student relationship early in your career, don't carry it too far. At the appropriate time, shift to independent status and seek support in establishing recognition for that independence. The persistence of the senior investigator as a participant in the young investigator's research program actually creates one of the biggest problems which the ASCI faces in selecting new members. There is no question that many highly qualified investigators are not elected to membership in the ASCI because senior investigators continue to appear as coauthors on their papers and, we presume, are significant co-participants in their research. If you do not receive support from your superiors in achieving independent status as your career develops, seriously consider other options which may enhance such independence.

Give yourself a fair opportunity in a faculty position. One of the major catastrophes I have observed concerns the young individual who obtains the appropriate training and has the proper tools for success, yet after a year or two of limited success in achieving research support at the faculty level, he or she gives up and moves into practice. For most individuals including some of the very best, a period of two to three years is necessary to develop a strong funding base. This is often a period of considerable insecurity when you will need support from above. Hang in there. The new Physician Scientist Award from the National Institutes of Health should also help in this regard.

While it is almost equally catastrophic to watch the continued unsuccessful efforts and frustrations of the individual who clearly made the wrong career choice, usually a persistent lack of external funds helps to define the future for such an individual.

As your career matures, it is important to understand the natural history of the successful clinical investigator. For most of us, a career shift toward either a more clinically oriented or a more administratively oriented position will probably be appropriate after a number of years. It is an unusual clinical investigator who is able to maintain an active, creative, productive, and well-funded laboratory until the time of retirement at age 65 or 70. While I recognize that many of those unusually productive clinical investigators with lifelong crescendo careers in the laboratory are concentrated in this society, I would still submit that, in many if not most cases, it is appropriate at

some point for the individual to change the focus of his or her career. A change in direction after 20 or 25 years is not failure but part of our natural history. Define that point for yourself prospectively and attempt to act on it when the time comes. This may be the hardest call of all for many of us.

Finally, I would like to emphasize the importance of maintaining your role as a physician and teacher during the active research phase of your career. You are unique within the university in occupying the infamous three-legged stool of research, patient care, and teaching. Despite my emphasis on protected time early in your research career, I believe it is equally important to set aside time to continue to function in the care of patients. While you must not be overburdened with service responsibilities, you should maintain patient care contact particularly as it relates to your teaching responsibilities, to your own clinical research, and to the maintenance of your clinical skills. There has always been a tendency for the most successful investigators to try to minimize their patient care and teaching activities for obvious reasons. For the first time in my career, however, I am beginning to see more and more examples where there is actually a financial incentive not to see patients. In other words, there may be substantial financial incentive to commit time outside of the laboratory to industry rather than to patient care and teaching. This is going to increase in the future as the financing of clinical investigation evolves further away from patient care and more toward industry. Once removed completely from patient care at the faculty level, it is hard to return. If you do remove yourself from clinical activity, you will eventually lose the perspective of the authentic clinical investigator and, indeed, you may as well forget the time you spent as a medical student, resident, and fellow as well as your responsibility to the university. Most importantly, in my judgment, it is critical that you continue to think creatively about clinical problems by staying active clinically.

In conclusion, I would like to emphasize that in the United States today, a career in clinical investigation can be the most satisfying that one can possibly imagine. We have the direct gratification of making important advances which in one way or another may contribute to the relief of pain and disease. We have continuous stimulation and excitement from the regular influx of bright, young, creative minds with new thoughts and new approaches. We often are able to think, to create, to experiment, to try out our ideas, to set our own priorities, and to do what we believe is appropriate with a minimum of disruption. What a wonderful way to spend the day! Although some of us travel a great deal, let me remind you that we do so at our own choosing, taking advantage of opportunities to meet with our colleagues and to expand our horizons. We are often treated with the highest of esteem both at home and away. In addition to all of this, we are even paid well. While most of us will not become wealthy, we can usually provide a comfortable existence for our families and ourselves. While the clinical investigator of the future will be challenged, virtually all of the indicators are highly positive that this will continue to be a rewarding career choice.

I would like to close by briefly quoting again from Dr. Meltzer's inaugural Presidential Address to this society 75 years ago. In referring to the clinical investigator on the boat of progress, he made the following comment: "The men who you now see sitting on the bank left behind while the boat of progress swiftly glides away with fresh winds and under fresh sails, were themselves, in their youth, passengers of similar boats and cut faces at others who were left behind. Be generous to them, but do not repeat their mistakes. The secret is: never leave the boat." I would add in conclusion: get on the boat, follow the guidelines that I have shared with you, and stay with it as long as it is appropriate. It is a wonderful career and you will never be sorry. You are the future of clinical investigation.

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