



2011 Norma Berryhill Distinguished Lecture

**The Essential Need for a Climate of Creativity in
Academic Hospitals: The ANCA Vasculitis Story**

presented by

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I want to express my sincere gratitude to Chancellor Holden Thorp, Dean William Roper, the Berryhill family, Dean James Harper, and the Berryhill Committee for selecting me as the 2011 Norma Berryhill Distinguished Lecturer. It is my extraordinary honor and pleasure to speak to you today.

I begin at the customary close; the acknowledgements. My family and colleagues are my foundation and sustaining force. This is especially true of my wife Katherine, and my children, Benjamin, Kristine and John, who have graced me with constant compassion, everlasting love, and reality testing so necessary for ground wiring. My work family has similarly enriched me with colleagues and trainees that for over a quarter of a century have made UNC the intellectually stimulating and nurturing place that it is today. In particular, I am indebted to Charles Jennette, a mentor and friend who has provided constant intellectual stimulation and with whom hundreds of manuscripts have been written. I am a proud product of this medical school, internal medicine residency and my nephrology fellowship, and have spent my entire career at this wonderful institution. Kathy and I have had opportunities to look the world over, and the grass is really greener and the sky is really Carolina bluer in Chapel Hill. My studies began in Berryhill Hall where the warm collegial atmosphere of the University of North Carolina became palpably evident. This congenial atmosphere remains the heart and soul of this place and engenders the collaborative and fertile environment that many of us enjoy. This, then, is the Berryhill legacy of collegiality and hospitality that makes Carolina special; an environment most formative and critical to all that our team has accomplished.

Today I am going to consider a subject that is essential to the fabric of an academic health care system—the critical need for a vigorous climate of creativity. The word creativity comes from the Latin word *creō* (to create or make). Theories of creativity focus on the four p's: process, product, person, and place. The choice of the words “climate of creativity” focus on the fourth p, place; that is, an environment where creative forces flourish. On one hand, a climate of creativity is essential for the success of those

who wish to be innovators. On the other hand, the leveling of the technological playing field between academic and non-academic hospitals makes essential a climate of creativity to the very business model of academic hospitals. It is my hope to convince you of the veracity of both of these statements.

Translational research seeks to diminish the gap between basic science discoveries and clinical care and is the focus of considerable attention and funding on both the federal and local levels. This is appropriate, as the improved health of our citizenry relies on efficient translation of the explosive progress in basic and clinical sciences to the immediate health of our patients. This requires a climate that aligns those who wish to do translational research with willing patients and a supportive healthcare environment.

To best exemplify this balance, I will tell you the story of our research efforts and use them as the focal points for this discussion. Patients with vasculitis have inflamed blood vessels. In the past, their diagnosis, underlying cause of their disease and treatment were mired in a world of eponyms and dismal outcomes. Our involvement in vasculitis research began with a patient of the late pediatric nephrologist, Dr. Richard Morris, who wanted to know what was wrong with one of his patients. This was a 15-year-old girl who presented to the hospital coughing up substantial amounts of blood and who had a very aggressive glomerulonephritis, or inflammation of glomeruli, which are the filtering units of the kidney and are comprised of small blood vessels. Remarkably at the same time, an article appeared in the *Lancet* suggesting that a form of vasculitis was associated with an unusual autoantibody that reacted with normal neutrophils. We dribbled some of this 15 year old's serum on neutrophils and these observations spawned the detection of what are now known as anti-neutrophil cytoplasmic autoantibodies, or ANCA for short. Much of clinical medicine is based on descriptive studies that define disease on the basis of clinical and pathological findings, natural history and hopefully response to therapy. Vasculitis was difficult to diagnose, there were numerous overlapping patterns of disease, and at times diagnosis took months to years. The association of a biomarker with any disease typically changes the calculus of the diagnostic process. The clinical utility of ANCA serologic testing did just this.

The history of vasculitis has much to teach us today. Our investigative forefathers displayed remarkable curiosity with respect to individual patient cases. Hans Eppinger, a German pathologist, recovered the tissue from probably the earliest known patient with vasculitis described 35 years earlier and documented the first histology of vasculitis. In 1866, Adolf Kussmaul and Rudolf Maier, whose pictures and busts adorn their respective medical schools, separated small- and middle-sized vessel vasculitis on the basis of the careful analysis of only two patients. We still have much to learn by thinking about each patient. Over the course of the next half century, our understanding of vasculitis was refined by more precise descriptors of the pathology and clinical presentation. In 1954 a pathologist, Jacob Churg, realized that these vasculitides, known by a number of names, were morphologically and probably pathogenetically related.

Fast forward to the late 1980's and early 1990's. The discovery of ANCA in patients with small vessel vasculitis unfolded rather quickly. The initial description of these autoantibodies and their association with the Ross River arbovirus in Australia was not recognized by the mainstream scientific community. The seminal observations by the late Professor Fokko van der Woude published in the *Lancet* in 1985 triggered our interest in vasculitis and resulted in our findings that these autoantibodies were found in a wide array of patients with small vessel vasculitis. Further study revealed that one of these autoantibodies, known as perinuclear ANCA, reacted to myeloperoxidase, the protein that makes pus green. Quickly thereafter, the protein responsible for the other ANCA serotype, cytoplasmic ANCA, was

discovered by a group in the Netherlands and our own group. That protein, a novel serine proteinase, is known as proteinase 3.

We now know a great deal about these two autoantibodies, myeloperoxidase or MPO-ANCA and proteinase or PR3-ANCA. With modern technology, we are hard-pressed to find patients with small vessel vasculitis that do not have ANCA. These two autoantibodies have become the basis of a serologic and diagnostic test available throughout the world. No longer do we have to wait for patients to present with protean symptomatology and physical manifestations of disease. Consequently the morbidity and mortality associated with these diseases has diminished.

In the early 1990s, we began to investigate whether these autoantibodies were more than just serological markers. We asked the question of whether these autoantibodies could actually cause disease, and it turns out that they do. ANCA activate neutrophils and monocytes when the antigens myeloperoxidase or proteinase 3 are displayed on the surface of the cell. ANCA-activated neutrophils and monocytes have a “respiratory burst” that releases bleach into the microenvironment as well as noxious granule constituents. When ANCA activate neutrophils, they cause substantial injury to endothelial cells that line small blood vessels.

The kinds of studies that we have performed greatly rely on the phenomenal insights and collegial support of many members of our basic science faculty. Let me provide examples. From the outset, we realized that the autoantibody had to “see” its autoantigen, which usually hides inside cells. There are probably a number of ways that this may occur. While studying human neutrophils from a number of autoimmune diseases, we stumbled across an unusual finding. In normal individuals, neutrophil genes are typically silent. Using Affymetrix arrays to analyze leukocytes obtained from ANCA patients, we learned that neutrophil genes were turned on in patients with ANCA disease in a pattern much different than what is seen in patients with other autoimmune diseases such as systemic lupus erythematosus or rheumatoid arthritis. In patients with ANCA disease, two of the genes that were turned on were the autoantigen genes myeloperoxidase and proteinase 3, and they were coordinately turned on or off. Through collaboration with the brilliant genetic experts in our environment, we now know that these genes are being activated or silenced through epigenetic control; that is control of what turns on or off genes. These studies taught us much about normal biology and why patients with ANCA disease were turning on myeloperoxidase or proteinase 3 genes during disease activity and off in disease remission. We have much work left to do in this arena. These observations have had a broader impact on all autoantibody-mediated diseases by directing our focus not just on the autoantibody but also on the autoantigen. Perhaps therapy of these disorders should not just be aimed at quelling inflammation or more recently, getting rid of autoantibody. Perhaps silencing of the autoantigen is a therapeutic target.

With these in vitro data that support a mechanism for an autoantibody-mediated disease, we asked more specifically how we could prove that these autoantibodies actually cause disease. To answer the question, we used the generally recognized convention for proof known as Koch’s postulates that are aimed at proving that a pathogen, or in this case an autoantibody, is causative of disease. We fulfilled the necessary requirements with an animal model. Using myeloperoxidase knockout mice obtained from Nubuyo Madea, mice were immunized with mouse myeloperoxidase. These mice developed antibodies to myeloperoxidase, which were then transferred into naïve murine recipients that subsequently developed glomerulonephritis and vasculitic disease that closely resembles human disease. Investigators in England and Boston have now created animal models using antibodies to proteinase 3. ANCA are not just biomarkers of disease—they cause disease.

Along the way, we have made a host of other interesting observations. We learned that proteinase 3 and myeloperoxidase could enter and alter endothelial cell function. We discovered that our patients were not just making an autoantibody to proteinase 3, but also to a protein that was complementary in structure to proteinase 3. This discovery spawned our theory of autoantigen complementarity as a mechanism for the development of autoimmunity. We dissected what we learned from this theory and discovered that plasminogen is an additional target of autoantibody response, and that when patients make an antibody to that molecule they develop blood clots. We have studied the genetics of our patients. We wondered why so few African Americans developed ANCA disease and why it is primarily a Caucasian disease. We learned that African American patients have a particular HLA genotype that was found with an odds ratio of 35 in a population of African Americans with proteinase 3 ANCA disease but not in patients with MPO ANCA and not in Caucasians. There is another message in these studies. The basic science community has been pivotal in our progress. PhD scientists and epidemiologists that are integral parts of our Clinical Nephrology and Department of Medicine or Pathology faculty are the essential drivers of this work, but in the body politic of the School of Medicine do not receive the credit they deserve.

The Nephropathology Laboratory was the underpinning of our early forays into understanding the clinical and pathologic features of small vessel vasculitis, and is the backbone of the Glomerular Disease Collaborative Network that I will talk about in a moment. Our Glomerular Disease and Vasculitis Clinic was formed as a multidisciplinary clinic that now sees as many, in fact more patients with immune-mediated kidney diseases than probably any place else in the United States. Our patients participate in inception cohort studies in which patients are followed from their first visit, or at the time of diagnosis, until they die. This has produced a treasure trove of longitudinal data and is the basis for many of our translational studies. The longitudinal follow-up of these patients has allowed the gradual understanding that there are differences between myeloperoxidase ANCA disease and proteinase 3 ANCA disease from the clinical, pathologic and now genetic perspectives. For example, we learned that patients with PR3-ANCA disease are more likely to relapse. MPO-ANCA and PR3-ANCA diseases are similar, yet in a number of ways, they are very different diseases.

A greater understanding of vasculitis by the international community was the development of what is known as the Chapel Hill Consensus Conference for the nomenclature of vasculitis. This nomenclature has become the worldwide standard for the definitions of vasculitic disease.

Standardization of the nomenclature and world-wide ANCA testing resulted in a large number of randomized treatment trials that have changed the treatment landscape. If ANCA are really pathogenetic, then treatment aimed at getting rid of these antibodies should be the most effective. Plasmapheresis, in which the autoantibodies are removed by a machine, has been an effective treatment of severe disease. Getting rid of antibody-producing cells, B lymphocytes, should also be effective. Two side-by-side studies published in the *New England Journal of Medicine* examined the use of the drug rituximab that removes a type of lymphocyte important in producing autoantibody. Rituximab was as effective as conventional cytotoxic alkylating therapy at inducing a remission, and rituximab was better at quelling a relapse.

We have evolved from an era of eponyms to an era of understanding the underlying cause of disease, and target therapy to treat them. We are getting closer and closer to being able to answer the most common question that patients ask, “What caused my disease?” We have so much more to learn,

especially as it pertains to the biology of a remission and relapse. If Dr. Richard Morris' patient from 1985 would have presented in 2011, she would have been promptly diagnosed with an ANCA vasculitis, and effective therapy begun at once.

Translational research with human samples is a labor of love. Patients and their doctors want to participate in these kinds of studies, and have flocked to UNC in large numbers to participate in them. There are considerable demands, both clinical and scientific, associated with the care of these patients and of the biological samples they provide. T cells and B cells and RNA cannot sit in a coat pocket waiting until rounds are finished. If a patient is willing to donate tubes of their precious blood, it is incumbent upon the researcher to assure that the sample is processed in such a manner that the maximum amount of information can be obtained.

In our own environment, a dedicated group of young investigators have worked diligently and expeditiously to make sure that the human samples required for our studies are of the highest quality. Our regimen for sample collection requires that the clinical environment where patients are seen and the laboratories where samples are analyzed to be in relatively close proximity. Our laboratories within the Burnett Womack building are close to patients seen in the Ambulatory Care Clinics and the University of North Carolina Hospitals. "Location, location, location," and ease of patient access are of paramount importance. Another critical ingredient for the success of translational medicine is the interest and buy-in of healthcare providers of all stripes. In this regard, over the decades, we have had exceptionally helpful UNC hospital clinic and floor nurses who have always been eager to help in our endeavors. Just recently, compliance issues threatened the long-term follow-up of our patients. The Chief Compliance Officer of our institution responded by combing through my entire NIH Program Project with me to ferret out a solution to the problem. There is no question that translational research requires a climate of creativity and cooperation in academic medicine.

Our studies on ANCA vasculitis began with a single case. Would this case, or cases like it, become the focus of investigative concern in the current era? The short answer to this question is yes, but it has become more difficult to accomplish innovative work within any academic hospital. Declining support from the federal government including NIH grants, bundled Medicare payments, and waning graduate medical education support have squeezed all academic hospitals. State budgets have been forcibly shrunk. Insurers look for the best quality at the lowest cost and have little regard for whether their members go to an academic, regional or private hospital.

What is the business argument for the assertion that an academic hospital must create a climate of creativity? The technological gap between academic hospitals and outstanding community hospitals has closed. In reality, the clinical playing field has tipped in favor of outstanding community hospitals where clinical care is the only focus and parking is free. Some of our best and brightest trainees care for their patients in community hospitals, and they do so with state-of-the-art expertise. Continuing medical education, maintenance of certification, and practice improvement modules that very soon may become prerequisites for licensure assure that these community-based physicians are up-to-date. Clinical research organizations have made use of these very well-trained physicians to perform clinical trials in their practices. And why not? There is ready access to patients, the process of developing a contract is astonishing simple when compared to arcane and cumbersome University practices, and the private practice practitioner has garnered another source of income. Across the country and indeed across the developed world, academic health care systems are experiencing hurricane force swells. While their schools of medicine continue to be the focus of investigative prowess, their associated academic hospitals

have largely emulated private practice models. Many such systems are not faring well. Having had the privilege of being a visiting guest of most of the major academic healthcare systems in this country and many aboard, I will submit that UNC Health Care is elegantly navigating through these difficult waters.

For all of us in the clinical trenches, our current healthcare delivery system feels like an ever-spinning merry-go-round where physicians spend less and less time with each individual patient. More time is now spent charting and documenting the clinical interaction than engaging in the clinical interaction itself. The electronic medical record most certainly has wonderful and time-saving attributes, but much of what is being recorded is mind-numbing cut-and-paste drivel. The overarching effort to see more patients to generate a profit margin is contrary to what patients want. They want more face time with their health care provider, not less.

In an effort to sustain and grow market share, healthcare systems around the country, including our own, are expanding hospitals and clinics to capture more of the market in larger population centers closer to the homes of the target populations. This kind of expansion is akin to many commercial business models. There is a Wal-Mart or a Target in every community, but interestingly not a Sears or Borders or Circuit City. For those of us who grew up in the 1960's and 70's, it is hard to imagine how Sears has been so surpassed. How many of you in the audience grew up trying to get a seat at the grown-up table by sitting atop a Sears and Roebuck catalogue? How is it possible that this great company that was at the top of the retail empire and whose management was held in the highest esteem has fallen from their position of primacy? Why did they not follow Dayton department stores and develop a Target-like spin off? Why did they not shift their hardcover catalogue to an internet-based catalogue right off the bat? Why have so many companies, once common household names, fallen off our radar screens? The answers may lie in what Clayton M. Christensen describes in his book, The Innovator's Dilemma. As Christensen points out, the mangers of Sears were sustaining their existing customer needs and missed a number of disrupting forces. I pose this question. Is our own business model sustainable and expandable over the next 10 years? The answer is yes, but it must be modified.

There are a number of disrupting forces in the healthcare landscape. With cost containment and quality assurance as drivers, patient-centered medical homes of all stripes, from primary care to specialty care, are being actively pursued. Forget for a moment the looming changes in the structure of reimbursements. Long gone is the era when there were only a relatively small handful of tertiary and even quaternary care hospitals in our state. Now there are UNC, Duke, Wake Forest, ECU, Carolinas Medical, Mission, and with recent affiliations of hospitals in our state with the Cleveland Clinic. All of these health care systems are vying for a piece of the complex patient pie. For simple problems, consumers want simple and immediate solutions. These needs are being met in urban areas by primary care providers, urgent care facilities, and more and more by clinics in pharmacy chains who have bet on the notion that the informed consumer will go to one of their almost drive-through clinics, get cared for and leave with their prescription. In all aspects of medicine, there is a renewed and healthy focus on patient wants and needs as a consequence of fierce competition. As an academic health care center, we must cater to the sickest of the sick, and the most complicated of the complicated.

For me the most interesting and important disrupting force is the advent of what has been described by Alvin and Heidi Toffler as a "non-expert expert." Let us consider what this means in the health care arena. Suppose you or a family member have a serious medical illness. How would you decide where you would seek care? If you had a regular physician, you would ask them. You would also call a friend and probably simultaneously Google your illness. The vast array of information on the internet

would be mind boggling and confusing. Sooner or later, you would find valuable trustworthy information. If you had even rudimentary social networking skills, you would find a community of people with similar ills who would provide advice both good and bad. Through this process, you would become a non-expert expert, and you would have a notion about who the real experts are. These experts are very different from those in the media. Americans are at a complete loss in trying to understand the advice of experts that appear on the nightly news who frequently respond to new task force recommendations that may or may not be germane to the health of a specific patient. Your search will have found a very different group of experts germane to what you need. The next critical question is which one should you see? I predict you would want to know something about the quality of the physician practice and the institution in which they are practicing. Consumers have an ever-expanding array of instantly available measures to inform themselves about physicians and hospital quality and safety outcomes. We are all now rated in a manner akin to restaurants or hotels. If you have a trusted physician, you would ask for their advice. More often than not, you may know more than they do. So you or your physician would take the next step and see if the expert whose help you seek is willing to interact by phone or email. If you can make contact with an expert, one of their colleagues, or other health care providers in their group, you will figure out how to make your insurance work and travel the distance to have your knee replaced, your heart operation performed, your eye examined or your vasculitis treated.

It is interesting to me how we became experts in the vasculitis patient community. I would submit that we did so by a number of factors. First we conducted a substantial body of research in the area of vasculitis, second we engaged and integrated kidney physicians from around the southeastern United States in our research efforts through the Glomerular Disease Collaborative Network, and third we reported and broadcast our discoveries through the traditional approaches of publishing our findings and speaking at medical conferences, but also by interacting with patients in support group symposiums and most importantly through our website.

In 2010, we heralded the 25th anniversary of the Glomerular Disease Collaborative Network (GDCN), formed in 1985 as a collaborative effort with 15 private practice nephrologists in North Carolina. The GDCN was formed to help explore the causes, management strategies, and therapies available for specific glomerular diseases. This is an ongoing joint venture of academic and private practice nephrologists that now includes over 600 physicians from 283 clinics throughout the southeast and elsewhere. We have actively engaged in dialogue between our academic community and private practice physicians. They know we are experts in immune-mediated kidney diseases. We have learned how much private practice doctors want to partner with academic institutions to allow their patients the most *au courant* and at times experimental care. This phenomenon should be a cornerstone on which to build similar interactions accessible throughout our numerous clinical points of care.

What startled me was that despite all of our publications and speaking engagements, we had made little progress in gaining notice by internet search engines. To address this, we developed a patient education website targeting the non-expert expert, and that changed the playing field. Initially written by doctors for patients, the information was effectively translated from medical speak by a number of people who made sure our material could be clearly understood by our target audience. We have made podcasts that discuss very specific patient-centered health issues that can be listened to and translated into multiple languages. The UNC Kidney Center web site has become progressively active since we launched the site in 2007. There have been over 107,000 unique visitors since the beginning of this year, or an average of 13,400 per month. It is from this pool that we have seen more and more patients willing to travel great distances to see us. I hear your refrain. These are just well-educated and well-to-do patients. True, some

are. Others are of limited means, but whose illness motivates their loved ones to rally support to get them seen regardless of distance or cost.

Academic health systems need to play to their strengths. They must make their facilities and processes of care as modern, streamlined and productive as possible while emphasizing compassionate care. They must reengineer how patients are cared for to maximize provider- patient face time and not provider computer monitor face time.

Despite the tremendous importance of that endeavor, if that is all we do then we will experience increasing difficulty differentiating ourselves in a crowded market where one facility looks very much like the next and the lowest cost drives market share. Academic institutions are populated with individuals who in their very fabric want to innovate, discover, and research. UNC is fertile ground for those striving to make not just basic science or translational discoveries, but innovations in surgical techniques, innovations in processes of care, or innovations in the quality of healthcare delivery. This is our niche. If we do not exploit our niche by recruiting patients who want expert innovative care, we will only sustain the now. Our hospitals and clinics should be easily differentiated from our competitors by injecting and broadcasting in our business model and mission that this institution provides innovations in all aspects of patient care. In word and deed there should be no contest whether Rex or Wake Hospital have similar missions. An academic healthcare system must stimulate a climate where experts in multiple disciplines and venues develop, sustain, and grow a regional, national and international market share. We live in a world economy and our health care system must compete in that world as well. Stated simply, we cannot cater to the patients of the past but to what I believe will be the common phenomenon of the non-expert expert patient who knows what they want and will get what they need.

As part of its strategic plan, the UNC Health Care system has already incorporated innovation as one of its six fundamental pillars. Let us as a community embrace innovation and tear down the barriers that thwart it. Let us promote a conscious and systematic approach to assuring a climate of creativity in all aspects of our environment and our thinking. I hear from the podium the silent scream of appropriate worry from those who have made this great institution so much better than it was in the past. I know. I trained and practiced here when this was only the North Carolina Memorial Hospital, a hospital with open wards and subpar services. I hear your distrust of the words, “climate of creativity” as code speak for the flow of millions of dollars in funding that could spew into the blowing winds without a single new patient in a UNC hospital bed. I hear your frustration that clinical research is occurring under your noses without you even knowing about it—without the pride or profit derived from it, but all of the liability if something goes wrong. The innovation-based business model must be met with the same degree of scrutiny that any new business venture would undergo. Nor should opportunities for innovation be limited to those in pursuit of scientific discovery; rather, every person who participates in the process of patient care should be wrapped within this climate. This is what will enable us to effectively entice the non-expert expert patient to choose UNC as their place of care, as the place that is the most innovative, and the best able to provide them with state-of-the-art and compassionate care. We are so close to achieving that vision, yet we have some bridges to cross.

What would the prescription be to make this vision operational? I propose the creation of a position of a Chief Innovation Officer reporting to our CEO. This position would be responsible for the development of a climate of creativity across the UNC Health Care environment. Their job would be to systematically remove barriers to innovation across our system by forging a process whereby the school of medicine, UNC P&A and UNC hospitals were all participants in the pride and profit of discovery.

Their job would be to harness the mother lode of the rich resources of creative and willing faculty, staff, and administrators across our healthcare system, who often do not know each other and remain hidden in plain sight. Their job would be to create an environment where the basic and clinical sciences could coalesce into translational medicine teams. A college of senior investigators should form to consider perplexing medical cases, probed by those in the community best situated to think about these critical N = 1 opportunities. And each one of us who care for patients should forcibly make ourselves pause amidst the hubbub and ask the question of what we learned from that patient about science and humanity. We have made many inroads in mass communication, but we need to develop a portal for communication with the non-expert expert patient with high quality patient education material. Our experts must make the portals facile for interaction with these patients, and be allowed the time and reward for interacting with them without the assurance that they will ever generate a clinical charge. Stated simply, we must modify our current way of doing business and capitalize on our greatest strengths. We can do this, and we can do it well with the Carolina tradition of collegiality and hospitality. Let's take that next step by making UNC Health Care a place where compassionate care and innovative care are commonplace, and in so doing be the premiere public academic healthcare system in our nation.