

The *O*bservations of a *F*ormer Student
A Half Century of Constancy and Change



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and of Pathology and Laboratory Medicine

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Harold R. Roberts, MD

*H*arold R. Roberts, MD, the 2003 Norma Berryhill Distinguished Lecturer, is one of the world's foremost experts on bleeding and clotting disorders. His research revised the theory of blood clotting, and he has continued to make seminal contributions to the understanding of hemostasis and thrombosis. He also has been an international leader in translating research findings into new and more effective treatments for people with serious diseases of the blood. Here at home, he is known as a superb clinician and an exceptional teacher. Few members of any medical school faculty are as trusted and beloved by patients, as respected by colleagues, and as revered by students, residents, and fellows.

Dr. Roberts is the Sarah Graham Kenan Professor of Medicine and Pathology and Laboratory Medicine. For 20 years he served as director of the UNC Center for Thrombosis and Hemostasis, which he founded in 1978.

Born in Four Oaks, North Carolina, and raised in Sanford, Harold Roberts earned both his undergraduate and medical degrees in Chapel Hill. He served an internship in medicine at Vanderbilt University Hospital. In 1956 he went to the University of Copenhagen as a Fulbright Scholar in experimental pathology and worked with a leading expert in blood coagulation. After returning to this country, he served residencies in medicine at Vanderbilt and UNC, a fellowship in hematology at Vanderbilt, and fellowships in pathology and neurology at UNC.

Dr. Roberts joined the UNC faculty in 1961 as a research associate in pathology. The following year he became an instructor in pathology. Just six years later he was named chief of the Division of Hematology in the Department of Medicine, a position he held for 10 years.

He is a former director of the Clinical Coagulation Laboratory at North Carolina Memorial Hospital (now UNC Hospitals) and former director of UNC's Comprehensive Hemophilia Diagnostic and Treatment Center, which was renamed in his honor in 1999.

As a young scientist, Dr. Roberts worked with Dr. Kenneth Brinkhous and UNC's other legendary giants of blood coagulation research.

"Dr. Roberts came into a field in which the university already had great strength, and he did the most remarkable thing: he made a great program even greater," says Stuart Bondurant, MD, dean emeritus of the School of Medicine. "He built on an ex-

traordinary foundation to lead the program into greater accomplishments, both scientifically and clinically.”

An early focus of Dr. Roberts’ research was blood clotting factor IX. He was the first to show that factor IX mutations resulted in mild and moderate hemophilia, and he was the first to describe an abnormal factor IX molecule, which he named factor IX–Chapel Hill. He also discovered the second abnormal molecule and named it factor IX–Alabama in honor of patients of his who were ardent University of Alabama football fans.

Dr. Roberts discovered these clotting factor defects using biological and molecular genetic techniques. He also was the first to describe the antibody nature of some of the inhibitors to the clotting factor. “After that, we wanted to understand the process of normal hemostasis and what it is that keeps us from bleeding,” Dr. Roberts says. The cell-based clotting assay he designed showed that clotting is initiated by tissue factor on the cells surrounding blood vessels. When a vessel breaks, the neighboring cells express a tissue factor that binds to and activates clotting factor VII in the blood. His work revised the generally accepted clotting theory of the day by showing that the clotting mechanism is localized at the site of bleeding.

“If you looked at the theories of coagulation before Dr. Roberts’ work, you would see that there wasn’t any real mechanism for understanding hemophilia on a theoretical basis,” says Dougald M. “Mac” Monroe III, PhD, research associate professor of medicine. “Regardless of what he is working on, Dr. Roberts has a wonderful ability to see very broadly what is important. He is able to focus in on the core of a question and on how to analyze it.”

In 1965 Dr. Roberts, Dr. Brinkhous, and their colleagues developed the first highly purified dried concentrate of blood clotting factor VIII, the primary therapy for hemophilia. This development enabled patients to treat themselves at home.

In the mid-1970s, a friend of Dr. Roberts in Denmark, Ulla Hedner, isolated a blood clotting enzyme called factor VIIa. The two scientists investigated this factor as a possible treatment for hemophilia patients who did not respond to factor VIII. They found that factor VIIa eliminated, at least partially, the need for factor VIII.

One of Dr. Roberts’ patients was only the second person in the world to receive factor VIIa. Since then Dr. Roberts and his colleagues have become recognized worldwide as experts in using factor VIIa to treat hemophiliacs who develop antibodies to factor VIII. They also have found that it effectively stops bleeding in people who do not have bleeding disorders. For example, it can be used to control excessive or persistent bleeding during surgery.

Dr. Roberts also pioneered the use of factor VIIa in treating acquired bleeding disorders in non-hemophiliacs. He demonstrated that factor VIIa helps seal leaking vessels at the site of bleeding and does not cause any systemic defects. Because of his work on factor VIIa as a potential “universal hemostatic agent,” the University of Lund (Sweden) awarded him an honorary doctor of medicine degree in May 2000.

Dr. Roberts realized that products derived from human blood can carry all of the risks of whole blood, and he was an early advocate of the use of recombinant materials in treating blood disorders. Unlike products derived from human blood, recombinant products are free of transmissible infectious agents such as HIV and hepatitis viruses. “Through his encouragement and his willingness to use recombinant products when they became available, he influenced a generation of physicians in the United States,” says Dr. Monroe. In 1987, as part of a UNC clinical trial in which Dr. Roberts participated, a patient with hemophilia A became the first person to be infused with recombinant factor VIII, a synthetic clotting factor.

Although the majority of Dr. Roberts’ research has focused on bleeding disorders, he also has made significant contributions to the understanding and treatment of thrombosis. He has used and continues to study factor VIIa, an inhibitive derivative of factor VIIa that stops clotting. He also was among the first to use some of the newer and more effective inhibitors to clotting factors, such as low-molecular-weight heparin.

Dr. Roberts has received numerous awards for his achievements in hematology research, including the French International Prize for Research in Hemophilia, the Kenneth Brinkhous Award for Excellence in Clinical Research from the National Hemophilia Foundation, the American Society of Hematology’s Henry M. Stratton Medal, and two awards from the International Society of Thrombosis and Haemostasis, the Distinguished Career Award for Contributions to Hemostasis and the Grant Medal. In 1964 Dr. Roberts became a consultant to the International Committee on Haemostasis and Thrombosis, which worked to eliminate inconsistencies in nomenclature, methods, and standards that stood in the way of research progress. He succeeded Dr. Brinkhous as the committee’s secretary general in 1978. In 1987 Dr. Roberts became the first executive director of the International Society on Thrombosis and Haemostasis, a position he held until 1999. The society, which has members from more than 70 countries, is headquartered in Chapel Hill.

“Dr. Roberts is known within the society as the *grand homme* because of his expertise and his lifetime of service to the international research community,” says Catherine Cole, director of the society’s headquarters. “He is loved for his graciousness and consideration, his unfailingly unbiased treatment of his colleagues, and his wisdom in arbitration. He has always been wholeheartedly supportive of students and other learners, particularly those from less advantaged backgrounds and countries.”

In 2001 the Harold R. Roberts Distinguished Professorship was created in the UNC Center for Thrombosis and Hemostasis under the leadership of Gilbert C. White II, MD, professor of medicine and director of the center. Novo Nordisk, a Danish company that manufactures products used in treating coagulation disorders, was the leading contributor to the professorship endowment. Dr. Roberts’ research has been instrumental in the development of Novo Nordisk products, and he has served on the company’s advisory board for many years.

Last year Dr. Roberts was honored as a Knight of the Order of Christopher Columbus by the president of the Dominican Republic for his help in establishing that country's first thrombosis and hemostasis center.

Dr. Roberts has chaired a number of boards and advisory committees of the National Institutes of Health; the National Heart, Lung and Blood Institute; and the National Hemophilia Foundation. "He is the only person I know who has chaired an NIH study section three times," Dr. White says. "It is an honor to be asked to do it once."

Dr. Roberts is the quintessential physician-scientist, a model of excellence in both research and patient care. "The skills of a successful researcher and the skills of an outstanding physician are so different that it is very difficult to be both, but Dr. Roberts has managed it," Dr. Monroe says. "Despite his great interest in research, he has always put the patient first. He never lets theoretical considerations stand in the way of doing what he thinks is best for his patients." Patients understand that, and they sense that his concern for them is genuine. They not only respect and trust him, they regard him with affection. "His patients are unbelievably loyal to him," Dr. Monroe says. "They don't want to be seen by anybody else."

One such patient was L. B. Hestor of Sanford, who had developed von Willebrand's disease. "L. B. thought the world of Harold," says Mr. Hestor's widow, Virginia. "He has a fantastic relationship with patients." Mrs. Hestor, who took her husband's seat on the UNC Medical Foundation board when he died, has known Dr. Roberts since he was a high school student and she was a teacher. "He was a wonderful student, and he is a great human being," she says. Dr. Roberts still sees patients in the hematology clinic, and he attends on the consult service.

His skills as a physician and an investigator are matched by his talent and enthusiasm as a teacher. "I find a lot of satisfaction in teaching," he says. "I have never viewed myself as being any more than a student of medicine, because things change so much that we are always students. So, when I look at the fellows, residents, and medical students, I identify with them at their level. I try to teach them what I know, and I am always receptive to their ideas, as well. Ken Brinkhous, Carl Gottschalk, Bill Blythe, Gil White, Don Gabriel, and others taught me what I suppose I unconsciously knew, that we are all students after a fashion."

Dr. Roberts enjoys interacting with medical students because they are eager to learn and ask questions that sometimes suggest new ways of looking at a problem. "They have fresh minds that haven't been contaminated with the thinking of the day," he says. "That's the nice thing about being at a university; it keeps your mind sharp."

Dr. Roberts received the medical school's Basic Science Teaching Award in 1965, and in 2000 he was presented the Medical Alumni Distinguished Faculty Award. "Every fellow who has been here remembers Dr. Roberts as someone who took a personal interest in them, helped them when they had problems, and got them thinking on a higher level about their patients," Dr. Monroe says.

Dr. White agrees that his former teacher is universally admired by those he has

taught and trained. “He is very loyal to the people who go through this program, and he tries to help them in their careers after they leave. People also respect him because he seems to fight for the right things. He has great insight into issues and has the ability to boil things down to their essence and get to the heart of the matter.”

Dr. White has previously been quoted as saying of Dr. Roberts: “We do what we do because of his remarkably clear and incisive second-year lectures, because of his encyclopedic clinical knowledge, because of his human touch with patients, because he cared for us as individuals and professionals and, maybe most of all, because of his passion, his belief in the academic process, his dedication to the highest possible standards of patient care, and his commitment to research.” Dr. Bondurant credits Dr. Roberts with “inspiring scores of people who are now making great contributions as leading researchers and clinicians in their own right.”

In his quiet and unassuming way, Dr. Roberts also has had considerable influence on administrative and policy issues within the School of Medicine. “He is a very thoughtful person whose expressions are well reasoned and, because of that, he is consistently worth listening to,” Dr. Bondurant says.

As one of the medical school’s most distinguished and accomplished faculty members, Dr. Roberts has had many opportunities to go to other institutions, but he has always felt that Chapel Hill is where he belongs. “I enjoyed my days at Vanderbilt, and Copenhagen is one of my favorite cities. But when I first came to Chapel Hill as an undergraduate, I felt liberated all of a sudden. Ever since that time, the town, the academic environment, and the free thinking on this campus have appealed to me. I also find that, especially here in the medical school, there is a lot of camaraderie among people. There is peer pressure and competition, of course, but it is good and constructive.”

Jeffrey Houpt, MD, dean of the School of Medicine, says that in recruiting department chairs and center directors, he looks for people who not only have impeccable credentials, but who also embody the values and traditions that Dr. Roberts has honored and nurtured. “People like him, who have been part of this school for so much of its history, have really defined this place,” Dean Houpt says. “He has the highest standards and exemplifies the best when it comes to scholarship. And his legacy is not only his own work, but the accomplishments of his protégés who have gone on to exceptional careers.”

September 28, 2003

The Observations of a Former Student

A Half Century of Constancy and Change

Dean Houpt, colleagues, family, friends, ladies and gentlemen: I am deeply honored to be chosen to deliver this lecture named for the great lady of the School of Medicine, Norma Berryhill. I came to know her when I entered medical school in 1951. Dean Berryhill was one of the first people I met as a freshman medical student. He was clearly a man in charge. He had overseen the expansion of the medical school from two years to four and had recruited an outstanding faculty. These accomplishments were a testament to his ability and vision.

Dr. Berryhill's accomplishments were not all due to him because, even as students, we were all well aware of the great influence that Mrs. Berryhill had not only on the dean, but also on the development of the medical school and its faculty. Her graciousness became evident soon after school convened, and we students were all charmed by her personality and her obvious interest in our welfare. It became evident to all of us who knew Dr. and Mrs. Berryhill that the unique character and ambience of the School of Medicine was created by them and continues to exist as part of their legacy.

There is a special feeling at Carolina as so eloquently described in a previous lecture by Chancellor Fordham as the "Magic of Carolina." Those of us on the faculty, new and old alike, owe Norma Berryhill our gratitude for creating the atmosphere so characteristic of Carolina.

I have chosen as the title of this lecture "A Half Century of Constancy and Change." I can claim a half century because I started undergraduate school here in 1948 after turning down a scholarship at Duke. Thus, my aim today is simple—namely, to reminisce about my experiences here over the last half century or so and to reflect on those things I deem to be more or less constant and those things that I think represent the most dramatic changes during that period. I hope to end by using some examples of my field of research to illustrate the most remarkable change of all in the last half century, and that is the progress made in medical research.

The Faculty

One of the most constant characteristics of the school has been the caliber of the faculty, both research and clinical. I could give you many illustrative examples, but simply put, our faculty ranks with the best of any medical school in the country. I will give you an example of the high caliber of our faculty. I am obliged to highlight Dr. Kenneth Brinkhous, who arrived here in 1946. With unbridled enthusiasm he rapidly established one of the most prominent groups of coagulationists in the country—and, for that matter, the world. I will document some of Dr. Brinkhous' discoveries later, but suffice it to say at this time that his accomplishments in biomedical investigation were sufficient to warrant his nomination for the Nobel Prize. I was told this by Professor Inge Marie Nilsson, a consultant to the Nobel Committee of the Karolinska Institute. While he did not win the prize, his accomplishments were certainly in that league. So are the accomplishments of others, such as Jud van Wyk, Carl Gottschalk, and Oliver Smithies.

The excellence of the faculty has continued to present day, but I can't mention the names of current stars because there are so many of them. However, I am sure that my point is made—and that is, the quality of faculty at UNC has been constant over the last 50 years.

House Staff

The greatness of any school is measured not only by the quality of the faculty but also by the caliber of the house staff and student body. During my tenure here, I have been impressed by the consistently high quality of the house staff. I have a special feeling for one particular house staff member who once saved me from bodily injury by preventing a patient from literally stabbing me in the back with a fork he acquired from his lunch tray. I don't wish to leave the impression that I am the type of physician whom patients like to stab, but this particular patient was well-known to me. I knew that he had been in and out of jail for numerous minor offenses. When I chastised him for not taking his medicine, he became angry. When I turned to leave the room he aimed a fork at my left lung, but my house staff colleague caught his arm and said, "No one stabs Dr. Roberts in the back while I am around." He told me later that it simply would not look good for a coagulationist to bleed to death at UNC. My appreciation for the house staff knew no bounds that day. He not only saved me from having a hemothorax, but he was an excellent hematology fellow and is currently a successful hematologist in Raleigh. The patient, by the way, continued under my care for the next 20 years but recently died owing to infectious complications. I always liked this patient, but I was careful not to visit him during mealtime, when dangerous utensils lay around.

Students

With respect to our students, the comments of two of my former teachers come to mind. One was made by Dr. Brinkhous, who once told me, "I learn more from students than I do from the faculty." The other was made by Dr. Carl Gottschalk, who, when attending on the ward, walked into a patient's room with a group of students. The patient asked if he could be seen without students, to which Dr. Gottschalk replied, "We are all students after a fashion." These statements characterize the relationship between faculty and students at UNC.

I must admit, however, that sometimes during the late 1960s and early 1970s, during the time of changing curricula and changing social mores, I was afraid that the caliber of the student body might deteriorate, fears that never materialized. I have recently had the opportunity of serving as a faculty member to interview potential medical students. It is very pleasing to me that despite all the difficulties currently facing the medical profession and all the changing social mores, candidates for admission to the school are still the cream of the crop, not just intellectually, but also in terms of their personal and professional attributes and their sense of social responsibility.

I was in a class of about 65 students, of which only one was a woman. Sometime in the 1970s or 1980s, it dawned on me that there were a lot of women around me. The change was so subtle, or I was so unobservant, that I was not fully conscious of the number of women in medicine. I can only imagine that at the time I was blind to gender, having been liberated in the 1950s by my wife. However, the presence of the female gender was dramatically brought home to me one day while making rounds on the consultation service. At the end of rounds one day, one of the students called attention to the fact that all five members of the consultation team were women. One of them asked, "How does it feel to be in the minority?" Wrong question, because it felt very good indeed. All five were excellent students, but what impressed me even more about them was that they invited me to lunch and insisted on paying for it. Obviously one of the changes over the past 50 years has been the emergence of women doctors in all disciplines of medicine.

My class was unique for another reason. The first African American student to be admitted to the four-year school was in my class of 1951. This was before the Supreme Court decision of 1954. Since then the admission committees have seen to it that the rights of minorities are recognized. The recognition of women and minorities, although long overdue, has been one of the better changes in our profession.

As a faculty member, I have come to cherish my association with students. I was an assistant professor at the time Chris Fordham was chancellor, and one day I received a telephone call from him. Assistant professors are not used to being called by chancellors. It causes a bit of nervousness, to say the least, given the chancellor's power over tenure and that sort of thing. But to my relief, his request was interesting and illustrates our role in student teaching. Chancellor Fordham informed me that he had

identified 10 highly qualified, exceptional sophomore undergraduates, all of whom had an interest in medicine. He asked me if I could arrange a special undergraduate seminar for them, a seminar designed to introduce these students to the possibilities and excitement of academic medicine. I agreed to do this, and Dr. Robert Goyer agreed to help me. We came up with the idea to create for these students the facts that faced Linus Pauling, who described the molecular defect in sickle cell disease, and the facts facing Fleming, Chain, and Florey before they won the Nobel Prize for the discovery of penicillin. We fed the students the initial observations of these scientists before they had solved their respective problems, and then challenged these students to interpret the findings. As the students interpreted the results, we required them to design further experiments and so on throughout the semester. To our pleasant surprise, the thought processes of these students came very close to those of Pauling, Fleming, Chain, and Florey. Although the students had some coaching, all did well in the seminar, and eight of them ended up in academic medicine in institutions all over the country. To be allowed to be a part of this experience I count as one of the greatest pleasures I have had with a group of students. Sadly, two of them had fatal drowning accidents the following summer, both from accidents that occurred while scuba diving in separate places.

Growth

One of the most visible changes over the years has been the growth of the school, not just in physical structures but also in the staff. Obviously, growth is most certainly preferable to stagnation and is inevitable, but it does have drawbacks. If we are not careful, communications between the faculty as well as between the faculty and students can be decreased, to our mutual detriment. Perhaps I am overly concerned about rapid growth in this era of rapid and easy electronic communication, but I find it more satisfying and certainly more pleasant to have personal contact with my colleagues. Growth also has the potential of decreasing the feeling of community within an institution, such that there is a danger of doing things for selfish reasons without regard for the welfare of the school as a whole. This is a danger we all must be aware of, and it is easier to be aware of it when groups are smaller. Nevertheless, the Carolina tradition holds that our actions be so structured that they serve the good of the institution rather than purely personal aims.

Research Funding

One of the most dramatic changes during my some 50 years at UNC has been the increasing competition for funding of research from NIH [the National Institutes of Health] and other sources. The increasing competition for research funds may be

due to our own success, in that we have trained so many qualified MD and PhD investigators that we cannot afford to take advantage of all the available research opportunities.

Fortunately, the University of North Carolina has competed very successfully for research funding. Last year the school was number 13 in the nation for research funding, and the Department of Medicine was ranked 13th out of 127 departments. When adjusted for the number of faculty, the Department of Medicine actually ranks 4th out of 127 departments across the country. My message to the new faculty is, don't be discouraged by dire forecasts of federal funding. If I can stay funded for 43 years, so can you. I urge all of you to follow the example of Ken Brinkhous, who holds the record for having the longest continuously funded NIH grant in U.S. history. He held the same individual research grant from 1946 until his death in 2000—54 years of continuous funding, a record unlikely to be equaled.

The Legal Crisis

One of the most dramatic changes that have occurred in recent years has been the legal crisis resulting from increasing litigation for malpractice and the enormous awards that are being handed out by juries. My fear is that the ever-increasing threat of huge awards and frivolous lawsuits may one day reduce both the number of doctors and the quality of medical care. I can't help but recall the old Jewish proverb that says, "Don't live in a town without doctors." When President Clinton stated that the medical profession was broken, I thought that he had confused our profession with the legal profession. I am quite sure of the public need for superb judges and lawyers. Their public responsibility equals ours. But my sympathy for malpractice lawyers has virtually evaporated over the years, and I hope not because I am a physician but because I genuinely do not think that the public interest is well served by opposition to tort reform by malpractice attorneys. It is inherently unjust when a physician must defend himself or herself against frivolous lawsuits without recourse to compensation from the other side. To those of you who may be going through the terrible ordeal of being sued, the immortal words of Winston Churchill come to mind: "If you are going through hell, don't stop." Of the malpractice cases referred to me over the last five years, most have been either frivolous or of doubtful significance. That is not to say that there are not legitimate complaints of negligence, but all too often there is failure to distinguish between true malpractice and unavoidable adverse reactions. The public may not be aware that the constant threat of huge liability expenses may unfortunately result in the delay of future progress and a decrease in the caliber of current medical care.

The Great Bureaucracy

I must also mention another change affecting our profession, and that is the burdensome bureaucracy now facing us. I need only point out the obsessive documentation requirements of Medicare and other insurance carriers as well as the time-consuming bureaucracy concerning research on animals. Some of these requirements are insulting to anyone who can read and write, yet we have capitulated to some of these demands in the interest of financial compensation. Excessive bureaucracy has several drawbacks. In our case, the time taken to satisfy excessive bureaucratic requirements is essentially nonproductive and is time taken away from teaching, research, and patient care. So, in the end, the public suffers as much as the medical profession. Medical leaders and the rest of the profession need to unite and insist on simplification of an unnecessarily burdensome bureaucracy.

Progress Continues

Despite some onerous requirements imposed on physicians, I should make it clear to all of you that the greatest change in medicine is the astonishing progress made in both basic research and translation of that research into better clinical care. The evidence for this can be found in our own school. Witness the tremendous success of the centers for cancer, cystic fibrosis, vascular biology, and all the other programs of excellence at this institution.

Medical progress and discoveries over the last 50 years have been staggering. Just as an illustration of this, permit me to point out some of the ramifications resulting from studies of blood coagulation. This is the only subject I feel I can use to illustrate my point, since this has been my area of research during my tenure at UNC. Studies on the blood clotting mechanism at UNC were initiated by Ken Brinkhous in 1946. He was a mentor to a whole host of UNC faculty members, including myself, who have continued the investigations he began. As an introduction, I need to point out that the blood clotting system is so designed that circulating blood remains fluid; but when a leak occurs in a blood vessel, that leak can be plugged by a fibrin clot precisely when it is needed. However, when the blood clotting system is disturbed, it can result in bleeding, on the one hand, or excessive clotting, on the other. The latter can result in heart attacks and strokes, which are the leading causes of death in the Western world. There are 14 soluble clotting factors circulating in the fluid part of blood (see Figure 4.1). Those shown in yellow are of particular interest to me because the UNC group has either characterized or discovered these factors. There are also very small cells, called platelets, the surface of which serves as a platform on which the clotting factors interact to ultimately form a fibrin clot. To illustrate recent progress over the years, I would like to highlight only a few of the many discoveries made by the coagulation group at UNC that have led to advances in our understanding of the normal blood clotting sys-

tem and how these discoveries have led to better diagnosis and treatment of bleeding and clotting disorders.

When Brinkhous arrived here in 1946, he had already discovered one of the 14 clotting factors which he named antihemophilic factor, now known by its Roman numeral as factor VIII. When factor VIII is missing, classic hemophilia develops and frequent bleeding, especially into joints, takes place, resulting in crippling joint disease. Shortly after coming here, Brinkhous was contacted by a veterinarian in New York who noticed that some of his male Irish setter dogs had a severe bleeding disorder very similar to human hemophilia. Dr. William Blythe was working

here at the time, and he accompanied Dr. Brinkhous to New York to bring the female carrier dogs back to Chapel Hill with the aim of setting up an animal model of hemophilia. The story goes that Bill was dispatched by Brinkhous to catch one of the carrier dogs, who had escaped into a pasture, so Bill had to scale a fence, which was lined with barbed wire, to catch one of the first female carriers of hemophilia. From this carrier the first animal colony of classic hemophilia was established. The colony is now housed at the Francis Owen Blood Research Laboratory at University Lake. There are several other animal colonies at the Francis Owen facility, including dogs with hemophilia B due to a deficiency of blood clotting factor IX, dogs with factor VII deficiency, and swine with von Willebrand disease. These animals are housed in comfortable quarters, they are well fed, and they receive regular treatment for their disorders. This collection of animal models has been recognized by the National Heart, Lung and Blood Institute as a national resource and is available to investigators across the country. They have been used to test and characterize new clotting factor concentrates and to study the physiology of coagulation in general. More recently they have served as animal models for gene therapy of hereditary bleeding disorders.

The creation of a pig colony of von Willebrand disease has been of enormous benefit in our understanding of heart attacks. These animals are deficient in a blood clotting factor called von Willebrand factor, a large, sticky protein that is necessary for blood platelets to stick to blood vessels and plug small leaks in the blood vessels that happen with the minor trauma of everyday living. Humans have a similar disease, and persons lacking this factor tend to have a mild bleeding tendency involving mucous membranes and the gastrointestinal tract. Drs. Thomas Griggs, Marjorie Read, and Tim Nichols showed that the lack of von Willebrand factor in these pigs protected the animals from having heart attacks. An artery from a pig that has not eaten a fatty diet is shown on your right (see Figure 4.2). The artery of a pig on a fatty diet is shown on your left. The pig on your left can rupture the atherosclerotic plaque and have a heart

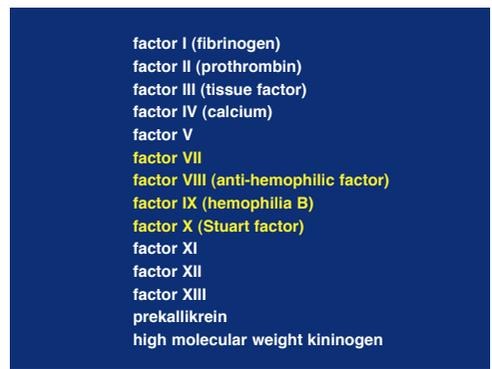


Figure 4.1. Soluble clotting factors circulating in the fluid part of the blood

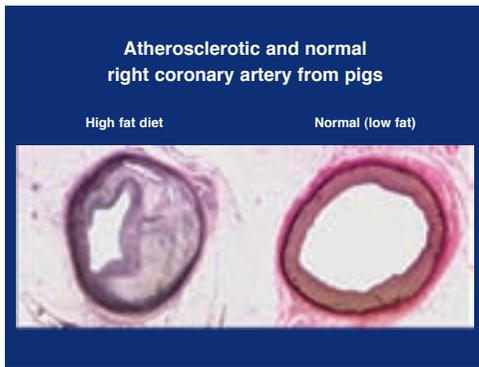


Figure 4.2. Atherosclerotic and normal coronary arteries from pigs

attack, but if that same pig lacked the von Willebrand factor he would still have atherosclerosis but would be protected from a heart attack. The potential of these findings is obvious. Since the greatest cause of death in the United States is from heart attacks, perhaps all of us should be treated with inhibitors of von Willebrand factor when we have chest pain. Studies designed to test this hypothesis are being planned.

One of the major accomplishments of the coagulation group at Chapel Hill was the first preparation of a plasma-derived factor VIII concentrate to treat patients with hemophilia. In the 1940s hemophilic patients had a life span of about 18 to 20 years and there was nothing available for treatment. From studies on

the hemophilic dogs, it was found that the lack of factor VIII could be partially replaced by infusions of normal plasma. When I came back to Chapel Hill in 1960, patients with hemophilia who were lacking factor VIII could only be treated with normal plasma that contained factor VIII. However, using plasma alone, one could not raise the factor VIII level higher than 10–20 percent of normal. This was not enough to stop all bleeds but was enough to stop many minor and some moderate bleeding episodes. Unfortunately, however, one had to use so much plasma that the patient sometimes went into heart failure. Thus our group sought to produce concentrated forms of factor VIII. This work was carried out by Dr. Robert Wagner. Wagner developed a simple method for the purification of canine factor VIII from plasma by precipitating it with glycine, a simple common amino acid. This resulted in a 200-fold purification of factor VIII. When purified, the factor could be concentrated in a very small volume; and when infused into hemophilic dogs, the factor VIII levels could be raised from zero to 100 percent of normal. This was the first time in history that 100 percent levels of factor VIII could be achieved in hemophilic dogs without risking heart failure from infusion of large amounts of plasma. Dr. Wagner's method for purifying factor VIII from dog plasma was applied to human plasma by Dr. Phil Webster and myself in 1965. We performed most of this work on the third floor of the hospital in a little room on 3 East in the vicinity of what is now the Nurses Station. When we gave the first human factor VIII concentrate to a hemophilic patient, the subject's factor VIII plasma level was raised to normal levels. This was the first time in the long history of human hemophilia that this was possible. The purification method was acquired by Baxter Laboratories, and this company made the first commercially available factor VIII concentrate so that hemophiliacs all over the world could be treated and their hemophilic condition controlled. This was the boost needed for the establishment of a burgeoning commercial plasma fractionation industry, which led to the creation of plasma collection centers all over the country and the building of factories for production of clotting fac-

tor derivatives from plasma. This industry still thrives today and has created literally thousands of new jobs and careers. Plasma-derived blood clotting concentrates became contaminated in the early 1980s, but they are now safe, and hemophilic patients can now be treated prophylactically. They now have a virtually normal life span, a dramatic improvement over the last 50 years.

Another accomplishment of the group was the first demonstration of a molecular defect in factor IX, a deficiency of which results in hemophilia B, a bleeding disorder clinically identical to classic hemophilia. Dr. Mac Monroe and I showed that the genetic mutation causing one form of hemophilia B resulted in the substitution in the factor IX molecule of a normal arginine residue by a histidine at position 145. This mutation results in a dysfunctional molecule, that is, a molecule that doesn't work. We named this form of factor IX, "factor IX–Chapel Hill." The second abnormal factor IX molecule was also described at UNC and was called "factor IX–Alabama" because the patients who had this form of hemophilia were referred to us from Alabama. Actually, the patients were Alabama football fanatics and really preferred that we call it factor IX–Crimson Tide, but traditional nomenclature required that we name the factor after the place of discovery. These types of discoveries led to many others, such that now we know that there are over 400 distinct genetic mutations that lead to hemophilia B.

Perhaps one of the most important contributions of the Chapel Hill group to our knowledge of blood coagulation was the discovery in 1953 of the partial thromboplastin time, a simple test of clotting function, by Drs. Brinkhous, Wagner, and Langdell. The partial thromboplastin time is now used millions of times a day all over the world for the diagnosis and treatment of bleeding and clotting disorders, and it forms the basis of assays of specific clotting factors. This test, too, has created an industry of several international companies that make instruments that measure the test.

Another major development in the coagulation field was the discovery of blood clotting factor X, which was initially called the Stuart factor. This clotting factor turned out to be the central enzyme in the clotting pathway. The discovery was published in 1957 by Cecil Hougie, Emily Barrow, and the inimitable John Graham. Mr. Stuart lacked factor X and had a severe bleeding tendency. He was a willing donor and was proud to have his plasma shipped all over the world. He frequently appeared before our medical school classes and loved to tell the students about his symptoms. I doubt that we could use the name of a patient today to describe a syndrome, given the recent federal regulations governing patient privacy, but Mr. Stuart, who passed away many years ago, was adamant that his name be used for the factor. Mr. Stuart lived to a ripe old age and died of cancer, not of bleeding.

Let me tell you about another major accomplishment by our staff. You are all aware of the acquired immune deficiency syndrome, better known as AIDS. Initially the cause of AIDS was completely unknown, though some suspected that the causative agent was a virus. I doubt that many of you know that the first isolation of the AIDS virus was from one of our hemophilic patients. My colleague Dr. Gilbert White was

responsible for the discovery. He sent an enlarged lymph node from one of our multi-transfused hemophilic patients to Dr. Robert Gallo in 1983. From this lymph node Dr. Gallo and his team were able to isolate a virus that they called HTLV-III, now known as HIV. Drs. Gallo, White, and others published their findings in *Science* in 1984.¹ I am humbled by reminding myself of this discovery. One day in the hemophilia clinic, Dr. White came to me and said, "This patient with severe hemophilia has received a lot of plasma-derived factor VIII and has recently not been feeling well. He has very large lymph nodes, and the biopsy doesn't show anything but benign changes. Do you think that he might be developing AIDS from a virus that could have contaminated the plasma which was used for the purification of factor VIII, and do you think we should send this node to Dr. Gallo just to see if he can find anything?" My answer was classic. I remember saying to Gil White, "You can send it, but I very much doubt that you will find anything." It just goes to show you that you only find what you look for, and I was pleased that Dr. White pursued his beliefs even in face of my serious doubts. As indicated earlier, the blood supply became contaminated with the AIDS virus as early as 1978, and since the blood clotting factor concentrates were made from lots of plasma donated by 10,000 to 20,000 donors, some lots of these concentrates were able to infect some of our hemophilic patients. Although plasma is now considered to be safe due to testing for all sorts of viruses and is subjected to techniques that eradicate viruses, many of us now prefer to use genetically engineered factor concentrates, which I will discuss next.

Our group was the first to conduct human trials of a genetically engineered recombinant factor VIII for the treatment of hemophilia. This was the first time that a blood clotting factor was made by genetic engineering and was not purified from plasma. The trial was performed here in 1987. The study was led by Drs. White and McMillan. All patients who received the genetically engineered product did very well, and their hemophilic condition could be ameliorated. The advent of genetically engineered clotting factor preparations has obviated the danger of transmission of diseases that might be transmitted by human blood products. We know that even given the current tests for safety of blood derived products, there is always the danger that some viruses not eradicated by current techniques might one day contaminate the blood supply. That is why we have favored the use of genetically engineered products that are manufactured in highly controlled conditions and are not subject to potential contamination from products derived from pools of human blood often collected from as many as 10,000 to 20,000 donors.

More recently we have introduced a new clotting factor, recombinant activated factor VIIa, for the treatment of excessive hemorrhage not only in hemophiliacs, but in otherwise normal people undergoing surgery or trauma. Let me give you an example. A soldier was shot in the abdomen and bled extensively before arriving at a hospital. During operations he bled profusely from the operative site and required at least 20 liters of blood. His clotting factors and platelet count became low, but even though all

known clotting factors and platelets were replaced, he continued to bleed. His surgeons were desperate, and the soldier was in imminent danger of dying on the operating table. Infusion of a small amount of recombinant activated factor VII (VIIa) resulted in dramatic cessation of bleeding. We were the first in the United States to use factor VIIa in 1991. Factor VIIa is now being used to treat uncontrollable hemorrhage in such diverse conditions as bleeding from the lungs, bleeding following cardiac surgery, and bleeding from massive trauma, as well as bleeding due to hemophilia unresponsive to conventional therapy. Just recently Drs. Don Gabriel and David Henke had a patient bleeding profusely from the lungs, such that there was a danger of the patient drowning in his own blood. He was unresponsive to the usual treatment, but following the administration of relatively small amounts of factor VIIa, cessation of bleeding occurred within a short time, much to the relief of the doctors and patient alike.

The first trials of gene therapy for hemophilia A and B were also carried out by the UNC group. The initial trials of gene therapy for hemophilia were carried out on the dogs with hemophilia, and later gene therapy trials were carried out on human volunteers from our patients in the hemophilia clinic. These studies were done in hemophilic dogs by Drs. Read and Nichols and in humans by Dr. White. Although gene therapy for use in genetic diseases is not perfected, the preliminary results are still promising. We gave the gene for factor IX to a patient with hemophilia B in an effort to cure the genetic defect. Given my interest in factor IX and hemophilia B, Dr. White allowed me to infuse the gene in a patient and saved the syringe (after cleaning) for historical purposes. The patient did express factor IX, but not permanently. However, efforts to improve gene therapy are ongoing, particularly in our gene therapy center.

A more recent advance has been a revision of our concept of how the clotting system works. The older concept is extremely complicated. Our studies indicate that the system is much simpler. Basically, coagulation takes place on cells and not in test tubes, which is no surprise. The work leading to this new concept has been carried out by Drs. Monroe and Hoffman and myself and is now published in standard texts of hematology and the recently revised edition of the *Oxford Textbook of Medicine*.

A more recent discovery is that of Darrel Stafford, a molecular biologist who joined the coagulation group a few years ago. He has recently worked out the pathway of vitamin K metabolism. As you know, K stands for coagulation, which in Danish is spelled with a K. His contribution has for the first time explained the defect in the congenital deficiencies of all the vitamin K-dependent clotting factors. Dr. Stafford has isolated and cloned both the vitamin K carboxylase and, just a month ago, the vitamin K reductase, singular and very important accomplishments.

These are just examples of the discoveries resulting from studies on the blood clotting mechanism and esoteric clinical disorders like hemophilia. Hemophilia may be a rare disease, but as the basis of the study of blood coagulation and its relationship to common diseases like heart disease, it has been invaluable. Just think of all the other original discoveries made at this institution by other investigators, particularly from

the various Centers of Excellence but also from individual investigators. When one looks at the advances in medicine made by other investigators in the country and the world, it's very obvious that the profession of medicine has made staggering continuous progress in diagnosis and treatment of all sorts of diseases. More advances can be made, but only if the resources are made available.

When I began this lecture I noted that I first came to this institution in 1948 and departed in 1955 to do house staff and hematology training at Vanderbilt University in Nashville, Tennessee. After that I had the opportunity to study blood coagulation and vascular biology at the Carlsberg Institute in Denmark, initially under the direction of Dr. Tage Astrup in 1956 and later at the University of Aarhus with Dr. Staffan Magnusson. It was in the library of the Carlsberg Institute that I met my wife, who was also working there even before I arrived. She was trying to isolate tissue plasminogen activator, TPA, which for the lay members in the audience is what is given in the emergency room to the patient at the first sign of a heart attack to dissolve a blood clot in the coronary artery. During our stay at the Carlsberg Institute I remember my wife spending hours carefully stripping endothelial cells from the linings of blood vessels from cows. She took these endothelial cells, extracted them with potassium thiocyanate, and showed that they contained a tissue plasminogen activator that was extremely potent in dissolving blood clots. So my wife was one of the first people to show that tissue plasminogen activator was present in endothelial cells. She published this work in an article in *Science* with Dr. Tage Astrup. I have often wondered if it would have been better for my wife to continue in biomedical science rather than myself, but I have never asked her that question because I was afraid of what her answer might be. Perhaps I should have stayed home and taken care of the children. When our sons came along in the 1950s it was not easy to find daycare that would allow both of the parents to continue their work. Nevertheless, my wife and I have been partners in both careers for a long time, which I hope will continue for years to come.

Finally, let me thank my colleagues with whom I have worked for many years, especially Drs. Gilbert White, Don Gabriel, and Gene Orringer, who were all fellows of mine. I have enjoyed my long association with my friend and colleague Dr. Mac Monroe, who has worked with me on the biochemistry of blood coagulation for a very long time, and my current and past colleagues Drs. Rodger Lundblad, Darrel Stafford, Frank Church, Alice Ma, Herbert Whinna, Stephan Moll, and David Clemmons, who have been extremely supportive of my work and who have shared with me their equipment, knowledge, and know-how. And last but not least, I would like to thank my family members, who are here today.

I love the University of North Carolina. Most of my adult life has been spent in the halls of this place. While there have been emotional lows and highs in my career, the lows have helped me grow wiser, and the highs have been my reward, and I regret nei-

ther. I just wish that whatever wisdom I have acquired over the years could have come from fewer “lows,” but that is life.

Let me end these musings by expressing my gratitude to Norma Berryhill for all her good influence on the School of Medicine and for her legacy of a tradition that has made the UNC School of Medicine such an attractive place to work.

Thank you all for coming.

Note

1. See Gallo RC, Salahuddin SZ, Popovic M, Shearer GM, Kaplan M, Haynes BF, Palker TJ, Redfield R, Oleske J, Safai B, White II GC, Foster P, Markham PD. Frequent detection and isolation of cytopathic retroviruses (HTLV-III) from patients with AIDS and at risk for AIDS. *Science*. 1984;224:500–503.

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