

BUDGETMarch 29, 1999

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Angie**Prologue**

The bodily process which controls hemorrhage following trauma to blood vessels is called the "hemostatic mechanism." A clot or plug forms in an injured blood vessel after an appropriate interaction of multiple plasma proteins and a blood cell called the platelet. Disorders of "the hemostatic mechanism" are diagnosed fairly commonly in clinical medicine. Some disorders may lead to life threatening hemorrhage if untreated, and others cause less frequent harm or perhaps no harm at all. The commonest hemostatic disorder that members of this audience will recognize is hemophilia, described as early as the second century in the Talmud in males following circumcision. The bulk of this discussion, however, will be about a familial disorder of a coagulation protein which seldom - if ever - causes a hemorrhagic problem when it is deficient, but looks to the unwary like a defect of major importance. An epidemiological and sociological study of a colorful family of hill folk portraying this disorder is the subject of this paper.

Chapter 1

In 1953 and in 1954 three patients with unusual laboratory findings suggesting a major disorder in hemostasis were studied in the laboratories of Dr. Oscar Ratnoff at the Case Western University School of Medicine. The first of these patients studies was John Hageman. The coagulation defect in Mr. Hageman was detected in a blood sample taken prior to anticipated surgery. His blood did not clot in a glass test tube in a normal period of time. Because of a severe peptic ulcer syndrome and because the laboratory abnormality suggested hemophilia, he was operated on in 1954 using three and a half liters of fresh whole blood infusions during and after the procedure. No excessive bleeding ensued and healing following the procedure was uneventful. Mr. Hageman, a freight brakeman, fell from a ladder of a boxcar on March 11, 1968, and fractured his pelvis. He was treated symptomatically and in a few days was allowed to walk on crutches. No blood transfusions were given. On the twelfth hospital day he was found gasping for breath, and despite resuscitative measures he died in a matter of minutes. An autopsy revealed multiple blood clots in both arteries leading into the lungs, the antithesis of what one would expect from the test tube observations. Subsequently, the substance deficient in Mr. Hageman's blood but present in most of the rest of us has been identified as a plasma protein which participates in a number of the body's defenses. It was named "Hageman factor" in honor of Mr. Hageman. The fact that a deficiency of Hageman factor does not lead to bleeding suggests that there is more than one way that the body triggers the formation of clots following injury to blood vessel walls. This hypothesis has been proven subsequently.

Chapter 2

The time now is the spring of 1972. I answered the phone early one evening and heard the voice at the other end say, "Hi! It's Warren Webster. I'm in the Air Force now, a Captain. I'm stationed at the Kincheloe Air Force Base in Michigan and just completed a pre-op exam on a young woman who is scheduled to have

a thyroid nodule removed. It could be malignant. Her partial thromboplastin time (a newly devised test which measures the clottability of plasma) is extremely prolonged. I had the test repeated - it's still prolonged." Webster, a graduate of our College of Medicine and of our medical residency program is an excellent physician and completely reliable. I strongly recommended that the surgery be delayed until the clotting problem was evaluated further. Warren pointed out that the surgeon was a Major and he was only a Captain. I said, "Tell him that you just talked to a hematologist at the College of Medicine in Cincinnati and he strongly recommends that we study the blood before the anticipated surgery. Call me back after you've talked to the Major." A few minutes later Warren called to say that he had talked to the Major and that surgery had been postponed. I thought that this woman whose name was Angie McCollum likely had Hageman factor deficiency. She had never had a bleeding episode in her life. I asked Warren to send me a sample of blood which he promised to do as soon as possible. He noted that there were daily trips of Air Force delivery planes to Lunken Airport and he could easily enclose a sample in dry ice and have the sample in our hands by the following day. Having made these arrangements, Warren called me the following day to tell me that the Services do not allow "private laboratories" to process such samples (even though the processing was to be free) until "all the resources of the Armed Forces had been explored and no laboratory was available to perform the requested tests." Another delay of two or three days and another phone call. "We're not allowed to send the sample on the Air Force plane, but we will send it by Federal Express and it should be in your hands tomorrow morning." The plasma sample arrived frozen solid in a FedEx package, costing the government a pretty penny. We studied Angie's blood. She had Hageman factor deficiency, and with complete confidence I informed Dr. Webster that surgery could proceed. She would not bleed. A few days later we learned that the surgery had been done successfully. The patient did not have cancer, and she did not bleed at the time of surgery. Some time later I received a beautiful handwritten note from Angie, thanking us for our service and questioning whether she could do anything for us. With very little hesitation I called

Angie to thank her for her note and also asked about her family's background. She said she was from a large clan in Southeastern Kentucky. I inquired whether we could get the clan together and study their blood since she had such a rare clotting disorder. She said, "Give me enough time and we can get people together." I had learned in this conversation that her family, including her husband's family, lived in or near a small town in Kentucky called Salyersville, a town in the mining district of Kentucky near the headwaters of the Licking River.

Chapter 3

During the same month that we were identifying the Hageman factor deficiency in Angie McCollum, I had on my staff a senior medical student, Ernie Arnett, one of the most gifted students with whom I've ever worked. I decided to give him the project of setting up a field trip to Salyersville where we could draw blood samples on Angie's family members, in order to study the natural inheritance of Hageman factor deficiency. This had never been done in such a large kindred. I put the information on Ernie's desk and went off to do hospital rounds. When I came back, I saw Ernie at the desk with a huge smile on his face. He informed me that his family was from Salyersville and that a doctor in the neighborhood, Dr. Lloyd Hall, would be happy to introduce us to Angie's family and play the important role of telling the family that we were really good guys trying to help Angie and them. The family members were duly notified, and some time in May of 1972 on an absolutely beautiful Saturday morning we drove to Salyersville. Ernie Arnett and his wife Donna drove in one car. My wife and I were in my Ford station wagon along with Dr. Helen Glueck and our head technician Mary Ann Miller. In each vehicle we had stowed the necessary equipment including needles, syringes, a small centrifuge, test tubes, test tube racks, labels, alcohol sponges, arm tourniquets, history sheets, permits, soft drinks and lunch. The trip to Salyersville took a couple of hours - I-75 to Lexington, and then east on the Mountain Parkway to Salyersville. We stopped briefly to say hello to Dr. Hall and to thank him for his effort and also ask him

for directions to the Conley cabin, our designated meeting place. I don't remember the directions exactly, but I do know that they involved identifying certain barns, trees, rocks, and small streams. We wove through the increasingly wild countryside probably for 20 minutes and arrived at about 10:30 AM at the end of a poorly marked, rocky, auto path at what might have been the Conley cabin as described by Lloyd Hall. We saw a log cabin about 150 feet from where we parked, on the other side of a small stream spanned by a footbridge. No one was in sight. The crude shutters of the cabin were closed. We did, however, see a wisp of smoke spin skyward from a single chimney. No automobiles were in the area. We climbed out of our vehicles, somewhat frightened and wondering — "are we in the right place?" Finally, after a long moment we called out, "Hello." A voice from within the cabin said, "Who you lookin' for?" I responded by saying, "We're the doctors from Cincinnati. We're the ones that helped Angie." Immediately the shuttered windows and front door of the cabin opened and people began pouring out welcoming us and directing us across the footbridge to the porch of the cabin. It took us two or three trips to get all of our equipment across, each of us carrying a few items. It took us a while to "set up shop" and to explain what we had planned. In a few minutes Jeannine, Donna Arnett, and Helen Glueck, each carrying a clipboard, identified and recorded members of the family present and their relationship to Angie. Mary Ann, Ernie and I drew the blood from the family members, some of whom were quite reluctant but willing to do it for Angie. At the very beginning, obviously the most important family member was on the porch. Nancy Allen Conley, a very old woman, exact age unknown, and nearly stone deaf was sitting in a homemade rocker smoking a corn cob pipe, wearing a bonnet and a full length print cotton dress. She seemed unaware of the surroundings, and when I asked, "Who wants to go first?" at least 20 sets of fingers pointed right at Nancy. With a needle, syringe and alcohol sponge in my hand as well as a tourniquet I leaned right into Nancy's ear and told her, "We want to draw some blood. It's for Angie." She looked at me for a moment, broke into a big toothless smile, and stuck out her arm. The rest of the day was easy. On that day and during a subsequent visit, we drew more

than 50 blood samples. On more than one occasion while taking the histories of those present, we learned that several offered to be blood donors who weren't family members. They thought they would just come and help. During our first visit, one woman, while giving her history, volunteered that her maiden name and married name were the same but "the Mister ain't no kin," she said, "caus he's from way on the other side of the mountain." After working for an hour or so I smelled coffee, obviously being brewed in the cabin. One of the members of Angie's family offered us a cup of coffee with the comment, "We don't ordinarily have coffee, but we knew you were coming, so we went and bought some." The water supply for the coffee was from a well situated next to the cabin. Above the cabin on a hill were a small barn, a chicken coop, and the outhouse. From a public health point of view, this was the worst place in the world to have a well, but I figured if the coffee boiled long enough, any bacteria, viruses or parasites that were present very likely would be killed. After stalling for about an hour or so, each of us drank part of a cup of coffee and thanked the family member offering it. We survived!

The blood collections went smoothly. Toward the end of the day we drove several miles with one of Angie's brothers to find yet another brother who's "slightly tetchd." He was on his porch when we arrived. His rifled propped against the nearest wall was within easy reach. We approached cautiously. Once more I used the magic word - "Angie." He stuck out his arm. We obtained the sample and left immediately. On the way back I began to breathe again.

We were able to process all of our samples prior to heading home. We packed up and departed after many handshakes and hugs. "Thank you for helping Angie."

On the way home Helen regaled us with stories of her medical school life, her Internal Medicine oral board exam, her early years on the College of Medicine faculty, and of trips with her archeologist husband, Nelson Glueck, a highly respected member of the Literary Club and President of Hebrew Union College. The time went quickly. On arrival home we unpacked and carefully put our samples in our freezer. We ended the

day at Helen's home where we each had at least one generous adult beverage. We slept well that night.

Epilogue

Our studies of blood samples of four generations of the Conley clan documented the inheritance pattern of Hageman factor deficiency, a rare coagulation disorder. In addition, we confirmed that this deficiency is not associated with a bleeding problem.

Clinical research begins by observing a disease state for which an explanation of the abnormal pathophysiology is not readily available. Finding answers to the questions raised by these "errors of nature" frequently helps our understanding of normal physiology and, therefore, our ability to control the abnormal.

Herbert Flessa

Making a Bee-Line

Case finding is a recognized health-care activity, and in some circumstances a useful one. For many diseases, early recognition leads to a better chance of successful treatment, and for some it leads to a better chance of survival. Think, though, of the importance of tuberculosis case finding 50 years ago, when I first started working with it. At that time, tuberculosis killed more people than heart disease or cancer; and it killed them slowly, in their youth. Almost all of those who developed tuberculosis caught it from someone with whom they have been in close contact. New cases of tuberculosis were mostly infectious for many months before they developed symptoms that led to their diagnosis. Finding a case early might save not just one life, but many. It might save the lives of the two

to three contacts, friends and family, who would on average be infected between the time that a patient first became infectious, and the time that she developed symptoms that would lead to her diagnosis. I say "she" because at that time the age-sex group with most tuberculosis was that of females aged 16 to 25. Now it is men over the age of 80 – much less interesting to treat. So we developed tuberculin skin-testing programs, mass x-ray surveys, and other methods now no longer useful in most of the western world.

As new drugs were developed, case finding increased in value, but also in difficulty. There were fewer needles to find in the haystack. Shortly after arriving at the Southeast Kansas Tuberculosis Hospital I saw an outpatient referred to us because he had been found to have pulmonary tuberculosis. He was the State Bee Inspector for Kansas. He looked very well. His chief complaint was that he was feeling well, but the bees were stinging him. He had learned over the years that bees would sting him only if he had a cold or got sick, and that didn't happen very often. They never stung him otherwise – or presumably he would have taken up a different profession. But for the last month he had been stung frequently, and he didn't feel sick. So he went to his doctor and told him that he felt fine but must be sick, and told him the story.

He was lucky. His doctor listened to him. Some doctors prefer to listen only to a patient's answers to questions, and to ignore any symptoms that the patient provides voluntarily or in his own words. Not only did his doctor listen to him, he believed him. None of the "I'm the doctor, I know best" stuff. So he was sent off for a few routine tests: blood chemistry, urine testing, complete blood count, and chest x-ray. The chest x-ray showed a cavity in the upper lobe of his left lung, and this was soon shown to be tuberculosis by a positive sputum test. And he was sent to us for treatment, and he got better. I was fascinated by his story, and asked him if he had any idea why the bees stung him when he was sick: "I guess they smell it on me", he said.

A few years later I found a copy of the "Journal of Irreproducible Results" lying on a table in the library. I had never heard of that journal before: this issue was volume 1, number 3, only 16 pages. The statement of editorial policy was rather jocular, and so were the contents. The one that caught my eye was a brief description by a family practitioner of the diagnostic ability of his pet spaniel, which would, as he walked through the waiting room, stop by any patient who had a trichomonas vaginalis infection, sniffing in a decorous fashion. This reminded me of the bee inspector, so I wrote a brief description of the story, with the comment that I understood that bees finding a good source of honey would come back to the hive and do a little dance to tell the other bees where it was. Perhaps we could figure out a way to interpret the dances? Do they have one dance for clover, and a different dance for tuberculous people who should be stung? I sent this as a brief note to the Journal of Irreproducible Results. Six weeks later I got a postcard saying that the Journal had ceased publication, and was accepting no more manuscripts. I suppose that was better than a rejection, but I could think of nowhere else to send it. I let the matter rest.

Another few years later our entomologist daughter was spending a few summer days with us. We had tea out on the porch. It was very pleasant except for the wasps which shared our meal with enjoyment and persistence. I apologized to Kate, and explained to her between swats that I had filled some holes in the wall close to the porch, from which I had seen wasps flying, but there must be some more wasps' nests nearby: I had looked for them but could not find any. How could we track them down to their lair?

"Easy", she said. "Anesthetize them, tie a yard of thread around one of their hind legs, and follow the wasps back to their nest. The thread slows them down."

"Anesthetize a wasp? How?"

"I'll show you." And she inverted an empty glass on top of a saucer on which a wasp was enjoying some raspberry jam, picked up the wasp buzzing in its trap,

and put saucer, glass, and wasp in the refrigerator. "Give it half an hour, then we'll take it out, tie a thread on its leg, let it warm up, and it will take off for home, thread and all."

Half an hour later we took the wasp out of the refrigerator, and Kate tied the thread to its hind leg. The wasp looked dead to me, but I was assured it would wake up in another half an hour or so. It didn't but it had started to move around a little. As we had to leave for a short while we tied the other end of the thread to a heavy stick. When we got back, the stick and most of the thread were there, but there was no sign of the wasp. Either it had recovered enough to bite its way through the thread and head for home, or perhaps a bird had been by.

So we are left with what might be described as a promising approach to case finding, with a few loose ends still to be tied up. First, it is fifty years too late. Tuberculosis continues to decline in importance, and getting patients to comply with treatment is now much more important than case finding. Second, details of experimental design would need a lot of work before they would meet the requirements of any National Institutes of Health Study Section. A series of experiments to flush out the methods, and pursue the necessary pilot interdisciplinary studies, would combine entomology, insect choreography, ultra-microscopic global positioning devices, and Public Health nurses in helicopters. But medical research has never been easy, and as Pooh Bear exclaimed as he fell out of a beehive tree with bees swarming around him, "You can never tell about bees."

Robert G. Loudon

Frustrations

For the past 50 years we have spent at least part of each summer at our cottage on Lake Leelanau, Michigan. I have a garden - vegetables, flowers, and red raspberries - 525 miles from our Cincinnati home. For any of my friends who prefer a peaceful and restful summer, I'd advise against creating such an arrangement. It challenges muscles and intellect, both to be deplored. The muscular challenges are quite obvious. The intellectual ones are less so, but they are very real. For instance, I have waged war with several varieties of beetles, grubs, crows, rabbits, squirrels, deer and raccoons and frequently lost. I did outwit the potato beetles that have become resistant to all the frequently used pesticides that the state of Michigan considers safe. However, a consultant at Cincinnati's Natorp Garden Store suggested trying Rotenone. Perhaps because it has not been used for such a purpose for years, it worked, and beetles bit the dust, literally.

There are also raspberry beetles that eat the white petals of any flower - daisies, grapes and mountain ash - but their main love is the raspberry and so is mine. They, too, are resistant to any pesticide safe for use on human foods, so I stole an idea from Infectious Disease experts and the cancer chemotherapists - when one drug doesn't work use three. I tried Diazanon, Sevin, and Malathion. These are insecticides approved for use on foods, with limitations, of course. So far the multiple insecticide approach has been successful. We had a bumper crop of raspberries.

The onion grub that also attacks turnips and radishes is said to be killed by Diazanon, but don't believe everything you hear about gardening. This past summer my spring onion crop was wiped out by these grubs in spite of Diazanon in the soil and on the sprouts as they rose out of the soil. The radishes and turnips fared badly also because of the same scourge. This year carrots, too, were attacked. I'll have to

wait for another summer to try Rotenone or the multiple drug approach.

Deer and rabbits in the spring eat freshly planted tomatoes or tiny, tender vegetable spouts. A doe dropped a fawn in the middle of the garden on one occasion while Mama was after my tomato plants. I have a picture of the baby to prove the incident. Crows also love freshly germinated beet seedlings, so wire netting is required over the beet row. But these creatures don't attack the garden later in the season if I don't attract them by growing corn. I presume they congregate around the corn-growing farms.

I've often remarked that I'm glad I don't depend upon the garden for a livelihood. It's a hobby and an interesting, though often frustrating, challenge. But the greatest challenge I face has been presented by the beasts of the woods and fields - particularly the squirrels. They have successfully raided my bird feeders for years and made life for the birds most unhappy. I like happy birds. We've had some remarkable bird sightings during "fly by" season - indigo buntings, scarlet tanagers, woodland grosbeaks, occasional orioles as well as the usual finches, cardinals, red-breasted grosbeaks, chickadees, warblers, nuthatches and creepers. We love to watch them and photograph them and don't like interference from the squirrels. I've tried every method to foil them that my friends or I could suggest. I've strung a tight wire between two trees, and suspended the feeders from the wire. The little red squirrels are accomplished acrobats. They run across the wire, slip down to the feeder, and munch away at my bird seed until I scare them off with a loud noise or if they become too brazen, a pellet rifle. Unfortunately, I do more damage to the bird feeder with the pellets than to the squirrels. If I come to the doorway with a rifle after they've had some experience with my marksmanship, they're off and away before I have a chance to shoot at them, only to return to their feeding spots as soon as I go into the house. The big black squirrels have more trouble with the wire, but some finally master the art of tightrope running. I've tried all kinds of baffles with no success. A plastic hood covering the feeder like an umbrella at first created a serious challenge

for the black squirrels, but not for long. They learned to use their weight to tilt the hood down toward one side of the feeder and happily slide down to the feeder platform. Or they jump at the feeder or fall on it, knocking a portion of the seeds to the ground where they eat them with great gusto. I tried a really ingenious contraption consisting of a metal pole to hold the feeder. It is sunk in the ground and stabilized by concrete. The feeder hangs in a semicircular bend in the pole. Hoods acting as baffles have been fitted both below and above the feeder. I've even greased the metal pole and the baffles. One such contraption thwarted the squirrels during the day, but during the night a raccoon toppled the apparatus, bending the rod and destroying the feeder to get to the seeds. I counted that a failure.

So, I went back to the wire and a new plastic feeder. I observed exactly how the squirrels managed to run across the wire to the feeder - hang onto the wire with their hind legs, tilt the baffle down until they can grab one of the feeder perches with their fore legs, release hind legs to grasp the feeding platform from which they hang head down. Then they curl their bodies and heads back 180 degrees to eat the seeds from the recessed openings in the sides of the feeder. It appeared to be very awkward, even for the squirrels. To make it even more difficult for them, I lengthened the distance from the wire to the feeder increasing the distance their bodies had to stretch but that maneuver put the feeder close to the ground so they could jump up to the platform to feed. The "fall of the feeder" technique seemed to be their favorite sport and pastime. They were able to contrive a solution in their favor to any technique I could devise. And that is how the season ended. By all methods of calculation, the squirrels were ahead.

My granddaughters, ever anxious to help poor old grandpa, gave him an electrified bird feeder for Christmas. It's a very unique, ingenious, but unwieldy contraption, about two and a half feet tall with transparent plastic sides, a metal tray on the bottom, and a metal and plastic umbrella covering the top. A 9-volt battery and an induction coil produce a startling but nondamaging shock when a squirrel,

chipmunk, or raccoon sits either on the metal tray or the metal top and tries to eat from any of the seed ports in the plastic sides. They complete the electric circuit and receive a shock whereas birds sitting on plastic perches are not bothered. The chief problem with the contraption is its weight. When full of seed it weighs about ten pounds, too much for most tree branches near the windows of our cottage. It is certainly too heavy for the wire I've been using behind the house. Fortunately, I did find a suitable branch for it on one tree in our front yard, easily visible through our living room picture window. In order to avoid the need for a ladder each time the apparatus had to be taken down for seed replacement or cleaning, I contrived a rope and pulley system to raise and lower it. The feeder was filled, raised into place, the rope locked around a cleat screwed to the tree with surplus rope hanging from another cleat. The current was turned on and checked to be sure it was functioning, I being the subject. It made me jump, and I hope that the squirrels would react in the same way. No squirrels appeared until the next day when two black ones gave it the once-over, running out on the branch trying to get down to the platform where at least one could sit and eat. As the squirrel slid down the metal rod and touched the metal roof it felt the shock and gave a mighty leap to the ground. Both squirrels ran off to more friendly territory. I thought I had won. Next morning when I looked at the feeder it was apparent that disaster had befallen. It still hung in the tree, but had been partially disassembled, one of the partitions removed, the wire carrying the current disconnected. Most of the seed was on the ground. Though I had not seen the marauder, it must have been a raccoon. How it was able to remove the top and disconnect the wire without getting a shock, I do not know. But I'll give serious thought to hiring that raccoon for my next electrical job. I swept up the seed, replaced the partition, and connected the wire from the current source to the tray and top. Since we were driving back to Cincinnati the next day, I stored the feeder in a back room. It had not been badly damaged. Three weeks later, when we returned, I hoisted the contraption to its hook, but to make the approach to it more difficult for the raccoon, I interposed a protective plastic hood between the branch

and the feeder roof. It looked totally resistant to all furry marauders, but strangely enough none came. No squirrels, no raccoons, no chipmunks. Even no birds. There is hung, utterly rejected, ostracized. Finches, chickadees and a red-breasted grosbeak visited the old feeder in the back of our house but they apparently disliked the front location. As days passed occasional birds visited the feeder and ate a few seeds. But there were no regular visitors. Surprisingly, I have not seen a squirrel since we returned and there was only one night raid by a raccoon which was unsuccessful. It had chewed the redundant non-functional end of the clothesline into four pieces as it hung loosely around the second cleat but had not touched the working end of the line. There are a few low IQ raccoons. That was the only raid that occurred. No beast tried to get food from the feeder by way of the metal roof or bottom platform, the dangerous pathways. Did the original marauders feel the shocks and carry the word back to their furry friends that we were dangerous people? But why don't the birds like the front yard location? Maybe next year they will. I have won a battle, but so far I have lost the war. I'm still frustrated.

Richard W. Vilter

BEYOND THE CALL

April 5, 1999

Milo R. Beran

There is a brotherhood of the highest order among seafaring men. The brotherhood displays no emblems, requires no rituals, never discriminates, is free of judgments. Its existence is rarely given voice. It is manifest in deeds.

In early December, 1942, it would have been impossible to foresee the several events that would