

## Reflections on Thirty Years in Hemophilia Care

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A development by a scientist is only a beginning. Implementation of that development is much more difficult. It requires a kind of expertise that is represented by the American Blood Resources Association. Society doesn't value that expertise as it does the work of the scientist. Implementation involves deciding which developments to pursue, raising the funds, accomplishing production and quality control and clinical trials and the regulatory process and marketing and, finally, getting third party payers to pay for a new product.

On this occasion, I looked back at the circumstances that got me into the field of coagulation and how far we've come in a short time.

My career in coagulation came about by chance. In 1962, I applied for a Fellowship in hematology in San Francisco with Dr. Paul Aggeler. He sat me down and told me about all the disadvantages of that particular Fellowship. I didn't know whether he was trying to get rid of me or whether he was the most honest man I'd ever met. He did turn out to be a very honest man, careful and reflective. Sometimes a study didn't turn out the way I expected. Dr. Aggeler was never disappointed. He'd find fascinating implications in the results, whatever they were.

In 1952, ten years before I began my Fellowship, Dr. Aggeler had described a second kind of hemophilia, which we now call hemophilia B, in a teen-ager, Kent Kincaid. He called the deficient factor "plasma thromboplastin component", PTC. The same year, in England, Rosemary Biggs described the same new kind of hemophilia but called it "Christmas disease" after the name of her patient, Stephen Christmas. That factor is now known as factor IX.

Factor IX remained of great interest to Dr. Aggeler. His research lab was a modest place, the office furnished with cast-offs, which taught me that great reputations need not be nurtured in deluxe surroundings. The hemophilia center, so to speak, was a cot in the corner of the lab. One of my jobs as a Fellow was to thaw plasma in the water bath

and infuse it into patients with hemophilia. Kent, who was then my own age, was working his way through college as one of the lab's bottle-washers (an occupation now just about extinct). His job kept him handy as a recipient of early concentrates. In those days, we relied heavily on mutual trust and good will. Written consents were rare and brief. The term "Institutional Review Board" had not yet been invented. (I don't think we've truly progressed much.)

Kent had a marvelous cheery personality. He was the guy who arranged the parties. He wanted to go skiing, for the first time in his life. He arranged a cheap group tour to Yosemite for the lab techs, bottle-washers and Fellows. I was shocked that he intended to go skiing but he said he'd be safe if I went along because I had the same blood type as his. (Kent was a natural athlete and went swooshing down the hill while I fell all over and accumulated the only bruises!)

It was a momentous time to be working in coagulation. In early 1963, I had to take care of a woman with moderately severe hemophilia who was having all her remaining teeth out because they were rotten and infected and she was malnourished. She was in the hospital more than two weeks and I poured dozens of units of plasma and red cells into her, mostly at night. She was exhausted and so was I. Later that year, I was told that another person, with severe hemophilia, was to have extraction of all his teeth and I thought that perhaps I should have listened to Dr. Aggeler when he tried to talk me out of this Fellowship. But, we had our first few vials of an early factor VIII concentrate that Cutter (later Bayer) had made, across the bay in Berkeley, enough for a pre-op dose and one or two post-op doses. My job was to get it into solution, which took an hour. The man did not bleed at all after his extractions. That was an incredible day, the most memorable of my medical training.

Dr. Aggeler and Dr. Silvija Hoag also were testing the factor IX complex concentrate that eventually would be licensed as Konyne®. Kent, of course, was one of several patients who were infused to determine the recovery and half-life. As a

Fellow, I was one of the sample-collectors. I've always been an early-bird, so I took the 5 A.M. samples, and Mona Kropatkin, who later married Ted Spaet, was the night-owl who did the 2 AM samples. Decades later, I was still doing recoveries and half-lives on new concentrates.

I got to the Hemophilia Center at Orthopaedic Hospital through the mediation of Dr. Samuel Rapaport. The multi-specialty center had been there since Dr. Shelby Dietrich founded it in 1962 but in 1966 it still did not have a specifically-trained hematologist nor a coagulation laboratory. Dr. Rapaport was stationed at the Los Angeles County-University of Southern California Medical Center, some five miles away through heavy traffic. He knew that concentrates would soon be licensed. The Center needed to be able to distinguish the different types of hemophilia and to assay factor levels. He raised money from Courtland Laboratories (later taken over by Abbott, then Alpha, then Grifols) for lab equipment and put me in his USC hematology division as an Assistant Professor, stationed at Orthopaedic Hospital.

In thanks to Courtland, I agreed to conduct clinical trials of the factor VIII concentrate they were developing. We decided to compare the efficacy of the concentrate on different prophylactic schedules. When we wanted to evaluate daily doses, we tried something really daring, we allowed patients to give the concentrate to themselves at home. That was the beginning of the home program in the western USA (there already were small programs in Boston and Philadelphia). One young man, age 16 at the time, was a special revelation to me. He had the honor of having more frequent hemorrhages than anyone else in the Center. When I first met him, he was curled up in a corner, sucking his thumb. He had wonderful big veins and he was inherently intelligent, one of our brightest patients. After he got on self-infusion and prophylaxis, he blossomed. He went, all by himself, by public bus, on a tour of western ghost towns. When he came home, he showed me his diary illustrated by his own sketches. His college career started well, but the concentrate experiment ended. His insurance said that prophylaxis was experimental, not eligible for insurance coverage. He went back to frequent hemorrhages, and that botched college. He never got a steady job. That was my introduction to the impact that uninformed re-imburement policies can have.

I carried out clinical trials on a great many factor VIII concentrates including, in the late 1960's, starting with the first cryoprecipitate made in Los Angeles, thanks to Dr. Byron Myhre who was at the Red Cross Blood Bank at the time. I continued with many lyophilized plasma-derived products to early recombinant ones. I had more influence, however, on factor IX concentrates. As soon as we had a good supply of concentrates at Orthopaedic Hospital, we started performing orthopedic surgical operations to correct the worst of the joint damage in our patients. Orthopedic surgery in hemophilia A started in 1968 and went well. Factor IX complex concentrate (prothrombin complex concentrate) became available in 1970. After the first 13 operations, we knew we had a problem. Six of those 13 patients had thromboses, superficial or deep, whereas by that time we'd operated on 72 persons with hemophilia A without thrombotic complications. We stopped doing elective surgery and wrote a letter of warning to the "New England Journal of Medicine" (289:160,1973). We presumed that thrombosis somehow resulted from the presence of activated forms of the clotting factors.

In France, Dr. Doris Menache, who made the factor IX complex known as PPSB, noticed our letter. She set up a Task Force to investigate the extent of the problem, through the International Society on Thrombosis and Hemostasis. Dr. Menache, another very honest hematologist, was aware of a few problems with PPSB. The major problem encountered by the Task Force was nationalistic defensiveness. Many countries made their own concentrates in their own fractionation laboratories. If you asked the official in charge, he would swear that the concentrate made in his own beloved homeland had never and would never cause problems like those terrible American concentrates! Dr. Menache wrote to hematologists around the world, asking whether they'd encountered problems. She found out that it wasn't just American concentrates, it was a general problem.

The Task Force met in 1974 and discussed what to do about it. As a temporary measure, we suggested adding heparin to the concentrate. That could not be done, not in the near future, by the manufacturers because they'd have to get new licenses for new formulations. So we recommended that heparin be added to factor IX concentrate after it was reconstituted, at the point of use. That recommendation coincided with a world-wide shortage of heparin, so it was not widely

implemented. At Orthopaedic Hospital, we kept to our ban on elective surgery in hemophilia B and only performed very urgent surgery, relying on a cocktail of plasma (as much as the patient could hold) plus small doses of factor IX complex concentrate plus heparin. As time went by, and patients with hemophilia A got their fancy repairs, their total hips and total knees, those with hemophilia B looked on with envy.

Dr. Menache thought the solution would be development of a concentrate of just factor IX. She was able to pursue that dream after she married Dr. David Aronson, moved to the USA and went to work at American Red Cross research labs. We pursued the dream throughout the 1980's. Dr. Menache developed a concentrate, we did clinical trials, and just at that point, it became evident that concentrates should be heat-treated to kill the new pathogen, HIV. She developed a heat-treated concentrate and we did the clinical trials and then it appeared that solvent-detergent viral inactivation might be better, and she developed an SD-treated concentrate and we did the trials and applied for a license and things got stalled. Finally her technique was adopted by Alpha for its Alphanine® and meanwhile Armour (later taken over by Rorer, then Aventis-Behring and then ZLB-Behring) developed its immuno-affinity purified Mononine® which also was a nice achievement.

As the years rolled by, we wondered why it was taking so long to get licensure. We found out that most people just didn't believe that there really was a problem with thrombosis. After all, the published reports were anecdotal, and involved only a few patients, and they'd been published a long time ago. Dr. Jeanne Lusher stepped in and put out a call for recent anecdotes about thrombotic complications of factor IX complex. She collected 72 cases occurring between 1987 and 1990, whereas we'd had only one DVT in a surgical patient using factor IX-only concentrate, out of a total of 19 such surgeries. (The patient was a 60 year old man having a hip replacement who had no anti-thrombotic prophylaxis.) At last, on December 31, 1990, the first coagulation factor IX concentrate (purified factor IX, only factor IX) was licensed.

I thought that was the end of the story. I'd been saying for years that I'd retire happy if a factor IX concentrate was licensed. My lab techs were getting nervous, thinking they'd be out of a job, but I reassured them that I had to pay for at least eight more years of my kids' college tuitions so

retirement was still far away. But licensure was not the end of the story. In the early 1990's, I kept hearing reports of patients with hemophilia B having surgery with factor IX complex and having DVTs. The most ironic instance concerned one of our patients originally reported in 1973. He knew he'd had a DVT, he knew he was supposed to use only purified factor IX, but he went in for surgery at another hospital, local to him, was given factor IX complex and got DVTs in both legs. It turned out that the doctors treating him didn't know the difference between factor IX complex and purified factor IX. At least he lived to tell me about it! What was needed then was a continuing big educational effort to let hematologists know why they should use the more-expensive purified factor IX for patients with hemophilia B in vulnerable situations.

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