"It is only on maturing that most of us realize that we can contribute more."

William M. Heller

(1972)

At the time he received this award, William M. Heller was the Executive Director of The United States Pharmacopeial Convention, Inc., Rockville, Maryland.

On Maturing

On Maturing. Isn't that an impressive title for a talk! Doesn't it sound profound? I hoped it would. But actually it's an idiot title, picked at a time when I didn't know what I wanted to talk about, picked as so non-indicative that I could develop any number of subjects and wiggle them around to fit.

For instance, it is only on maturing that most of us realize that we can contribute more and even carry our own pet ideas further if we have a good team, help our teammates join their ideas to ours, and then give them the freedom and wherewithal and finally the credit due them in pursuing those ideas with far more talent and time than we have at our own command. The satisfaction that we know as youngsters when we accomplish some new thing for the first time gives way, on maturing, to a greater joy in seeing the team win a big one, with individual members fulfilling their functions far more expertly than we could ever hope to.

I've been a lucky fellow all my career because of the teammates I've had, and I accept this Award tonight only as a token of recognition to them.

When I started at Arkansas in 1955, I was the one and only pharmacist in a one-

room pharmacy that served a 200-bed hospital with 60,000 outpatient visits per year—and didn't even have a typewriter or a file of yesterday's prescriptions. Into that mess came Louise Pope, who had learned from Leo Godley what a hospital pharmacy could do. Harold Hamilton joined us and, with his experience in retail pharmacy, started a teaching program that students recognized was relevant. Carl Brooks integrated our staff before Little Rock became a worldwide symbol.

A fellow named George Provost called from Watertown, New York, and was persuaded that Arkansas was indeed the Land of Opportunity, as the state slogan went. It didn't seem like that a couple years later when a big budget cut knocked off one-third of the beds in our new hospital. But just at that time a little sideline operation we had been working on for the ASHP was put on the market, and we suddenly realized that the *American Hospital Formulary Service* was going to need a full-time writer if we were going to keep it up-to-date as promised. We let George do it.

Not being too proud to take Yankee money in the absence of any prospects at home, we submitted a grant proposal to NIH to do a unit dose dispensing demonstration project. This was turned down in 1959. On my innocent inquiry as to why such an obviously good idea was rejected, I received a detailed explanation that was incomprehensible to me. With this rejection slip in hand, I met a big fellow who was finishing his residency at Florida under Warren McConnell. He was the first hospital pharmacist I'd known who had taken graduate work in the social sciences with the intention of making a career in research. His name was Ken Barker, and he interpreted that rejection slip for me. Said my proposal had been turned down for every reason in the social science research books except bad grammar and the idea itself.

Now Ken had listed himself in the ASHP's Personnel Placement Service as being willing to go anywhere except the South (which the Placement Service stated positively as a willingness to work in the North, East, or West), so I told him Arkansas was really the Southwest, just like Texas, and besides where else would anyone let him investigate medication errors and take drugs off the nursing units and supply only single doses. So he decided discretion was the better part of geography and took over a budget slot we had called Pharmacist in Charge of Central Sterile Supply and Infant Formula Room. Some two years and $80,000 worth of altered payroll slots, scrounged supplies, and unpaid overtime later, Ken had not one but two significant grants: one from the Hartford Foundation for a full-scale study of medication errors in a nonuniversity hospital and the second a Public Health Service grant for an experimental hospital medication system featuring automated data-processing control of medication orders and unit dose dispensing. These studies formed the scientific basis, I believe, for the sweeping changes in hospital medication systems and pharmacy practice of the last few years.

I shall ever be grateful to Arkansas for the opportunity we had there. At other universities, top faculty members would have been already immersed in their own research and not available to join the multidisciplinary research team that Ken put together. And few hospitals would be willing to suffer the disruption of having all its medical, surgical, and pediatric beds shifted to an experimental medication system where observers were popping in and out or constantly trailing people around, Tele-

types clacked away in the still of the night as well as the pandemonium of the day, and a 10,000-square-foot pharmacy was created by relocating several entire departments in a domino-like effect that ended up with the dean of medicine giving up the only classroom he had in the hospital.

Unfortunately, Arkansas couldn't afford to maintain the new system after the experiment ended, and the 27 pharmacists we had there at one time scattered to the four winds. The hospital administrator left; the director of nursing left; the project director left; I left: but Bert Kossler, who had joined us as our primary medication administration observer, stayed on and became chief pharmacist.

I ended up on the ASHP staff. So did George Downs, and May Douglas, and Ray Jang, and Brenda Martinez (which meant that Domingo was close by); and if we counted George Provost as an Arkansas alumnus, we were about even with the Duquesne crowd on the staff. This was a delightful two years. To a hospital pharmacist, accustomed to contesting for financial and territorial rights with the many other professions and vocations required to operate a modern hospital, it was a real pleasure to work where the entire staff shares a common background and works toward common goals.

Joe Oddis never did replace me when I left the staff. I was hesitant to ask him whether it was because I was irreplaceable or expendable—I rather suspected the latter since Mary Jo Reilly was doing a masterful job with the *Formulary Service*, May Douglas was all wrapped up in *DPIF* tape, and, early on, Dwight Tousignaut had been hornswoggled into taking on the editorship of *International Pharmaceutical Abstracts.*

Well, I've dropped names all over the place and doubtless have left out some that I should have mentioned, but these are the people who have every right to feel that they have earned a piece of the 1972 Whitney Award too—they and my family which, with varying degrees of resignation over the years, has allowed me to do "my thing."

Lloyd Miller said my recruiting courtship for the USP continued for over 10 years, and I'm sure he has had pangs of doubt both before and since retirement that he should ever have been so persistent. Sometimes hospital pharmacists still ask me why I left hospital pharmacy. I don't consider that I have. The basis on which I was hired by the USP Board of Trustees is a very simple analogy familiar to every hospital pharmacist: I said the USP ought to be the pharmacy and therapeutics committee of the country.

To help make these changes in direction of the USP organization, three hospital pharmacists have joined me on the staff: Ken Barker again, Ray Jang again, and, just to show that new blood is acceptable, Robert Henry. We have great hopes for this unique organization, not the least of which is to select the drugs for the federal formulary when and if one is legislated into being.

But that's another story.

Tonight I want to make just one point. I want to impress upon you as vividly as I can a perspective on the role of the pharmacist that is even more clear to me after three years on the USP staff. The story I am about to tell is true, as far as I know. You

all lived through it last year. This story was reconstructed in stirring detail by Wallace Werble and the editors of *Drug Research Reports*, "The Blue Sheet," in the May 26, 1971, issue. It is with Mr. Werble's kind permission that I am able to plagiarize in such abundant fashion. And I chance these extensive quotations because "The Blue Sheet" costs $200 a year and it's just possible that some hospital pharmacies don't subscribe.

This has to do with the septicemia epidemic that was linked to Abbott parenterals.

The Abbott investigation was a classic epidemiologic detective story, involving at one point around 100 people on the staff of the National Center for Disease Control (CDC) in Atlanta. The action took place there and in half a dozen hospitals around the country.

CDC has an annual budget of $48 million, about as much as the combined advertising budgets for Anacin and Alka-Seltzer. The CDC staff consists of both career Public Health Service officers and bright young men fresh from medical and graduate schools, doing a two-year stint in lieu of military service. Among them was Dennis Maki, a 31-year-old University of Wisconsin M.D., who completed his tour last June and is now a resident at Massachusetts General Hospital. Dr. Maki was one of the key figures in the Abbott affair.

On November 1, 1970, Dr. Maki lectured to the sophomore students of the Medical College of Virginia on hospital-caused (nosocomial) infections. After the talk, he was called aside by one of the MCV professors who told him about several septicemia cases at the hospital during the past summer. These had been investigated by Dr. Richard Duma, a young assistant professor of medicine. The study showed that 24 of 69 Abbott intravenous sets were contaminated with microorganisms. These contaminants were thought to have been introduced at the level of the screw cap through breaks in sterile handling techniques by the hospital staff. Dr. Duma was preparing a paper on his findings for the *New England Journal of Medicine.*

Dr. Duma and his coauthors, one another M.D. and one a Ph.D. microbiologist, were the first in a long while to point out that i.v.s can serve as a vehicle of contamination. An article describing a similar problem was published in *The Lancet* in 1953. Although numerous articles had been published in more recent years implicating indwelling catheters in infections, no one had looked up at the bottle hanging above.

Maki decided to find out whether other hospitals were having similar problems and whether, as MCV concluded, Abbott sets were more subject to contamination. Disguised questionnaires were sent to the 70 hospitals that regularly reported to the CDC's Hospital Infections Section.

Abbott users reported a seemingly higher incidence of primary bacteremias, but the difference was not statistically significant. That seemed to be the end of that.

A call from the University of Virginia Hospital in Charlottesville on December 1 revived interest, however. Four of the five patients in the coronary care unit had developed septicemias during the past week. CDC normally expects 5 to 10 bacteremias per 1000 admissions.

Maki and a microbiologist from the CDC went to the University of Virginia and cultured the bottles then hanging. One-fourth of 72 hanging bottles were contaminated, mostly with low numbers of organisms. Two were heavily infected with members

of the *Erwinia* group and *Enterobacter cloacae*, the same organisms cultured earlier from the coronary care bacteremia patients.

Erwinia is usually thought of as a plant pathogen, and hospital bacteriologists do not normally look for it. Furthermore, it tends to get lost in the usual mix of microbial contaminants cultured. But because *Erwinia* is such an unlikely contaminant, the CDC investigators turned it to their advantage and used it as a microbiological indicator.

Abbott officials meeting with the University of Virginia staff maintained there was nothing wrong with their products. Contamination resulted from sloppy hospital practices, they said. Lab studies at CDC showed that all freshly opened Abbott bottles were sterile, supporting Abbott's claims.

That was also the expectation of Dr. Carl Bruch, one of FDA's most consumer-oriented scientists and a man who has served enthusiastically on USP advisory panels. He was not unduly excited on reading a draft of Duma's report. Dr. Bruch had long been concerned with the sloppiness of aseptic techniques in hospitals. Only two months before, he had quashed a similar report of reputedly contaminated spinal tap trays, showing that there was nothing wrong with the trays and that the contaminators were the dirty-fingered hospital investigators themselves.

But other hospitals began reporting troubles with Abbott solutions. A former CDC man who had become chief of infectious diseases at Orange County Hospital, Irvine, California, called to report an outbreak of septicemias. *E. cloacae* was one of the infectious organisms.

During a routine inspection of i.v. systems at St. Anthony's Hospital in Denver, hospital bacteriologists discovered contamination with *E. cloacae.* Half the hospitals in the nation used Abbott parenterals, and the likelihood of three of them having the same problem was only one in eight. Furthermore, lab technicians at CDC headquarters found *Erwinia* in clinical isolates sent from St. Anthony's.

Maki and a CDC microbiologist studied and cultured the parenterals for five days at an Atlanta hospital using Baxter solutions. All new Baxter bottles were sterile, but 9% of the hanging bottles were contaminated. Significantly, however, the contaminants were neither *Erwinia* nor *E. cloacae.*

According to the textbooks, microbes just cannot live in dextrose solutions which lack organic nitrogen. Maki and a CDC bacteriologist cultured about 100 strains of hospital microbes in dextrose; 96 strains failed to live, but two that did were *E. cloacae* and *Erwinia.*

On January 26, the chief of infectious diseases at Detroit's Henry Ford Hospital reported an outbreak of septicemias. By then, Orange County Hospital had linked its septicemias with Abbott systems and had isolated *Erwinia*, the indicator.

Maki, a CDC microbiologist and a fourth-year medical student spending an elective semester at CDC, conducted a prospective study at the University of Virginia Hospital, comparing Abbott solutions with Cutter. They found that 2.5 times as many hanging Abbott units were contaminated. In eight of the Abbott systems, they isolated *E. cloacae* and *Erwinia.* One Cutter system may have had the same microbes. In the eight Abbott bottles, contamination was heavy, although patients being infused from them had not been diagnosed as clinically ill from those organisms.

Maki and his coworkers checked everything. They took cultures from tables, sheets, and walls. They talked to nurses to find out what hand lotions, soaps, lipsticks, cosmetics, and deodorants they used. They also cultured nurses' hands, discovering that 25% intermittently had *E. cloacae* and *Erwinia* on them, but none was a permanent carrier.

Fresh bottles and sets were cultured but gave only negative results. Finally, they disassembled a bottle cap aseptically, dropped it into broth, and got growth. University of Virginia microbiologists repeatedly got positive cultures from caps, and this discovery was confirmed under ideal conditions at the CDC's own laboratories in Atlanta.

FDA found that Abbott had made a change in the cap liner material the previous September.

CDC staffers, convinced that the Abbott cap was the villain, worked double shifts, seven days a week, for three weeks. They discovered they could release bacteria into Abbott fluids just by opening the bottles and closing them again in 25% of the instances in which cap liners were contaminated. Further testing showed that bacteria could also be released into the system just by banging the caps, a standard procedure of nurses dealing with the hard-to-open bottles.

Additional reports of trouble with Abbott solutions came from New York Hospital and from St. Joseph's Hospital in Ann Arbor, Michigan. St. Joseph's was the first hospital participating in CDC's regular nosocomial reporting system to come into the picture.

Abbott insisted that it could not be held responsible for contamination that was introduced when caps were banged. The firm had never made sterility claims for its cap liners.

CDC tested the Abbott production process, showing that organisms could enter the bottle system without opening or tapping the bottle cap. The whole bottle, not just the cap liner, could be contaminated by organisms in the water used in the firm's cooling procedures. When the bottles came out of the autoclave and were placed in water to cool, fluorescent dyes placed in the cooling bath were sucked right up into the bottles.

Almost a year after Duma started his work and four and a half months after CDC became involved, enough evidence had accumulated that FDA could force a recall of Abbott solutions. An unknown number of patients had died. Henry Ford Hospital reported eight, and the press nearly wrecked Ford. The *Detroit News* said, cynically, "It is unlikely that any of the eight patients will have septicemia listed as the immediate cause of death."

I haven't had time to develop the full flavor, as "The Blue Sheet" did, but I think that's a fascinating story—a medical detective story. Sometimes we are told equally fascinating detective stories by manufacturers who have been successful in developing a new product that they happen onto almost by chance. But this story deals with practice, with the places we all have been working—our nation's hospitals.

And when you think about it, it's the most damning indictment of pharmacy ever written.

The basic premise of having a pharmacist in the hospital is to make sure that the patient is protected from bad drugs. Physicians and nurses will make sure that patients get drugs, but only the pharmacist undergoes a long educational program, largely at public expense, to learn the components of drug product quality.

What happened here? What happened in American hospitals in 1970 and 1971? Had pharmacists developed quality assurance programs to insure that hospitals *obtained* drugs of suitable quality? Even more importantly, since the manufacturers, the compendia, and the FDA were working towards that end, had the pharmacists established quality control programs to assure that drug products were *handled safely* after entering the hospital?

They had not.

Nowhere in that "Blue Sheet" story is a pharmacist mentioned.

And the result of this abdication of responsibility for drug product quality?

Instead of a program of detecting defective drug products through routine in vitro control procedures, pharmacists left detection of defective products to physicians, whose only test method is death—death, or if they are suspicious soon enough, exacerbated illness of the patient at best.

What kind of a quality control system is that? Why should our patients have to get sicker, even die, in order to show that the drugs we have given them are defective?

The American people are desperately concerned about product quality. They want protection from defective automobiles, hazardous toys, flammable fabrics. They want quality built into a nickel candy bar. Why should we assume they aren't willing to pay for the quality control necessary to protect them from the very drugs they are hoping will make them well?

And would it cost that much more, really? In a study published in the Society's *Journal* in January 1972, Ken Barker reported that almost half—47%—of the time of the pharmacists observed in five hospitals for one week was accounted for by personal pursuits or just plain idleness. This is a sunk cost; the patient is already paying these salaries. Somehow, some way, we have to reach these pharmacists with the message of what it is they are there to do.

But I'm sure I'm like most preachers. Those sinners of omission are not in my congregation tonight. The members of this congregation and your fellow pharmacists back home work hard all day long. There never are enough hours in the day to get all your work caught up. I know. I've been there myself. We are the sinners of commission. We waste our time and our patients' money, not by failing to work conscientiously and hard, but by failing to work at the things that really matter.

How many hours of your day, of your pharmacists' day, are devoted to opening up the manufacturers' drug product packages and destroying the assurance of quality that was built into those packages through the manufacturers' own quality control programs, through the thousands of volunteer manhours devoted to the compendia in establishing quality specifications, through the millions of dollars you and your fellow taxpayers pour into the FDA compliance activities? The elaborate system we have developed to bring the world's highest quality drug products to our practition-

ers is compromised, and perhaps totally destroyed, as we repackage—repackage a drug product of unknown composition and unknown stability when outside the container in which it was tested—repackage it into a container providing an unknown degree of protection. And for what purpose? For financial control! We assume that the patient is willing to pay for our pharmacists' time in assuring that all the charges are properly placed—as a by-product of the act of subdividing larger packages, he won't be charged for doses he doesn't get. But do you really think he would opt for *financial* control over *quality* control if *he* could direct those manhours of pharmacists' time?

Meetings of the various sections of the Pharmaceutical Manufacturers Association are usually held in such watering places as the Greenbrier, Boca Raton, etc., but traditionally the Quality Control Section has one meeting each year in Washington so the USP, NF, and FDA people can attend inexpensively.

One of my friends in the control department of a major manufacturer, who shall remain nameless for obvious reasons, shared a coffee-break with me at the meeting last month. I told him how useful and important I thought it was that they had one of their meetings each year where the compendial and regulatory people could come. "Why not," he said, "you and I and the FDA are all in the same business: protecting the public from my company's products."

I commend that attitude to you as hospital pharmacists.

We are hearing much this week about our responsibilities in selecting and purchasing quality drug products. Certainly, that is a basic responsibility of hospital pharmacists. But just as basic is the pharmacist's responsibility for maintaining that quality after the product enters the hospital medication system.

Your national P&T committee, the USP, is dedicated to helping you in that responsibility. For decades, USP has trended towards standards and tests that can be applied practically only at the manufacturer and regulatory levels. We have no intention of deemphasizing that aspect of USP responsibility, but we do intend to try harder to introduce special procedures which practitioners can apply. The USP is not alone in this concern. The FDA has just awarded USP a $100,000 contract to coordinate a broad-scale approach of all the professional, scientific, and regulatory groups involved with large volume parenteral solutions. ASHP will be represented on this coordinating committee. Individual pharmacists are already involved with other health team workers on USP's own Advisory Panel on Hospital Practices. As Robert Henry says, we aim to assure the quality of i.v. solutions from the manufacturer to the needle point.

To get a broad perspective on hospital pharmacist's problems and to make them more aware of drug quality, we have been proud to participate with the ASHP and the FDA in a pilot study of a Drug Product Defect Reporting Program during the past year. The phenomenal interest of hospital pharmacists in this program prompted *Quality Control Reports*, Mr. Werble's "Gold Sheet," to state that "from the standpoint of the taxpayer, this is probably the lowest-cost nationwide government reporting program in existence." And just last month, the Deputy Director of the FDA Bureau

of Drugs, Dr. J. Richard Crout, said in a speech that the ASHP–USP–FDA Drug Product Defect Reporting Program was one of four major surveillance procedures used by FDA, the others being inplant inspections, premarketing batch certification, and industrywide testing of all brands of specific drug products in the FDA's new automated testing center. Dr. Crout said "that the return rate in terms of useful information per dollar spent is greater in our pharmacist-oriented drug defect reporting system than in any other voluntary reporting program we have in the Bureau of Drugs." Furthermore, FDA was willing to put its stamp of approval on this approach of extending quality control to the practitioner level by giving USP a $68,000 contract just last week, enabling us to offer this reporting system on a pilot basis to community pharmacists and to nurses.

When I talk about quality control, quality assurance, in the hospital, I'm not talking just about some laboratory next to that drug storeroom called "the pharmacy" down there in the basement. Hospital pharmacists have escaped from the basement. The whole hospital is "the pharmacy." The entire hospital medication system has become the pharmacist's responsibility. He has become patient oriented. Patient oriented, but—never forget—drug based. Nurses and physicians and physician's assistants are patient oriented too, and all have a part in the hospital medication system. But only the pharmacist is educated in drug product quality—how drug dosage forms are put together and what takes them apart. Your patients have only you to depend on for assuming the responsibility of providing them that quality assurance.

Back in the innocent days when I was graduated from grade school (grammar school, the city slickers called it), even some of the boys had autograph books. One of my classmates, Bob Gaither, asked me to write something in his. I remember envying Bob two things: he could make beautiful bulges with his biceps and I was just a skinny runt, and his dad had built a shower in their basement. Not many homes in Brighton, Illinois, had running water inside the house, let alone a shower—except when it rained. But Bob's father had built one in. Mr. Gaither was an electrician and handy with tools, but I had never thought of him as an intellectual. I don't know what I wrote in Bob's book, but I don't think I'll ever forget what his dad wrote there on the first page:

With maturity comes responsibility.

I think it's time for us to go home and grow up to assume responsibilities that really count—responsibility for hospital medication systems and community drug dispensing systems that protect our patients from our drugs.

Harvey A. K. Whitney Award Lectures (1950–2005)

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