Dr. Temple reflects on 30 years of improvements

Editor's note: Dr. Temple's article is adapted from his acceptance remarks for the 2005 Drug Information Association Distinguished Career Award.

By Robert J. Temple, M.D.

Career awards are scary. I watched Lewis B. Sheiner, M.D., receive a similar award—the 2004 Oscar B. Hunter Memorial Award in Therapeutics from the American Society for Clinical Pharmacology and Therapeutics.

One of the things he did at the award was show a survival curve of the award winners. A week after that, he died while traveling in Europe. So, none of that's going to happen—I have a better dose of statin than he did.

The DIA award offered a nice opportunity to reflect on what I've been doing for 30-plus years, and the thing you notice most, if you try to think back, is how different everything is. I doubt very many people will remember this, but in 1972 when I came, we at FDA and most people in industry were substantially clueless about how to do a proper randomized trial.

Some people knew—there were people at NIH who were

getting it—but mostly nobody knew much. We at FDA didn't help much. In fact, there was a viewpoint that if we helped someone design a trial, we were co-opted and couldn't properly review it. So people actually told me then that even when they saw a trial wasn't going to be any good and couldn't be used, they would let it go on because it would be wrong to do anything about it. That's ethically doubtful, and now in fact we can put a study like that on hold.

Meetings that we had then with industry were not very constructive and often fairly hostile. But things began to change a lot, which I think started with the arrival in 1973 of **J. Richard Crout, M.D.,** as director of the Bureau of Drugs, as the Center was known then. Dr. Crout, who served until 1982, was an academic and used to civilized discourse. He and **Marion Finkel, M.D.,** who directed what would now be called the Office of New Drugs, started massive changes: guidance documents were developed, we had advisory committees and things began to change.

For me, a major experience was participating in the Drug Efficacy Study Implementation. That was the program we conducted because we were obliged to review all the drugs we'd approved between 1938 and 1962 on the basis of safety only, to see if they worked.

We put out hundreds of reviews and Federal Register notices describing in enormous detail what was wrong with all the studies that had been submitted. It was a variety of incompetency experience—you learned all ways you could screw up a study. It was just fascinating. I was the final sign-off on most of those, so I got to see all of them. Nobody else can have that experience anymore, so that's too bad.

In 1972, we had maybe six or seven biostatisticians. Except for **Chuck Anello, Ph.D.,** and **Bob O'Neill, Ph.D.,** who is still here, most of them would be unrecognizable as statisticians. They were passionate about ethics and things like that, but they didn't know much about numbers.

Here are a few examples just to illustrate what we did. When cimetidine, the first H-2 antagonist came along—a very important drug—they did four studies of ulcer healing: two 2-week studies, a 4-week study and a 6-week study. As each patient completed the two weeks, four weeks or six weeks, they added up the score and calculated the P. As soon as the P value was less than 0.05, they stopped.

A novel, interesting approach—we didn't know. We wouldn't have even known that was not right. Nobody had ever thought about that before. The 2-week studies worked out for them, but the 4- and 6-week studies turned out a couple more cases came in after they crossed the 0.05 and it took them above. So their initial labeling never mentioned the 4- and 6-week studies. Obviously, nobody behaves that way now.

Around the same time, we got to review the Anturane Reinfarction Trial, a claim for sulfinpyrazone to prevent sudden death and reinfarction. We discovered at the end of the study six people who died on the active drug had been removed from the study because they really weren't qualified to be in the study. Of course, they did finish the study, in a sense.

Another major claim out of that study involved cause-specific mortality: sudden death versus heart attack death versus other death—and it was an entirely bogus procedure. So we had no idea about any of those things: that cause-specific mortality is treacherous, that you have to account for every patient, all of those things. Well, we've been learning them ever since.

We know about multiplicity, we're thinking about group sequential approaches and adapted designs and dose-response and non-inferiority studies—a very big deal, which actually I first raised at a DIA meeting in 1980. First time we actually thought about it much. Anyway, we didn't know any of those things when I first got there.

Safety reviews now (we all do an integrated summary of safety)—that concept was invisible prior to about 1980. I don't quite know what we did; I mean how else could you look at safety except to accumulate the data. But it was never discussed.

Actually, in a DIA paper for a meeting, I reviewed the history of that. Nobody thought about that before. We didn't focus on deaths and drop-outs, we didn't know that was important, all of those things.

So watching it change has been extraordinary. And probably the single thing about working in FDA that I notice most is the constant diverse input: you're doing legal thinking one day (not acting as a lawyer of course, that would be wrong), you're thinking about study design, you're negotiating. The infinite number of challenges; it's like a board game where people keep coming at you.

As anyone who reads the papers will notice, this is a tough time for FDA. People, including some internal people, are saying bad things about us, none of which I believe are true. It's interesting that when I arrived in 1972, the same thing was going on. There were stories in the newspapers about how devoted, loyal reviewers were being overruled by their cynical, sold-out managers. Really, the same thing; there were very, very unpleasant hearings before the Kennedy committee, they were very difficult. A review of the experience on the whole said that most of the charges were wrong.

But when I came, I had no idea what the reality was going to be. I had my own views of government agencies and they weren't entirely flattering. So I had no idea.

What I found, and what I believe is still true, is that the place was and is devoted to getting the right answer, it's perfectly comfortable with internal disagreement—celebrates it, in fact. It's been a wonderful place to work, and I've loved it all.

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