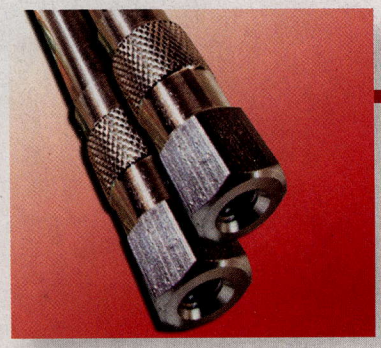

LC TROUBLESHOOTING

Past, Present, and Future — 30 Years of LC Troubleshooting

What's happened in the last 30 years? What will happen next?

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LC Troubleshooting Editor

October is my anniversary month with *LCGC* — it was October of 1983 (1) when I wrote my first "LC Troubleshooting" column. That's 30 years ago and, if my count is correct, 342 columns later. Whew! The only person associated with *LCGC* that's been around longer is my good friend and colleague, Ron Majors (editor of "Column Watch"), who started several months before I did. But I wasn't the first editor of "LC Troubleshooting" — that honor goes to Dennis Runser, who wrote the first few installments. I started by sharing the editing duties with Vern Berry, who went on to write meeting reviews for *LCGC,* and I took over sole proprietorship of "LC Troubleshooting" in July 1984. Of course, I've had guest authors from time to time as well as many coauthors. One joke in our laboratory was that if you really messed up you could get a by-line in "LC Troubleshooting." Indeed, practical problems in our laboratory and yours have been the mainstay of this column. I've never rerun a column, but this month I'm going to steal part of the title from March of 1992 (2). I do repeat themes occasionally, and I'll do that this month with a look at liquid chromatography (LC) in the past, what it has become today, and where I think it is going in the future.

Each year at the spring meeting of the Minnesota Chromatography Forum (MCF), Daron Decker of Agilent and I facilitate a special topics discussion related to gas chromatography (GC) and LC in a rather light-hearted competition between the two techniques. As we were preparing this year, it occurred to me that this is the 110th anniversary of the discovery of chromatography by Mikhail Tswett and I remembered that I had given the keynote address at the MCF meeting in 2003 on the topic of the centennial of chromatography. As I reviewed that talk, I discovered a gold mine of predictions that I had made over the years. I'd like to share some of those topics in this month's "LC Troubleshooting."

1992 — Into the 10th Year

In March of 1992, *LCGC* was starting its 10th year and had transitioned from its original title of just *LC* and expanded to *LC-GC* to include gas chromatography topics. In my "LC Troubleshooting" column (2) I listed the top five LC-related problems from the 1980s, as shown in Table I. Let's look briefly at these.

Air Bubbles

Air bubbles in the pump and detector were the nemesis of chromatographers in the 1970s and 1980s, usually showing up in the number one spot in surveys of LC-related problems. By 1992, we understood that mobile phases needed to be degassed, and nearly all users were degassing either by off-line vacuum degassing or helium sparging. Some LC systems were equipped with helium sparging units that continuously degassed the mobile phase. As a result of these changes, air bubbles were declining as a complaint by routine users.

Celebrating 30 Years

The editors congratulate John Dolan on 30 years of "LC Troubleshooting" columns in *LCGC*. The work of laboratory scientists around the world has been made easier because of your advice. See our tribute on page 840.

Table I: The 1980s	
Top problems	Air bubbles
	Pump seals
	Detector lamps
	Column lifetime
	Fittings problems
Predictions for 2002	Replacement components
	Built-in diagnostics
	Remote servicing
	Push-button experts

Pump Seals

There was a time in the 1970s when changing pump seals was a regular task in the laboratory — a seal change every few weeks was common. When we learned that a primary cause of pump seal wear was buffer deposits in the pump, the problem was addressed by cleaning buffers from the LC system before shut-down. As a result, pump seals were lasting much longer by 1992. And I said back then (2), "In fact, some manufacturers guarantee that their seals will last at least a year."

Detector Lamps

In the 1970s and early 1980s, if your UV detector lamp lasted 500 h, you felt like you had received your money's worth from the lamp. By the 1990s, detector manufacturers had added lamp-warm-up features, so short lamp lifetimes because of thermal shock were less of a problem. Additionally, lamp manufacturing techniques resulted in lamps that didn't leak deuterium out or oxygen in, even when they were sitting in the stockroom. Lamp lifetimes of 1000 h or more were common by 1992.

Column Lifetime

Column packing technology is a combination of a technical understanding of the column packing process and skills developed over years of packing experience. By the late 1980s, columns packed with 5-µm diameter (d_p), spherical particles were the workhorses of the routine LC method. Packing techniques had developed to the point that physically stable column beds were the norm, so you didn't have to open the end of the column and fill a void on a regular basis. Column-to-column reproducibility had improved, but was not very good by today's standards. We had learned that adding a small molecular weight base, such as triethylamine to the mobile phase could help to reduce peak tailing for basic analytes and minimize column-to-column differences in selectivity. In spite of these advances, column failure was a regular problem.

Fittings Problems

Before the advent of finger-tightened fittings made of polyetherether ketone (PEEK), we relied on stainless steel fittings. These were less convenient to use, and because column endfitting designs varied from one manufacturer to another, to get the best performance, it was necessary to have a specially constructed adaptor for each column brand. By 1992, finger-tightened PEEK fittings had been introduced, but were not widely accepted, as indicated by one statement (2), "Traditional stainless steel tubing and fittings are still the workhorses of LC, but plastic materials have made life much easier."

2002 — 10 Years Later

In 2002, I wrote another column (3) as *LCGC* entered its 20th year. First, I reviewed the problems discussed earlier (Table I). Air bubble problems were now a minor issue. Nearly everyone understood the need to degas the mobile phase, and vacuum in-line degassers were now offered on many of the new LC systems. Today, nearly all LC systems are purchased with an in-line degasser as standard equipment, so it is comforting to know that the number one problem in the early days of LC has been reduced to a nonproblem. Similarly, improvements in pump-seal technology, smoother pistons, and changes in pump design have made pump seals a nonproblem. By 2002, pump seal servicing had been relegated to annual maintenance in most laboratories. I still recommend that you change the seals at least once a year, but you could probably go longer if you wait for them to fail.

Perhaps the biggest change between 1992 and 2002 was in column technology. The type-B, high-purity silica columns were introduced in the early 1990s and were the standard for nearly all new columns by 2002. Type-B silica improved performance by reducing the metal content of the silica and stabilizing the distribution of the silanol groups on the surface. This, in turn, resulted in less peak tailing for bases, more stable columns, and better column-to-column reproducibility. It was no longer necessary to use chemical additives such as triethylamine to minimize tailing. Additionally, by 2002, 3- and 3.5-µm d_p particles had been introduced, providing faster and higher efficiency separations. Embedded polar bonded phases and "aqueous" phases were available from some manufacturers, giving new selectivity as well as the ability to use 100% aqueous mobile phases without column dewetting. In terms of fittings, PEEK tubing and fittings were commonly used in most laboratories — their convenience had quickly displaced stainless steel parts, particularly between the injector and column and between the column and detector.

How about the predictions from 1992 listed in Table I? I had predicted that modular replacement components such as snap-in pump heads would be common. Wrong! Instead, I think that better component design resulted in parts that lasted longer, so servicing was required less often. This meant that faster replacement of parts had marginal payback. I also predicted that most systems would have built-in diagnostic capability. By 2002, this was becoming a common feature in LC equipment, and today we see it as a standard part of the system. For example, many LC systems today perform a detector calibration check when the power is turned on. Also, extensive electronic testing is done during power-up. Many systems have counters to determine the number of injections made, the number of piston strokes over time, and the number of liters of solvent pumped. Each of these and other automated tests can help to predict when service should be performed to avoid system failure. This is a huge advance over the years, and is especially important as the LC system is just another analytical tool in the lab and specific troubleshooting skills are less common with routine operators.

Remote servicing of instruments via some sort of on-line diagnostic connection was another of my predictions in 1992. By 2002, this was not an option on most

Table II: 2002 predictions	
Detectors	LC–MS as common as DAD
	LC–MS for non-skilled users
Autosamplers	Faster cycle time
	Carryover reduction
Columns	Automatic lifetime tracking
	Something unexpected
Remote diagnostics	Routine application

systems. Today things have improved a bit, but I don't see widespread use of LC systems connected through the internet to factory-based technical support for diagnostic purposes. This is a bit puzzling, since I can push a button on my washing machine, hold my mobile phone next to the button, and send error codes to the manufacturer. I also had predicted that LC systems would have expert systems included as a standard feature to help diagnose problems. By 2002 there had been a little progress on this, but today, we have many tools at our disposal. The built-in diagnostics mentioned above have filled part of this need. In addition, computer-based service manuals allow the use of video clips to help instruct users how to perform certain service tasks, such as how to change a pump seal. And, of course, the internet now has nearly unlimited capability of accessing helpful information, whether it be manufacturers' web sites, on-line discussion groups such as ChromForum.org, or YouTube videos.

How did I do with my predictions? In 1992, I gave myself a generous 25% success rate (don't quit your day job, John . . .), and today that may have improved to 35%, so I'm not moving to Las Vegas. I also made a few predictions for 2002 that are listed in Table II.

2013 — 30 Years of LC Troubleshooting

Somehow I missed doing a 10-year review in March of 2012, so I'll do an 11 1/2–year review now. How did I do on those predictions of Table II?

Detectors

By 2002, mass spectrometry (MS) detectors were widely used in certain laboratories, such as those in the pharmaceutical industry studying drug metabolism. These were mainly tandem, or triple-quadrupole, MS-MS units, with price tags in the $300,000 range. The reliability was quite high and they could be operated by a competent technician, although it took a more experienced person to service the instrument. I predicted that LC–MS and LC–MS-MS systems would be as common as diode-array (DAD) UV detectors by 2012 and could be operated by anyone in the laboratory. We're not quite there yet, but considerable progress has been made. With continual price reductions, especially with single-quadrupole systems, plus improved reliability and simplicity, LC–MS systems are becoming more and more a part of the routine analytical laboratory. Many larger companies have "walk-up" LC–MS systems, where a user can put "any" sample

on the sample tray, run a generic separation, and get MS-based results. My guess is that we may be 25% of the way to the prediction, and I'll hold this one over for 2023, because I still think that LC–MS and LC–MS-MS will become the go-to approaches in the future.

Autosamplers

In 2002, autosamplers were mostly used for methods with run times of 10–20 min or more, so a preinjection cycle time of 1 min or more was adequate. As run times were getting shorter, I predicted a need for shorter autosampler cycle times, or these times would result in significant slowing of the method. At that time our laboratory had just installed several of the latest design autosamplers with 15 s cycle times that were necessary to support short LC–MS runs of 5–10 min. Over the past 10 years, more and more autosamplers have incorporated shorter cycle times — much of this has been driven by the wider use of LC–MS as well as ultrahigh-pressure liquid chromatography (UHPLC) methods with short run times. Today some manufacturers offer units with ≈10 s cycle times, and I predict that these times will drop even lower as method run times are reduced over the next 10 years. I also predicted that improved autosampler design would result in lower carryover. I'm not sure if we're where we should be on this today, but the ability to wash the outside as well as the inside of the injection needle is a common feature of autosamplers. Also, it is common to see the capability of using more than one autosampler wash solvent. Some carryover problems are not the fault of the autosampler, but are due to the selection of components that are inert to the analyte of concern and conditions that minimize carryover. I think we've achieved at least 50% of the prediction for autosamplers.

Columns

In 2002, some manufacturers had introduced "smart tags" that were attached to columns that allowed the LC system diagnostics to detect the presence of a particular column and thus track its usage. I predicted that this would become standard practice in the industry. However, although this system is used in some cases, I do not see widespread use of automatic column tracking. I get no points on this prediction.

The other column-related prediction was that something was going to happen that I didn't even expect. This was true in 2002, where I had not predicted the widespread use of 3- or 3.5-µm d_p columns or type-B silica. Similarly, this time I missed the advent of sub-2-µm columns used for UHPLC and the resurgence of superficially porous particles. I hedged my bets by saying that something would happen in column technology that would catch me by surprise. True, but I really can't get much credit for predicting what would happen. What's going to happen in the next 10 years? Ron Majors' recent "Column Watch" (4) gave predictions from experts in LC about what is going to happen. My personal bias is that we're going to settle on 2–3 µm d_p superficially porous particle columns as the standard. This is because it is possible to achieve 2-µm d_p efficiency with 3-µm d_p back pressure with these particles, plus, from a practical standpoint, 2-µm porosity frits are used to hold the particles in the column so that column blockage is minimized. I also think that the expiration of the patents on silica monolith columns will mean competitive advances in this field. Whether or not these lead to practical improvements is hard to predict, but I do think we'll see something new and exciting in the monolith area in the next 10 years.

Remote Diagnostics

I'm not sure if any progress has been made in this area from a practical standpoint in the last 10 years, but I'm going to keep it on my list for the next decade. If my credit card company can call me to question a purchase that is out of my buying pattern or my washing machine can send diagnostics to a service technician, why can't my LC system do just as well? Each system has internal diagnostics to track routine operation. When a problem or potential problem is encountered, often the user is notified. The user should be able to easily connect the LC system to a remote service site to get additional help to correct a problem. At the same time, the manufacturers could gather failure data to help improve instrument design. Maybe I'm just dreaming.

So, Where Are We?

Over the last 30 years, I've seen LC change from concentration on the LC system to the results of analysis. In the early years, poor reliability and instrument design meant that every successful user was also a skilled troubleshooter and repair technician. As instrumentation and column technology has improved over the years, in many ways LC has become a mature technique. Improvements in hardware and columns have made for reliable systems that can be depended upon to produce consistent, dependable results by laboratory workers with other interests than chromatography. The questions I receive today usually are related to separation problems, not instrumentation. This is a symptom of the reliability of the hardware. But it also reminds us that chromatography is all about separation chemistry — the hardware is just a tool to help get us there. The challenge, as it has been since the days of Mikhail Tswett, is to find the right combination of mobile phase and stationary phase to adequately separate two or more analytes.

My predictions over the years have not been very good. I completely missed the introduction and wide acceptance of UHPLC, sub-2-µm d_p columns, and the practical use of superficially porous particles. One prediction that I can make with a great deal of certainty is that it is very unlikely that I will still be writing "LC Troubleshooting" when chromatography celebrates its 120th birthday. I'll leave my successor to assess the situation in 2023.

References

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(3) J.W. Dolan, *LCGC* **20**(3), 268–275 (2002).

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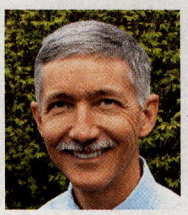

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