EDITORIAL

James V. Felicetta, MD, *Editor-in-Chief*

A Generation of Progress in Endocrinology, Especially Cardiovascular Endocrinology

This year we're going to focus on the phenomenal progress that the medical community has made in the 30 years of Federal Practitioner's *existence. Each month we'll feature an editorial written by one of our Editorial Advisory Association members, reminding us how much has changed in their particular medical field over the past 30 years. It should be a really exciting set of editorials this year. I'm going to get the ball rolling by summing up progress in my own field of endocrinology.*

So much has happened in the field of endocrinology over the past 30 years that it is truly a challenge to know where to begin. Since I fancy myself a cardiovascular endocrinologist who uses endocrine principles to reduce cardiovascular disease, I'll focus primarily on 3 related areas: diabetes, dyslipidemia, and hypertension.

The prevalence of type 2 diabetes has more than quadrupled over the past 30 years, primarily due to the massive epidemic of obesity and insulin resistance that has occurred in all Western nations. The culprits are legion and well known: decreased exercise; increased leisure time spent in sedentary activities, such as watching television, playing video games, or surfing the net; increased portion sizes, both at home and when eating out; and a probable effect of the widespread use of corn syrup in processed foods, which dates back to around 1980.

But the good news is that the therapeutic armamentarium we have to fight back with has improved dramatically over the past generation. In the early 1980s, we had only a single class of oral agents, the sulfonylureas, and a variety of animal insulin preparations derived from either pigs or cattle. There were not only intermittent supply problems related to the fluctuating supply of beef and pig pancreases, but also occasional problems with allergies and with lipodystrophies related to these nonhuman insulin preparations.

We now have highly purified human insulin preparations, such that issues of lypodystrophy and of insulin allergy are largely relics of the past. And we have a phenomenal panoply of other medications to help us lower blood sugar levels. The sulfonylureas remain a viable therapeutic option, but they have now been joined by biguanides (metformin), thiazolidinediones (glitazones), meglitinides, dipeptidyl peptidase-4 inhibitors, glucagon-like peptide-1 agonists (exenatide, liraglutide), alpha-glucosidase inhibitors, synthetic amylin, and bromocriptine mesylate, a sustained-release bromocriptine. There are many other very promising classes of antidiabetic medications in the pipeline, including sodium-glucose cotransporter 2 inhibitors, which increase renal excretion of glucose, glucagon antagonists, glucokinase activators, and dual peroxisome proliferator-activated receptor agonists. But while we have many more options in our therapeutic toolbox, controlling blood sugars can remain a daunting challenge.

Fortunately, our monitoring tools have also dramatically improved over the last generation. Thirty years ago insulin pumps were strictly experimental, with an occasional disaster when a "runaway pump" delivered too much insulin and produced severe hypoglycemia. Today we have highly sophisticated and reliable insulin pumps, some even wireless and controlled with a small device the size of a cell phone. We also have continuous glucose-monitoring systems for those interested in following their blood sugar fluctuations in real time.

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The progress in the treatment of dyslipidemia has been equally breathtaking over the past generation. In the early 1980s, our only therapeutic options were niacin and bile-acid sequestrants; the former caused nasty flushing, and the latter was an awful powder that often produced severe abdominal bloating and constipation. We were briefly infatuated with a drug called probucol, but it fell rapidly from favor when it was shown to decrease high-density lipoprotein cholesterol (HDL-C). That probably shouldn't have been the kiss of death for it, but it was more than enough

back then to polish off the product.

Then along came the statins in the early 1990s, and it was strictly Katie bar the door. We had a true revolution in lipid management on our hands. There was a lot of skepticism at first, and there were some concerns that statins might cause central nervous system dysfunction or maybe even cancer. But then the big studies were published, such as 4S (Scandinavian Simvastatin Survival Study), CARE (Cholesterol and Recurrent Events), AFCAPS/TexCAPS (Air Force/Texas Coronary Atherosclerosis Prevention Study), and many others, all of which demonstrated dramatic reductions (25%-30%) in hard events such as myocardial infarction, strokes, and cardiovascular deaths, both in primary and secondary prevention settings. This was truly a medical revolution, and before long, statins had become very, very mainstream, contributing mightily to the ongoing nationwide decline in the number of heart attacks and strokes.

For a time it looked as though the fibrates, such as gemfibrizil but more especially fenofibrate, might achieve a comparable standing as highly effective lipid-lowering agents. Unfortunately, a number of recent negative studies, including the FIELD (Fenofibrate Intervention and Event Lowering in Diabetes) study and the lipid arm of ACCORD (Action to Control Cardiovascular Risk in Diabetes) trial, have raised significant concerns as to their true efficacy. My old favorite, niacin, was dealt a body blow by the prematurely terminated (and poorly-run) AIM-HIGH (Atherothrombosis Intervention in Metabolic Syndrome With Low HDL/High Triglycerides: Impact on Global Health Outcomes) Trial. And the recent abrupt termination of the HPS2-THRIVE (Treatment of HDL to Reduce the Incidence of Vascular Events) study may well be the final nail in niacin's coffin. In the meantime, some other exciting drugs are showing tremendous promise, especially the PCSK9 inhibitors, which work to block a critical enzyme that metabolizes low-density lipoprotein cholesterol (LDL-C) receptors on the hepatocytes, thus increasing the density of LDL-C receptors as they work to pull LDL-C out of the bloodstream.

Finally, no discussion of cardiovascular endocrinology would be complete without mentioning the tremendous progress that has been made in the field of hypertension (HTN) detection and management. Better control of blood pressure has contributed mightily to the reduced rate of cardiovascular events that have been seen over the last generation in the U.S. In the early 1980s, we had only a limited number of useful medications available in our therapeutic arsenal. The 2 mainstays were the thiazide diuretics and the beta blockers, although we also had some less well-tolerated drugs, including hydralazine, reserpine, alpha-methyldopa, and guanethidine. The first angiotensin-converting enzyme (ACE) inhibitor, captopril, came on the market in 1981, but it was initially indicated only for the treatment of renal disease. The first calcium channel blockers (CCBs), nifidipine and diltiazem, also became available at about the same time, but neither was indicated for the treatment of HTN; they were to be prescribed only as antianginal agents in patients whose angina was refractory to older treatments such as nitrates and beta-blockers.

It was actually not until the late 1980s that both ACE inhibitors and CCBs gained widespread acceptance as effective antihypertensive agents in routine patients with essential HTN. In the mid-1990s, these agents were joined by the angiotensin-receptor blockers (ARBs), which generally have a cleaner adverse effect profile than that of the ACE inhibitors, particularly in that the dreaded angioneurotic edema occurs rarely with ARBs. The availability of these well-tolerated agents has significantly increased the fraction of the hypertensive population that is under control with medications, although much work remains to be done in this area.

I've just scratched the surface, but take my word for it, we've made phenomenal advances in our efforts to control blood sugar, dyslipidemias, and HTN over the past generation. There's also been good progress in other areas of endocrinology, although thyroid, adrenal, and pituitary disease management haven't moved forward as dramatically over the past 30 years. One exception that stands out, though, has been the management of osteoporosis, which has gone from the Stone Age into the modern era with the development of several major therapeutic classes, especially the bisphosphonates, which were represented only by the weak agent, etidronate, 30 years ago. The next 30 years will very probably prove to be even more exciting in terms of endocrine progress than the preceding 30 years. ●

Author disclosures

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