Personal and Historical Perspectives

Chlorothiazide
How the Thiazides Evolved as Antihypertensive Therapy
Karl H. Beyer

Today, the opportunity to pause and reflect on our participation in the development of the therapy of hypertensive cardiovascular disease is most welcome, even timely, as we look ahead. It has been 35 years since chlorothiazide was put into clinical trial. Fifty years ago, I graduated from the stimulating MD and PhD program at the University of Wisconsin Medical and Graduate Schools with some knowledge of what to do in medicine that would be worthwhile and how to do it. Thirty years of learning and doing—first at Sharp & Dohme, then the combined Merck Sharp & Dohme Research Laboratories, before 20 more years mostly in research and teaching as a Visiting Professor at The Milton S. Hershey Medical Center of The Pennsylvania State University School of Medicine, Hershey, Pa—have left little time to look back for looking forward, unless invited to do so. This is about chlorothiazide, how the thiazides evolved, and how they were expected to relate to edema and hypertension.

Saluretics: Concepts and Methodology
My Wisconsin training helped create a capability to identify clinical correlates of a “disease” with a best relevant expression of that function for manipulation in a most appropriate laboratory animal. Discovery of the thiazides was a second example of this from our research. The first example was the competitive inhibition of penicillin renal tubular secretion by first p-aminohippurate then ultimately probenecid (Benemid).1,2 By the time the probenecid work was completed, our renal clearance capability was well developed. We had started getting control of the fast-moving changes in electrolyte blood and urine chemistry, which we had to do precisely in order to use the clearance technique and concepts of how the kidney related to salt and water balance to assess diuretics. That took a while.

Clinical Correlates
So far as I was concerned in the 1940s, the concentrations of Na+, K+, Cl−, and HCO3− in extracellular-extravascular fluid, plasma water, and glomerular ultrafiltrate were conveniently close to being the same. Consequently, an alteration (inhibition) of reabsorption of equivalent Na+ and Cl− ions as the glomerular ultrafiltrate passed along the lumen of the tube would seem likely to increase water excretion on an osmotic basis without seriously perturbing electrolyte balance. To make it perfectly clear what we wanted, I referred to our hypothetical compound as a saluretic agent. It had to be diuretic but only if there was sufficient salt and water retention to create edema. It had to be antihypertensive if you disregarded some distinguished names in the field and held to the meticulous rice diet data Kempner published3 as really relating to a low-salt diet. It could be a saluretic carbonic anhydrase inhibitor if you took into consideration differences in rates of reabsorption of chloride and bicarbonate along the renal tube, not just how potent a carbonic anhydrase inhibitor it was.

Mecamylamine: Our First Antihypertensive Agent
Let’s pause in the elegantly rational (we thought) saluretic approach to antihypertensive therapy to mention our first-marketed antihypertensive agent, mecamylamine (Inversine). Mecamylamine set the stage for our company-wide familiarity with hypertension when chlorothiazide came along.

My associates of more than 30 years may recall my rumination about how to work “beyond the limits of knowledge,” which is quite different from working in the lab with clinical correlates, as mentioned previously. Our approach to working beyond the limits of knowledge was so simple I coined another term to make it more acceptable. I set up a large laboratory with several well-trained and discerning technicians who did assays of specific pharmacological effects. Many compounds were subjected to these assays, sometimes for no better reason than that a chemist thought the results on his compounds might be interesting. Sometimes we got compounds made for us, the biologists, for no better reason. I called that lab our “Pharmacometric Unit.” The term “screening unit” seemed to me an affront to the technical people working there. Pharmacometric research seemed more purposeful than screening.

One day shortly after the merger of Sharp & Dohme with Merck, Dr Karl Pfister, one of the “Merck Chemists” whom I knew from the Gordon Research Conferences, called to ask if we would like to look at some isocamphanes of his associates that he thought might be vasoconstrictors like arylalkylamines (sympathomimetic amines). Their structure was interesting. I offered to have a few compounds examined in the Pharmacometric Unit, and so they were submitted for testing. Shortly thereafter when I stopped by the Pharmacometric Unit on my way to lunch, Dr Clement Stone, who was in charge of the unit at the time, asked me to look at a

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blood pressure tracing on one of Pfister's compounds. Clem was right; this compound was a ganglionic blocking agent. More importantly, it was a secondary methylenamine, a 3-methylaminoisocamphan. It was not a quaternary ammonium compound like all antihypertensive ganglionic blocking agents known to us. The quaternary compounds were potent antihypertensive agents, but the drugs were notoriously poorly and erratically absorbed when administered orally.

At that time, we did not have the capability to get chemical methods quickly to check oral absorption just by asking for them. So I asked Clem to give a couple of Pfister's samples and two or three well-known quaternary ganglionic blocking drugs to Sam McKinney for acute oral and parenteral LD₅₀ values. (Sam could use mice for such a purpose with the precision of an analytic chemist.) I went off to a Fall physiology meeting at Madison to listen to a symposium on the optimal intramolecular distances between polar groups of quaternary ammonium ganglionic blockers and to decide what to do with our much more interesting aminoisocamphanes.

When I returned to the lab, the LD₅₀ data told us our compounds were well absorbed, whereas the marketed quaternary drugs were not. (The ratio of oral to parenteral LD₅₀ data for the isocamphanes was considerably less than for the quaternary compounds.) With all that information (from Clem's Pharmacometric Unit and Sam's LD₅₀ data), I decided to recommend to Corporate Management that we market the first compound we had tested, if it stood up to safety assessment and clinical trials. I think I made it clear that ganglionic blocking agents were a terrible way to treat hypertensive patients, but they worked. Our compounds were novel and they were well absorbed, given orally. Moreover, our marketing and sales people would know what to do with it. We called this the saluretic agent we wanted, our marketing and sales force to meet people active in the field. Then, when we found the saluretic agent we wanted, our marketing and sales people would know what to do with it. We called this compound, our first antihypertensive drug, mecamylamine (Inversine). I think we sold more Inversine in England, where the quaternary antihypertensive drugs evolved were identified with Dr Everett M. Schultz. Drs M.S. Glitzer, Sanford L. Steelman, and George M. Fanelli were key biologists in the amiloride research.

Depending on how one chose to read and interpret an important publication by Schwartz in 1949 that derived from Pitts' earlier research on urine acidification that involved the use of sulfanilamide, one might conclude that the use of sulfanilamide as a natriuretic-diuretic agent in cardiac-decompensated patients was either the wrong way to go, because it was a carbonic anhydrase inhibitor, or that where a carbonic anhydrase inhibitor principally worked in the kidney would be more important than potency of its enzymatic activity. Such a compound had to be predominantly natriuretic and chloruretic, if a proper anion:cation balance was to prevail systemically. Sulfanilamide was not such a compound. It increased sodium and bicarbonate excretion, causing a chloremic metabolic acidosis.

On exploring a number of key compounds submitted by the chemists, we found a simple p-carboxybenzenesulfonamide to be both natriuretic and chloruretic in dogs. This saluresis was confirmed in a few hypertensive patients for us by Crossley, Rowe, and Crompton (personal communication). The compound served that crucial purpose. Now, greater activity was needed. The second crucial step was finding that two sulfamoyl groups meta to each other were better than one. The third major step was the closure between adjacent sulfamoyl and amino groups on the benzene ring to give the benzothiadiazine heterocyclic nucleus. We called these compounds by the shorter name, thiazides.

Chlorothiazide: Preclinical

Back to saluretics. We had two attractive leads and two teams of chemists working on them in Dr. James M. Sprague's Department of Medicinal Chemistry: (1) sulfonamides, carbonic anhydrase inhibitors, and (2) compounds that inhibited sulfhydryl catalyzed systems, nonmercurial diuretics. Both leads gave us useful diuretics: chlorothiazide and ethacrynic acid. Chemists who were prominent in the sulfonamide work were identified with Dr. Frederick C. Novello. The chemists responsible for the effort from which ethacrynic acid evolved were identified with Dr. Everett M. Schultz. Dr. Edward J. Cracoe was a participant in both programs and was responsible later for the team effort from which amiloride evolved. Key biologists for the Renal Program included Dr. John E. Baer, my alternate and supervisor of our analytic chemistry; Horace F. Russo, who with his assistants performed the (mostly) renal clearance studies in trained dogs; and Dr. L. Sherman Watson, physiologist, who related to the animal work. Drs. M.S. Glitzer, Sanford L. Steelman, and George M. Fanelli were key biologists in the amiloride research.

For instance, a serious hazard was whether we should check out the antihypertensive effect of these thiazides in hypertensive rats before taking chlorothiazide to the clinic. We had some previous experience with hypertensive rats. I made it clear that nobody was to put one of these compounds in a hypertensive animal, at least not until it had been given to hypertensive human beings. If chlorothiazide was not hypertensive in rats, who would want to test it in hypertensive patients besides us? Years later, we studied the relation of the structure of benzothiadiazines to salt excretion (or retention) and antihypertensive effect in spontaneously hypertensive rats.
We did the right thing by waiting for a trial of chlorothiazide in hypertensive patients.

**Chlorothiazide: Clinical**

Instead, the strategy was to get the compound studied in edema, establish the fact that it worked and was safe clinically, and then find a friend or two or three who would carefully give chlorothiazide to a few hypertensive patients and see what happened. This was the task of a young medical associate of ours, Dr William (Bill) Wilkinson, who did his part very well.

By good fortune, the first clinicians simply added chlorothiazide to their patients’ ongoing antihypertensive therapy. The combined antihypertensive effect was dramatic. The other exploratory studies in hypertensive patients were exciting too. Names of these clinical investigators who first published preliminary notes on chlorothiazide in hypertensive patients in 1957 and who come to mind include Freis and Wilson; Hollander and Wilkins; and Moyer, Ford, and Spurr.

The effect of their pilot chlorothiazide studies that were soon followed by the work of Laragh et al., Dollery et al., and many others was explosive. An avalanche of publications attesting to the efficacy and safety of chlorothiazide (Diuril) evoked a chemical effort in the worldwide pharmaceutical industry that could not be kept up with. Every company seemed to want its very own patentable thiazide. What we wanted could not be kept up with. Every company seemed to do with their antihypertensive action? Briefly, only the thiazides that bear a free sulfamoyl group are both diuretic and antihypertensive; that is, unless it was conceivable that the appropriate cells of organs having different primary functions (kidneys and arterial vessels) might relate similarly to modulation of their sodium balance. Thus, in the presence of salt and water accumulation, edema, our thiazide ought to cause a diuresis secondary to induced saluresis. The antihypertensive effect might follow a drug-induced shift in arterial wall extracellular/intracellular sodium balance to which a renal reduction of salt-retention hypervolemia should contribute favorably.

That simplistic point of view was good enough to rationalize at the time what we intended to accomplish, why we thought it could be done, and how we went about it. Later, we called this approach to new therapy “Designed Discovery.” It was an exciting, rewarding way to work.

**Thiazides: Some General Considerations**

In our spare time, and with the support of publications by other investigators, we undertook to answer such questions as: What has carbonic anhydrase inhibition to do with the saluretic action of thiazides? How does one account for the tremendous dosage range of these compounds? What does their diuretic effect have to do with their antihypertensive action? Briefly, only the thiazides that bear a free sulfamoyl group are both carbonic anhydrase inhibitors and saluretic. A seeming dissociation of the two attributes was that 7-N-acetylchlorothiazide administration induced saluresis. What appeared to be a dissociation of saluresis from carbonic anhydrase inhibition by that compound was resolved when Duggan found that the N-acetyl group was deacylated in the kidney to yield the carbonic anhydrase inhibitor chlorothiazide. It was chlorothiazide that accumulated in the kidney sufficiently to induce saluresis. If probenecid was started before the same hydrochlorothiazide infusion was initiated, there was no thiazide-induced increase in salt excretion; its accumulation in tubule cells was blocked. Under these same probenecid conditions, except when the thiazide plasma concentration was increased equivalent to complete carbonic anhydrase inhibition (in vitro), its physical diffusion into and equilibrium in the cells of the proximal tubules resulted in a saluresis equivalent to that when no probenecid was used. The 1000-fold increase in natriuretic activity from chlorothiazide < hydrochlorothiazide < trichlorothiazide < cyclophenothiazide was directly related to their lipid solubility, which influenced their sequestration in the cells. Increased plasma protein binding correlated with lipid solubility so that their clearances ranged from greater to less glomerular filtration rate progressively. When probenecid was used to block tubular secretion and their renal clearances were corrected for binding, their clearance ratios to glomerular filtration rate approached 1.0, indicating tubular secretion of the compounds in addition to their glomerular ultrafiltration. The corresponding carbonic anhydrase inhibitory activity of the compounds increased only 10-fold and in the same order.

Back when whether lowering hypertensive blood pressure was good for you was as subject to debate as to discussion, it hardly seemed worth considering how a drug could be both diuretic and antihypertensive; that is, unless it was conceivable that the appropriate cells of organs having different primary functions (kidneys and arterial vessels) might relate similarly to modulation of their sodium balance. Thus, in the presence of salt and water accumulation, edema, our thiazide ought to cause a diuresis secondary to induced saluresis. The antihypertensive effect might follow a drug-induced shift in arterial wall extracellular/intracellular sodium balance to which a renal reduction of salt-retention hypervolemia should contribute favorably.

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**References**

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