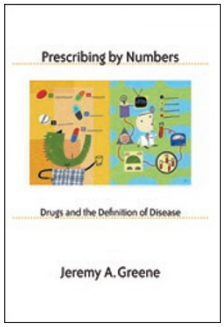
Progress in therapy: the delicate balance



Prescribing by Numbers: Drugs and the Definition of Disease

Jeremy A Greene

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Reviewed by Jesse Roth

Medical textbooks are misleading. The sturdy covers, durable bindings and fine paper resemble literary monuments like Shakespeare. By contrast, the reader of a brand new medical text will encounter some material that has already become outdated, and this deterioration will continue. These texts would serve audiences better if they were printed like the pulp magazines of the 1930s: flimsy covers, raw paper, smudgy ink and bindings that shed pages would transmit the fragile, tentative nature of medical knowledge.

In *Prescribing by Numbers*, Jeremy A. Greene traces the emergence of ideas about the treatment of hypertension, hypercholesterolemia and hyperglycemia over the second half of the twentieth century. Greene's chronicle of each of these conditions over time clearly communicates the disorderly process of how medicine progresses—with uncertain, wobbly steps interspersed with unexpected falls.

Led by dedicated academics deeply committed to patients' well being, these fields have changed slowly amidst controversy. The 'we better be careful' party struggled to slow those on the 'let's get on with treating these patients' track. The latter group had obvious allies in the pharmaceutical industry (and less obvious allies among editors, conference organizers and government officials—all committed to showing 'progress').

Greene begins with US president Franklin Roosevelt's severe symptomatic hypertension (that culminated in a lethal stroke). Two barriers blocked the path to treatment of hypertension. One hypothetical barrier, since discarded, was that the narrowness of the blood vessels (owing to 'hardening of the arteries') required elevated pressure to sustain blood flow, hence the label 'essential hypertension'.

And the other barrier: the available drugs carried a delicate balance between uncharted benefits and serious side effects. In 1959, when I moved from medical school in New York (where we were taught extreme reserve in treating hypertension) to an internship in St. Louis, I was awed by Washington University's prophetic physicians, who were aggressively treating their hypertensive patients. Greene tracks the novel concepts and medications (especially chlorthiazide) that were responsible for the current universal treatment of hypertension. His overarching thesis is that new drugs with fewer side effects catalyzed a major transformation in therapy: physicians now routinely target abnormal blood pressure or glucose levels in asymptomatic patients. The promotion of new medications influenced this evolution. Greene tracks how drug companies financed major studies of new drugs to provide evidence to support more aggressive approaches in wider target populations. These efforts, in many cases, resulted in distinctly improved outcomes.

My tentative interpretation is that pharmaceutical companies, though aggressive and zealous, provided superior microphones to amplify academic voices preaching particular therapeutic opinions that the companies favored, rather than setting the major treatment agendas. Greene simultaneously laments the transformation of the ethical drug companies of yesteryear (and their traditional respectful relationship with physicians) into the highly visible, Janus-like marketeers of today, with their aggressive advertising directly to patients, their focus on share prices and Wall Street targets for quarterly earnings, and their dwindling trustworthiness on issues of patient safety.

My field, diabetes, brings out many of the issues presented in Greene's book. Fifty years ago, we used insulin for treatment and crude measurements of glucose in urine as a guide, and there was wide disagreement about the role of hyperglycemia as an agent of pathology. In the 1970s, the *New England Journal of Medicine* carried a letter by leading academics pleading for tight control and normalization of blood glucose in people with diabetes. Other leaders responded that they, too, supported the theory of tight control but doubted that normal levels of blood glucose could be achieved safely. Their warning proved prescient; some who committed themselves to avoiding hyperglycemia died.

Since then, a cavalcade of new medications have been introduced, as have better glucose monitoring and insulin delivery systems. Hyperglycemia is widely agreed to be a leading mediator of diabetes pathology, allowing a clearer definition of targets for blood glucose. Control of glycemia is better but continues to be quite imperfect most of the time, and attempts to achieve perfection are still fraught with obstacles and dangers.

The goals of therapy for people with hypertension, hypercholesterolemia and hyperglycemia continue to be to restore 'normality' in the individual. This is an admirable goal, but Greene reminds us that the 'normal' range is a statistical construct derived from populations. Each individual has his or her own normal baseline, which may change over time. More importantly, as blood pressure and glucose are lowered toward normal, the further benefits of treatment accrue ever more slowly while the risks increase exponentially. The tools of therapy are still very crude, and the patient, like all biological targets, does not stand still. With the introduction by payers of ambitious pay-for-performance schemes meant to prod physicians and the promotion of ever more strict guidelines by oversight bodies, I can envision an increasing fraction of individuals being given higher doses of more drugs to drive them into some statistical normal range, even though that may not be a truly safe zone for that individual.

For older patients, my worries are heightened. The databases that support practice guidelines for them are often sparse with regard to their treatment, the potential benefits of their therapy are reduced and the likelihood of very serious complications for them are increased. (The analysis of the terminated arm of the ACCORD Trial to control glycemia strictly in older subjects with complications will be informative.) Thus, Osler's century-old dictum—"First, do no harm"—remains a useful guidepost.

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