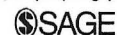


Book Review

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Endogenous Toxins: Targets for Disease Treatment and Prevention
Weinheim, Germany: Wiley-VCH Verlag GmbH & Co. KGaA,
2010. 994 p., \$365.00 USD. ISBN: 978-3-527-32363-0.

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Once in a while, a new publication appears that, for some reason, generates attention and interest. *Endogenous Toxins: Targets for Disease Treatment and Prevention* may be such a 2-volume book. The editors not only arranged for 75 contributors who provided a new and interesting view of toxicology but they also provided medical scientists a new perspective for potential treatments. In his Nobel Prize address, Albert Szent-Gyorgyi said, "Discovery consists of looking at the same thing as everyone else and thinking something different."¹ This book, for the practicing toxicologist, is a discovery of the past principles and practices he or she used, but it is also a foundation for discoveries in the future—an opportunity for "thinking something different": toxicity originating from within.

Endogenous Toxins: Targets for Disease Treatment and Prevention brings into focus complex issues, approaching conundrum status: Is the toxicity of endogenous chemicals the result of disease or the cause of it? Whatever the answer, there are subsequent questions such as: What are the physiological and biological regulatory control processes that have gone awry and why? If an exogenous toxicant causes the perturbation of an endogenous chemical, is the resulting toxicity endogenous and exogenous? The toxicologist venturing into this new arena will quickly recognize new opportunities for understanding how various toxicities occur.

Determining causation when endogenous chemicals and exogenous toxins meet in an organism is a complex task requiring more than determining dose-response and no-effect levels. If there was any doubt, and there should not be, *Endogenous Toxins: Targets for Disease Treatment and Prevention* places toxicology in the middle of basic medical science. This alignment for toxicology comes with philosophical challenges. Nowhere is it more apparent than excessive reactive oxygen species (ROS) generation from normal metabolic processes and ROS generation in diabetic or obese conditions or ROS generated in the process of detoxifying a xenobiotic. Attention medical scientist: the toxicologist with his/her tools-of-trade can be your friend and is not the *de facto* bearer of bad news!

In more than 900 pages, distributed among 36 chapters in 2 volumes, with more than 4300 reference citations forces one to consider *Endogenous Toxins: Targets for Disease Treatment and Prevention* a significant treatise. The 36 chapters are organized into 4 parts: (1) Endogenous Toxins Associated with Excessive Sugar, Fat, Meat or Alcohol Consumption; (2) Genetics: Endogenous Toxins Associated With Inborn Errors of Metabolism; (3) Examples of Endogenous Toxins Associated With Acquired Diseases or Animal Disease or Animal Models; and (4) Therapeutics Proposed for Decreasing Endogenous Toxins. Accompanying the book's 4 parts are Contents, Preface, List of Contributors, Abbreviations, Appendix—Questions for Discussion and Index. The outline of the book in the Contents section allows the reader to get a quick focus of topics of interest with a crisp and descriptive structure.

Each of the chapters has the same basic structure: an introduction to the material covered in the chapter followed by the body of the topical material with a summary or conclusion and finally finishing with a list of references. The chapter introductions are brief, usually less than a page, providing informative overviews of the topical material. The body of each chapter varies in length but each is true to the respective overviews outlined in the chapter's introduction. The summary or conclusion for each chapter brings the key elements of the chapter into focus for the reader and only a few chapters do not have conclusion sections. Although some of the chapters identified suggested future research directions for the topical material, it would have added value to the book if all of the chapters had suggested avenues for future research. If the chapter authors would have pointed the reader to where the future lies for their topics, the book would have been more true to its title: "... Targets for Disease Treatment and Prevention."

Part I (257 pages) is subdivided into 2 subparts: (1) Chemistry and Biochemistry and (2) Molecular Toxicology Mechanisms of Dietary Endogenous Toxins. Each of the subparts has 5 chapters. There is a logical flow in the Chemistry and Biochemistry subpart that includes damage to DNA followed by attack on proteins. The remaining 3 chapters of the first subpart focus on free radical chemistry and examples of how endogenously generated free radicals cause damage. The Chemistry and Biochemistry subpart lays the foundation for subsequent discussions, of which there are many in the following chapters, on ROS and free-radical biology. The second subpart discusses carbohydrates, estrogens, and the endogenous generation of ROS.

Part II (178 pages), Genetics: Endogenous Toxins Associated With Inborn Errors of Metabolism, describes the toxicity

of endogenous metabolites and metabolic endproducts that occur in selected genetic disorders. The part covers hyperoxaluria, hepatobiliary pathology, fatty acid oxidation disorders, homocysteine in cardiovascular disease, uric acid alterations, disruption in copper mobility, and polyglutamine diseases. Part II concludes the first of the 2-volume book.

The second volume begins with Part III, Examples of Endogenous Toxins Associated With Acquired Diseases or Animal Disease Models. This is the largest part (335 pages) in the 4-part book. There are 15 chapters, the first 2 addressing ethanol-induced toxicities.

The third chapter in Part III presents the complex relationship among gut bacteria, diet, endotoxemia, and diseases. The next 2 chapters focus on diabetes and its relationship to endogenous toxins. The sixth chapter of Part III discusses the relationship of glycation endproducts with nonalcoholic steatohepatitis and sets the stage for the next 3 chapters that cover selected consequences of oxidative stress.

The next 3 chapters of Part III address endogenous toxins that relate to neurotoxicity. The subject matter of chapters 28 and 29 is dopamine-related toxicity and Parkinson disease, while chapter 30 provides a diverse examination of endogenous neurotoxins with an emphasis on the condensation product of tetrahydropapaveroline (THP). Tetrahydropapaveroline is the condensation of dopamine and 3,4-dihydroxyphenylacetaldehyde.

The concluding 2 chapters of Part III address chemical-induced autoimmunity and endogenous toxins that play a role in aging, the latter being related to ROS and oxidative damage.

Part IV is the smallest of all of the parts, containing 117 pages distributed among 4 chapters. The first 3 chapters discuss decreasing homocysteine, increasing antioxidants to alleviate oxidative stress and the reduction of endogenous estrogens as a means to dampen the consequences of estrogen-mediated genotoxicity. The fourth and final chapter discusses the role of antioxidants in nutritional intervention for regulating cellular oxidation and ultimately chronic disease. Part IV, in essence, is the second half of the book's title, "Targets for Disease Treatment and Prevention," yet it is the smallest Part of the book. To be sure, there are other potential targets identified in the other 3 Parts, and an editor's summary in Part IV of these targets from the other Parts would have added value to the book and its title.

The last section of the book is the Appendix and it is titled: Questions for Discussion. The editors list 7 questions related to the topics, which are covered, to varying degrees, in the 2 volumes. As an interesting closure to the book, the editors urge readers to add their thoughts to the origin and importance of endogenous toxins. To that aim, the editors provide their email addresses. This last section, especially requesting the readers' thoughts and comments, is consistent with what the editors envisioned in the Preface for their treatise: a "conference in a book"

Endogenous Toxins: Targets for Disease Treatment and Prevention is not a typical toxicology book; it should not be nor can it be. But it is toxicology, nonetheless. *Endogenous Toxins: Targets for Disease Treatment and Prevention* puts toxicology squarely at the axis of the spinning world of medicine and gives

quantification and dimension to disease while at the same time providing insight for therapeutic strategies. The editors and chapter authors give insightful perspectives for the practicing toxicologist, the clinician who is treating diseases, and the pharmaceutical industry scientists who are developing therapies. Ah yes, there is something for everyone who would venture to pick up the book having been aroused by its title; but it may not contain exactly what the concept "endogenous toxins" may trigger in an individual's mind.

The toxicologist, having a familiarity with *Endogenous Toxins: Targets for Disease Treatment and Prevention*, will quickly recognize that a toxic response is not limited to an exogenous toxicant having a direct attack on a target structure or molecule. Indeed, the task for a toxicologist when assessing the adverse effects of a toxicant may be one of acquiring an understanding of the toxicant's impact on normal endogenous chemicals already present in the animal or human. Consequently, an exogenous toxicant distorting the homeostatic balance of endogenous metabolites and metabolic endproducts may be the explanation of the observed adverse effect. Arguably, *Endogenous Toxins: Targets for Disease Treatment and Prevention* could be considered an approach or foundation for elucidating how an exogenous chemical does its dirty deeds. At least, endogenous toxins could be the indirect causation of toxicity for an exogenous material. Could examination of endogenous toxins be, in reality, mechanistic toxicology in disguise?

The clinician, understanding that a disease condition is a distortion of endogenous chemicals, will be better equipped to treat their patients. Toxicity for the clinician is more than something that should be avoided; it is something to be understood. Once a clinician appreciates the causation of a diseased state at the molecular level, more options and avenues for treatment can be devised. In a similar manner, scientists developing therapies for diseases will have a better insight to the options available to them if they know the mechanism by which endogenous toxins are exerting their adverse effects.

There are flaws or shortcomings with the book. The significance of the flaws can best be determined by the readers and users of the 2-volume set. However, the majority of the flaws are omissions and not obvious errors of commission in the material covered. In short, the book's shortcomings are an inevitable consequence of the magnitude of the topic colliding with the practical consequence of creating a treatise of manageable size.

The first important omission is the absence of a suitable treatment of homeostasis. Although biologic imbalance is an underlying thread through several chapters, and indeed the cornerstone of a diseased state, treating the subject would have added a cohesiveness lacking in the book, and it would have unified the apparent discontinuity among some of the chapters.

The second important omission is an explanation why certain topics were selected and how the selected topics serve as witness to the book's title and intent. The editors could have been more true to their objective of creating a "conference in a book" by laying out the terrain on which the parts, subparts, and chapters unfold. If there were brief introductory comments

by the editors or session chairs because it is a "conference in a book," the reader (conference attendee) would have a better understanding of the session's intent. The concept of a "conference in a book" is a novel and clever idea that is a worthy structure for a treatise such as this. However, the conference organizers (editors) are required to give some level of continuity within and among the sessions (parts and subparts).

Further to the editors' task of setting the stage for the "conference," they could have explained why certain important and pressing topics in medicine were not covered. One example of this type of omission was the absence of a chapter discussing prions in neurological disorders. The mere mention of endogenous toxins cries out for addressing subjects such as inflammation, sepsis, immune responses, the anaphylaxis process, disseminated intravascular coagulation, and so on. It follows that these topics necessitate attention be paid to important endogenous chemicals such as IgE, histamine, prostaglandins, leukotrienes, chemokines, c-reactive protein, platelet-activating factor, and so on that fall outside of their respective homeostatic ranges. In fairness to the editors, they should not be chided for limiting the treatise so that it remains a manageable size. Rather, any identified omissions point the editors and the publisher toward topics in future treatments of endogenous toxins.

The book has its greatest value for toxicologists that are intimately involved in the pharmaceutical industry developing new therapies for diseases. Nonpharmaceutical toxicologists surely will find the book a valuable resource as a continuing education instrument; however, the price may be prohibitive for the book to become part of their personal library. For all toxicologists, the book is a reminder that adverse consequences observed in a target species may not exclusively be the result of an exogenous toxicant's direct effect.

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