Drug Metabolism During Drug Design and Development

Poster presented at the
IUPAC Congress/General Assembly
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Abstract

This poster summarizes three projects that have been initiated by the IUPAC Medicinal Chemistry Section in the area of **drug metabolism**.

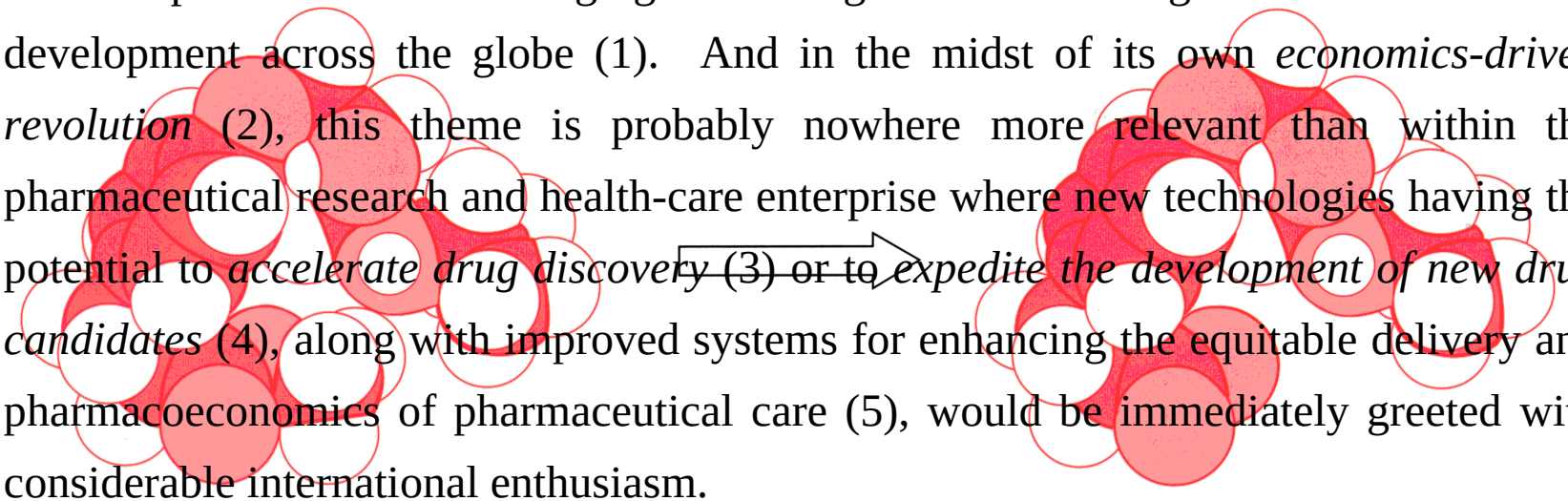
• the *first* project undertook a **practitioners' review of using databases and high-throughput testing** during drug design and development.
The review culminated in the publication of an IUPAC book.

• the *second* project seeks to **standardize some of the terminology** associated with drug metabolism. It is being undertaken by a working party of 15 experts.

• the *third* project seeks to mount a **human drug metabolism database** on the www that can be used by investigators in a non-profit format.
This project is also being sponsored by the IUPHAR who were instrumental toward obtaining seed funding from the ICSU.

Drug Metabolism - an IUPAC reference

Given the exponential proliferation of technical data and our increasing ability to rapidly disseminate it through a vast maze of electronic networks, it is no wonder that new systems capable of *managing and integrating information* are regarded among the most important of the emerging technologies for future growth and economic development across the globe (1). And in the midst of its own *economics-driven revolution* (2), this theme is probably nowhere more relevant than within the pharmaceutical research and health-care enterprise where new technologies having the potential to *accelerate drug discovery* (3) or to *expedite the development of new drug candidates* (4), along with improved systems for enhancing the equitable delivery and pharmacoeconomics of pharmaceutical care (5), would be immediately greeted with considerable international enthusiasm.



It was into this climate that IUPAC chose to initiate a Working Party (WP) whose specific mission would be to consider the topic *'Metabolism Databases and Their Potential Utility in the Development of New Drugs.'*

The figures convey the programmed metabolic hydrolysis of esmolol to its inactive metabolite.*

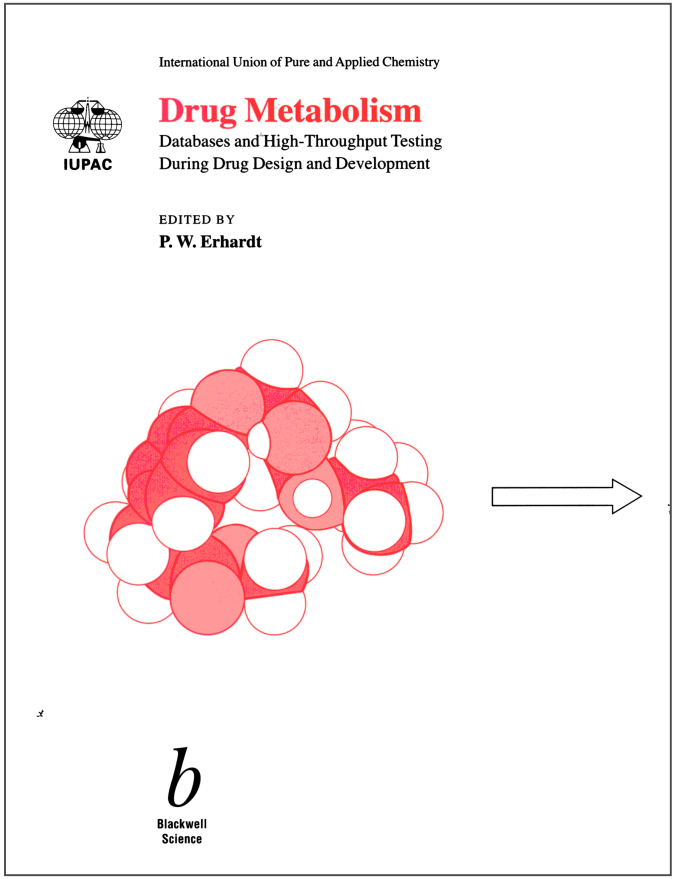
Contents

After a brief **Introduction** which provides an overview of the extensive background literature associated with this interdisciplinary topic, several short **Case Studies** are offered by various practitioners from the pharmaceutical industry. Many of these studies convey some of the industry's very first experiences with the use of metabolism databases. Besides providing historical lessons and establishing an initial backdrop for the further consideration of this topic, importantly, these case studies were immediately shared within the WP so as to afford an overall theme for this project that was thus prompted from the onset by way of real, practical examples. In several instances, these examples helped shape the contributions offered within the third and most prominent section of the monograph which pertains to **New Directions**. Interestingly, as the New Directions section was being elaborated by a mix of academic and industrial participants, it became very clear that metabolism databases may be able to be constructed and manipulated so as to partner with *enhanced-throughput metabolism data acquisition methodologies* in a truly synergistic manner. This unique relationship between 'old' and 'new' technologies was ultimately captured within the final title for our text.

Participating in a manner explicitly separate from that of the WP, vendors of key commercial products pertinent to this field were also asked to submit contributions. The latter have been gathered within a section entitled **Emerging Products**. Finally, a **Summary** chapter, two quick reference **Tables** to the available metabolism databases and to high-throughput metabolism contract research organizations, respectively, and a **Glossary** are offered as a wrap-up for the text while also serving to further highlight some of the key points within the overall work.

Drug discovery stands on the brink of a revolution. An enormous proliferation of technical data, coupled with new information systems capable of managing and integrating it, have great potential to accelerate drug discovery and the development of new drug candidates.

This book (ISBN 0-632-05342-9) **represents a significant advance in the use of metabolism data in the discovery and development of new drugs.**



Preface References

(1) Interactive Video Conference: *The Role of Higher Education in Economic Development*, Old Dominion University Academic Television Services; University of Toledo site, January 31, 1997.

(2) Pharmacopeial Convention: *Quinquennial Meeting*, The United States Pharmacopeia; Washington D.C., March 9-12, 1995.

(3) Annual Meeting: *Lead Generation & Optimization*, Strategic Research Institute; San Diego, June 23-25, 1997.

(4) International Bio/Technology Event: *Emerging Technologies for Drug Discovery*, National Managed Health Care Congress; Boston, May 19-22, 1997.

(5) Interim Meeting: *Pharmaceutical Education*, The American Association of Colleges of Pharmacy; Washington D.C., March 2-4, 1997.

(6) National Research Council Report: *Bits of Power: Issues in Global Access to Scientific Data;* Press Release as conveyed in *Chem. & Eng. News p.* 8, April 14, 1997.

Metabolism Terms

About 250 terms are being compiled by a working party consisting of 15 experts in the field of drug metabolism, several of whom hold editorial positions for some of this field's key journals. The terms list will be disseminated to the scientific community via publication in journals pertinent to xenobiotic metabolism as well as by publication in *Pure and Applied Chemistry.*

The dissemination will help achieve a common definition base across various publications and should allow for a more uniform use of these terms in the future construction of databases pertaining to the field's information and its overlap with medicinal chemistry.

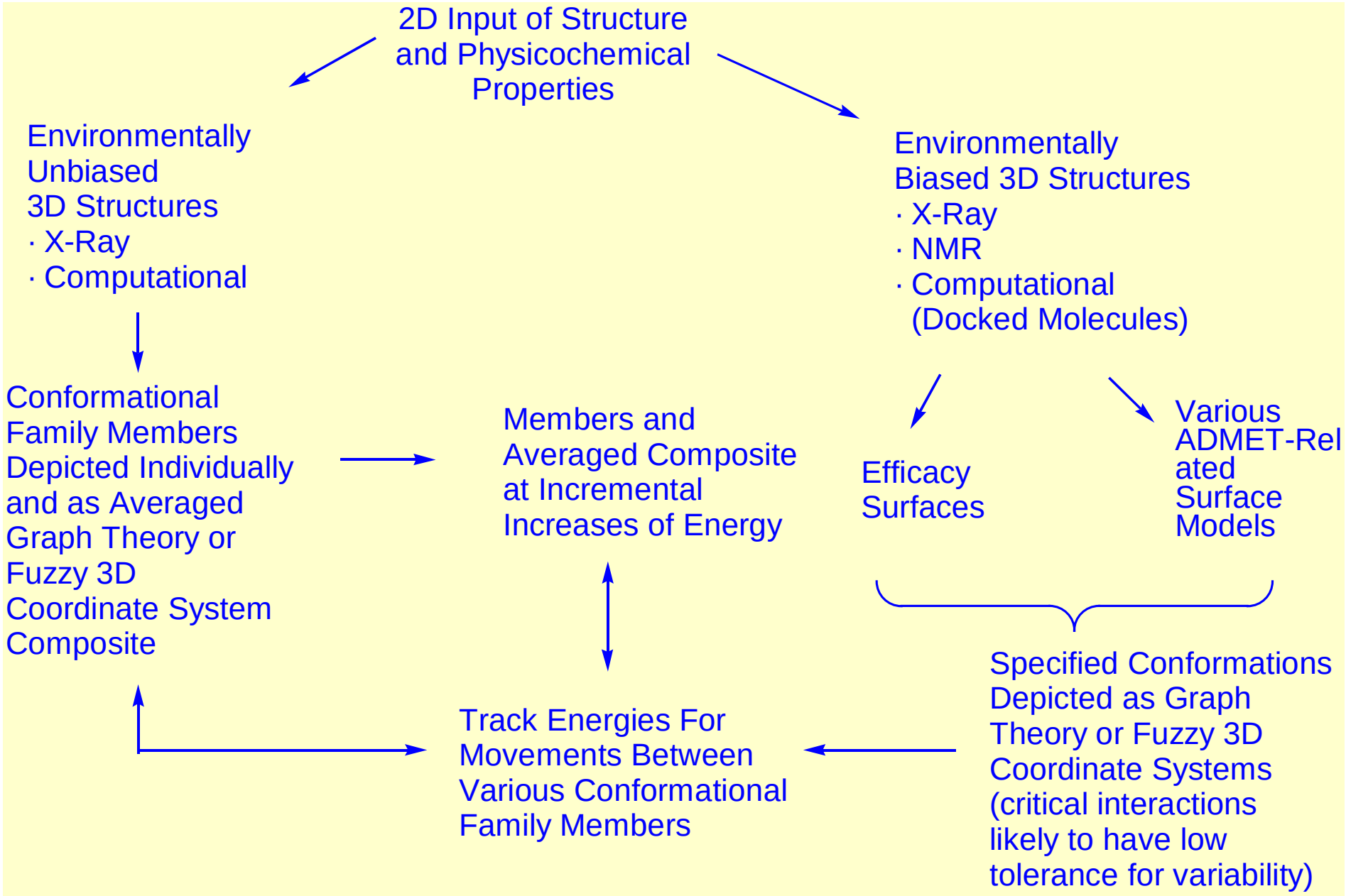
It is anticipated that this project will be completed by the end of 2001 so that the publications can be initiated in early 2002.

Human Drug Metabolism Database

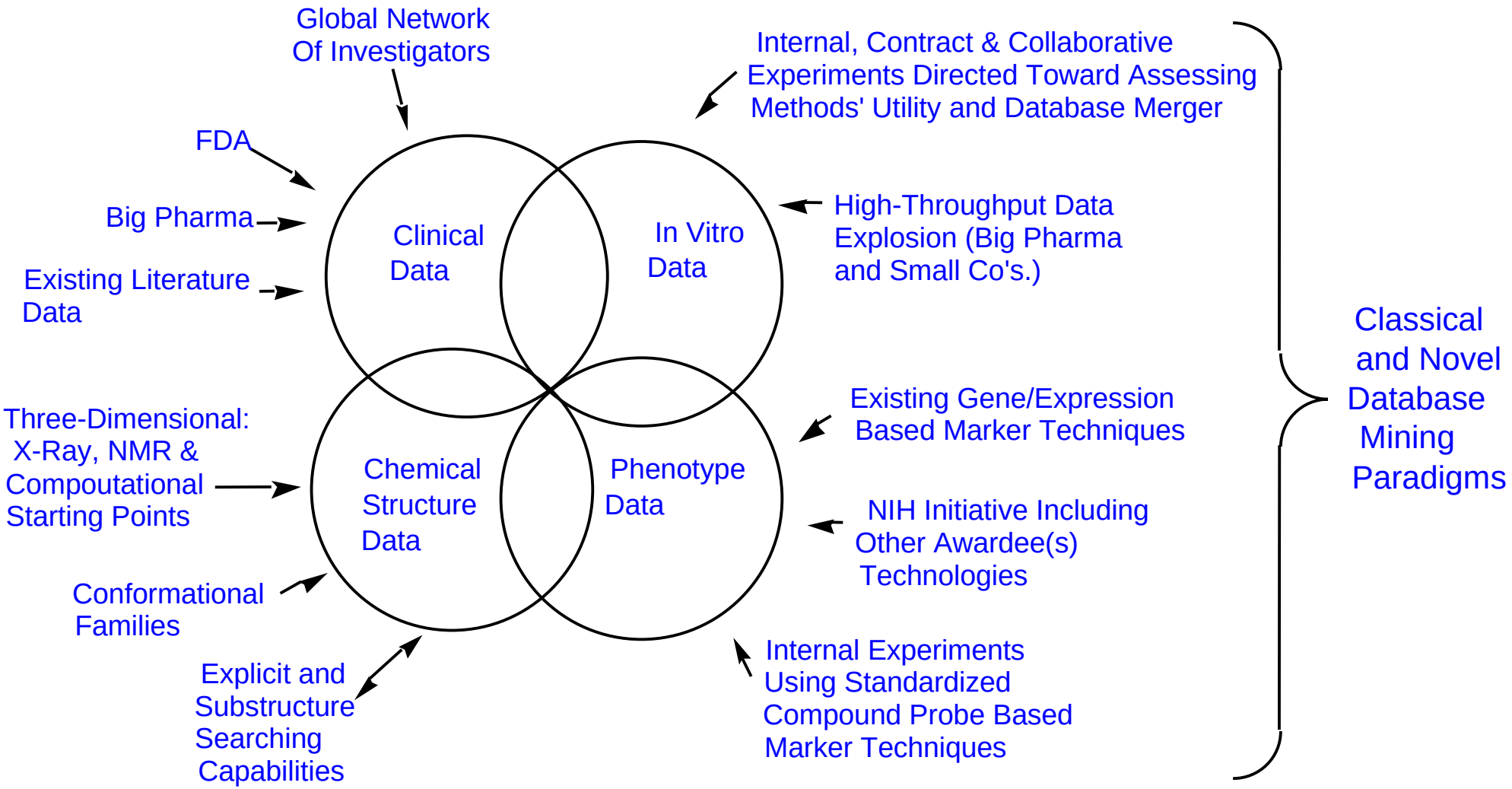
While there will be several useful ramifications of this project, perhaps the most immediately important is that the assembly of this type of commonly held database may be the *only way* to assess and validate the actual utility of the ongoing explosion of biochemical and *in vitro* metabolism data and techniques as they are now being applied to the process of drug discovery and development.

Some of the features of the database are highlighted pictorially on the following two panels. It is anticipated that a preliminary version will become mounted on the www by mid year 2002 with the University of Toledo Center for Drug Design and Development overseeing the overall construction and serving to initially host the prototype platform.

Handling of chemical structures



Overlap of components to be included in the human drug metabolism database



Through a collaboration with the IUPHAR and some seed funding from the ICSU, considerations pertaining to the development of this database are being sought on a global basis such that its ultimate users will not be limited to just the U.S. and European nations.

Project Coordinator:

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on behalf of the IUPAC Medicinal Chemistry Section and its three working parties assembled to address specific topics in this area.

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* The molecular modeling studies illustrated on the front and back cover of the book were undertaken by **Dr. Jeffrey Sarver** (cd3).

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