THE MECHANISM OF ACTION OF INSULIN

A Symposium

Organized by

THE BRITISH INSULIN MANUFACTURERS

Allen & Hanburys Ltd.
British Drug Houses Ltd.
Boots Pure Drug Co. Ltd.
Burroughs Wellcome & Co. Ltd.

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Together with certain members of the scientific staff of the British Insulin Manufacturers.

* Session Chairman.
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INTRODUCTION

F. G. YOUNG

It is at once a salutary fact and a challenge to research that nearly 40 years after the discovery of insulin much disagreement still exists about the mechanism of action of this important hormone. The annual volume of publications on this subject is enormous and is still rapidly growing; nevertheless, ideas about the way in which insulin acts appear to steer an unsteady course between the Charybdis of sugar transport and the Scylla of direct action on identifiable enzyme systems, with occasional sidelong glances at other possibilities. Perhaps in the end Charybdis will engulf Scylla and we shall understand the action of insulin in terms of a promotion of transport of glucose into a cell by virtue of an influence of insulin on certain enzymes or co-enzymes which are themselves concerned with the transport of sugar across permeability barriers of the cell. Already a few rays of light shine in this hopeful direction, and the account of the contributions and discussions recorded in this volume shows that there need be no deep dissatisfaction with the progress made in recent years.

Although meetings for the discussion of current research, and the subsequent publication of a record of the contributions and discussion, are becoming not uncommon these days, the meeting of which this volume is the published record differed from many others in two respects. The subject of discussion was in theory a narrow one, although in practice the discussions were wide, while those taking part included both chemists and clinicians with a common interest. Insulin was the focus of all, providing the cohesive force which held the meeting together in vigorous discussion for two successive days.

The absence of Professor Loubatières, who was kept away at the last moment by family illness, was most disappointing but those present were deeply indebted to Rachmael Levine for filling the gap at the last moment and giving a masterly survey of the researches of Professor Loubatières and others on the action of anti-diabetic sulphonamides.

Although a full record of the discussions was made, the members of the meeting agreed at the beginning that anybody was free to excise from the record remarks which, on due reflection, they preferred not to be recorded in print. With this in mind members were

urged to be informal and frank in their discussions, and not to hesitate to ask simple questions as well as those that might display the erudition of the questioner. The simple questions can sometimes be the most penetrating. How far this exhortation was effective can be seen from the following pages, but it is refreshing to note that very little of the recorded discussions was in fact excised by the contributors.

The expenses of the meeting, including much of the travel costs of the members, were provided by the British Insulin Manufacturers. This organization was formed as the result of an agreement between the four manufacturers of insulin in Great Britain (Allen & Hanburys Ltd., Boots Pure Drug Co. Ltd., British Drug Houses Ltd., and Burroughs Wellcome & Co. Ltd.) to provide for exchange of information and the fostering of research on insulin. The conference was the first held, under the auspices of the British Insulin Manufacturers, of which an account is published. The editing of the record was undertaken jointly by Mr W. A. Broom of Boots Pure Drug Co. Ltd., and Dr F. W. Wolff of Burroughs Wellcome Ltd. Dr Wolff also undertook most successfully the detailed administrative duties involved in the organization of the conference. On behalf of the British Insulin Manufacturers the Chairman of their Technical Committee, Dr G. I. Hobday of Boots Pure Drug Co. Ltd., opened the meeting, which was held in the Wellcome Building, London, on September 9th and 10th, 1958.

All those present hoped that the first meeting of this sort will not prove also to be the last, and the published record may reveal some of the reasons for this hope to those concerned in some way or another with the substance that has saved more lives, and made an almost normal life possible for more people, than any other hormone. As was said at the meeting, it is indeed fortunate that ability to use insulin therapeutically in no way depends on a detailed knowledge of its mechanism of action. But nobody can properly doubt that growth in the understanding of insulin and its ways will inevitably bring with it a wider and more effective therapeutic application. The more the laboratory worker and the clinician understand each other's tasks, the more quickly the results of research can become fruitful in the treatment of disease. This book is published as a contribution to this end.

May 2nd, 1959 F. G. YOUNG

CONTENTS

PART IV

Insulin and the Liver

Chairman: Professor C. F. Cori

PART V

Insulin and Protein Synthesis

Chairman: Professor F. Dickens

PART VI

Bio-Assay of Insulin

Chairman: Professor T. Russell Fraser

PART VII

Insulin Antagonists

Chairman: Professor T. Russell Fraser

PART VIII

Mechanism of Action of Insulin and other Hypoglycaemic Substances

Chairman: Professor C. de Duve

PART IX

Clinical Aspects of Diabetes and Pre-Diabetes

Chairman: Professor F. G. Young

PART I

CHEMICAL NATURE OF INSULIN

Chairman: PROFESSOR F. G. YOUNG

THE ACTIVITY OF MODIFIED FORMS OF INSULIN

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The purpose of testing the activity of chemical structures related to insulin is to discover the essential site of activity in the molecule as this may help towards revealing the mechanism of its action. Another aspect of investigations of this nature, which will not be dealt with here, is the important one of discovering modifications which are more valuable and convenient in the treatment of diabetes.

Although retrospective in time, Sanger's formula of insulin[37] will help us to describe briefly previous results in the main field of re-

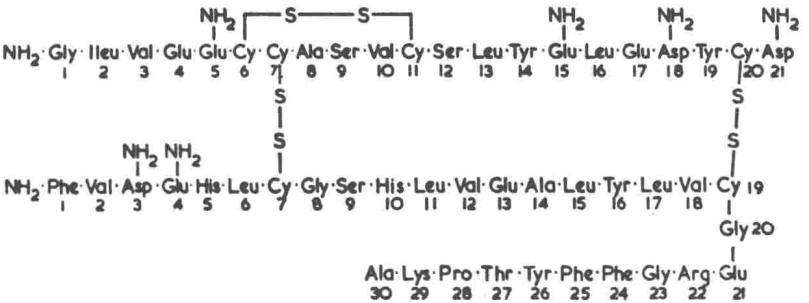

Fig. 1. The structure of ox insulin.

lating structure to activity (Fig. 1). Various reviews are available on this subject. Among them are those of Anfinsen and Redfield,[3] Li,[29] Porter[35] and Sanger.[39] A prepared table (see Table I) of some of the distinguished work of the past 35 years in the chemical modification of insulin would lead to the conclusions that the essential groups or linkages were the free carboxyl group, the phenolic hydroxyl groups and the disulphide bonds; and that the non-essential bonds were the amino groups, the guanidino groups, the amide groups and the aliphatic hydroxyl groups.

* Beit Memorial Fellow for Medical Research; J. R. Wolf, Medical Fellow of Christ's College, Cambridge.