A Ciba Foundation Symposium

Control of GLYCOGEN METABOLISM

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CONTROL OF GLYCOGEN METABOLISM

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and

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Under the guidance of its distinguished Trustees, the Foundation offers accommodation to scientists from all over the world at its home in Portland Place. Foremost in its activities is the organization of small conferences, the proceedings of which are published in book form in the manner of the present volume. The Foundation convenes many other informal discussions between research workers of different disciplines and different nationalities and each year invites an outstanding authority to deliver a special lecture. An exchange programme between French and British postgraduates is conducted and a library service is available. Furthermore, the Ciba Foundation attempts in every other way possible to aid scientists, whether they be Nobel Laureates or young graduates making their first original contribution to research.

The purpose of the Ciba Foundation, which is to promote international co-operation in medical and chemical research, is symbolized in the armorial bearings by five interlaced rings representing the continents, a black sacrificial cock (emblem of Aesculapius) holding a medical caduceus, and three regular hexagons for chemistry. Its domicile in London is indicated by the red sword of St. Paul and the British lion; the wyvern and the crozier, symbols associated with Basle, refer to the sponsoring firm located in this ancient Swiss town.

The Ciba Foundation

for the Promotion of International Co-operation in Medical and Chemical Research
41 PORTLAND PLACE, LONDON, W.1

Preface

THIS symposium was designed to cover the synthesis and breakdown of glycogen, and their control by enzymic and hormonal factors. This is an area where mechanisms of the normal metabolic processes have been illuminated by the findings in diseases involving specific enzyme defects—the glycogen storage diseases. The suggestion for holding this meeting originated with Dr. W. J. Whelan, and was supported and extended by Professor F. G. Young. Dr. Whelan and Professor C. F. Cori outlined the basic programme, choosing to have an unusually large number of very short papers and allowing more co-authors to participate than is usual at our meetings.

We were fortunate that Professor Leloir was able to travel from Buenos Aires to attend this meeting and to give the 4th Hopkins Memorial Lecture of The Biochemical Society.

The Editors wish to express their gratitude to the Chairman, Professor F. G. Young, for his skilful handling of a complex programme, and particularly for his rôle in the initiation and development of the general discussions.

Membership

Symposium on Control of Glycogen Metabolism held 23rd–25th July, 1963

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D. G. Walker	Dept. of Biochemistry, University of Birmingham
W. J. Whelan	Lister Institute of Preventive Medicine, London
F. G. Young	Dept. of Biochemistry, University of Cambridge

* Unable to attend; paper read by Dr. Whelan.

PATHWAYS OF GLYCOGEN METABOLISM IN RABBIT MUSCLE

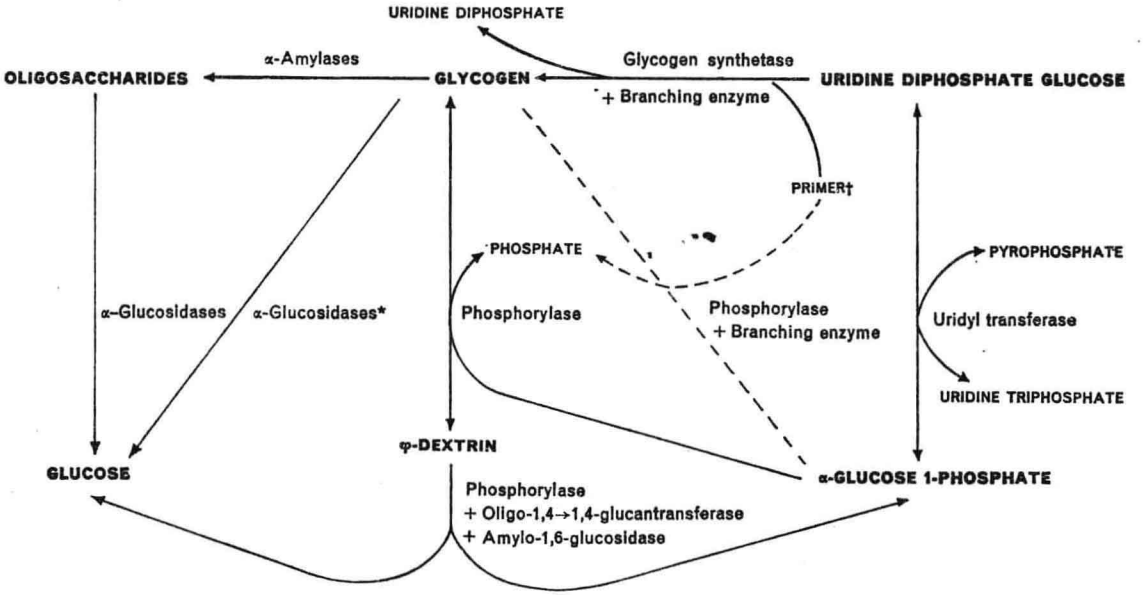

FIG. 1. Although many features of glycogen synthesis and degradation are still controversial, the participants in this symposium have agreed on the pathways shown in this diagram (see pp. 401–412 for discussion). Broken lines indicate pathways considered to be of possible significance but not of major significance *in vivo*.

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OPENING REMARKS

F. G. YOUNG

IT is a very great pleasure for me to be here on this occasion, to see so many old friends, and to meet some whom I have not known personally before but whose work is well known to me.

It is always difficult to know how serious the chairman should be in introductory remarks of this sort—whether he should try to provide a sort of black-market scientific communication or merely make some light-hearted remarks—but I shall try to steer a possibly unsteady course between two extremes.

I should like to say first some words about the genesis of Ciba Foundation Colloquia and Symposia: like some other processes of biosynthesis, the mechanism of their production is not fully understood. The initiating step usually involves an interaction—a fruitful collision—of two individuals, sometimes more, one of whom is the Director of the Foundation. An effective response from the Director usually demands a stimulus from more than one individual over an irregular period of time—it may sometimes be quite long, it's sometimes relatively short. Other members of the Foundation's staff early become involved, including in this case Peggy Cameron and Nancy Spufford. Ultimately an embryo takes definite shape and is then named. The naming, rather interestingly, usually takes place well before birth. Greek mythology relates how Pallas Athene sprang fully armed from the head of Zeus after the god had been struck on the head. I think it was natural that Zeus suffered a headache as a result of this traumatic experience. This analogy is not quite exact with respect to Gordon Wolstenholme's rôle in the origin of a conference, though I think that the process of gestation and birth of a conference could

sometimes give him a headache if he were susceptible to such weakness.

The genesis of this present symposium was relatively easy and swift. It was obvious to many that rapidly developing aspects of knowledge concerning the mechanism of action of enzymes and their activators, the influence of hormones on metabolic processes, and the chemical structures of complex substances, might profitably be brought together at the present time. The integration of interest in related fields of medical and chemical research is an important function of the Ciba Foundation and here was an excellent opportunity to bring together groups of lively investigators representing the different interests involved.

Dr. Whelan was, I think, the one who struck the first blow, but many others rallied quickly round—Dr. Carl Cori particularly gave great help—and with the co-operation of many in and out of the Foundation the present Conference rapidly took shape. It isn't quite clear to me how I became Chairman. Maybe it was just a matter of habit on the part of the Foundation to invite me; another possible reason is that although I have long been interested in glycogen and hormones and carbohydrate metabolism, I had no intention of presenting a paper to this Conference!

It is perhaps not inappropriate to recall that it is 106 years ago, to be precise on 21 March 1857, that Claude Bernard communicated to the Société de Biologie in Paris a description of the isolation of glycogen from liver tissue, and of its chemical and physical properties. Two days later he delivered a communication on the same subject to the Académie des Sciences. It is remarkable how much Bernard knew about the simple chemical properties of glycogen, and about its breakdown, but it is only relatively recently that the study of the mechanisms whereby complex substances are built up in nature has become productive, and this possibility has in many instances led to the realization that the processes of degradation are often more complex than was at first thought likely.

One could perhaps reasonably date the beginning of the present rapid growth of knowledge of biosynthesis to about 1940. Until 1940 metabolic knowledge was largely about catabolic processes. The biosynthesis of complex substances was often considered, without much direct evidence, to be due to a reversal of the catabolic pathways, which were known much better. I think we can say now that this view is in general not correct. The idea of coupled reactions, whereby an exergonic process could be driven backwards at the expense of an integrated endergonic process made the study of synthetic pathways possible in a new way. The development of the concept of "high-energy phosphate bonds" by Lipmann helped to add fuel to the biosynthetic fire that was being lit nearly 25 years ago.

As far as carbohydrate metabolism is concerned, a realization that phosphate derivatives of hexoses play an important intermediary rôle in the catabolism of glucose in yeast and animal tissue derived from the investigations of Harden and Young in the early years of the present century, and of Embden and Meyerhof a quarter of a century later. With the recent rapid development in the study of the immunochemistry of substances of metabolic importance it is perhaps of interest to recall that the important discoveries of Harden and Young (the late Dr. W. J. Young was no relation of mine, I'm sorry to say) arose out of a concern—and I quote Harden's words: "with the production of antiferments by the injection of yeast juice into animals" (Harden, 1932). In this connexion "the experiment was made of carrying out the fermentation [with yeast juice] in the presence of serum, with the result that about 60 to 80 per cent more sugar was fermented than in the absence of serum" (Harden, 1903). This effect was ultimately traced, at least in the main part, to the presence of phosphates in the serum, and so very fruitful research on the isolation of phosphates of sugars was begun at this time.

I think one could say that the recognition of glucose 1-phosphate by Cori and Cori around 1936 was the culmination of this phase of

development and was of particular importance in providing a most interestingly reactive derivative of glucose and one whose potentialities were quickly apparent. I recall with particular pleasure the demonstration by Carl Cori at the Federation Meetings in April 1939 of the reversibility of the action of liver phosphorylase, whereby a polysaccharide could be formed from glucose 1-phosphate *in vitro*. It is a very brave man who does a demonstration at a large meeting, but Dr. Cori succeeded magnificently in this demonstration, and the tubes passed round, to which iodine had been added, really did show the development of a blue colour characteristic of what we now recognize as an unbranched polysaccharide. The fact that a polysaccharide could now be formed *in vitro* made one realize that the overworked term "epoch-making discovery" was perhaps not then as inappropriate as it often is. We now know, of course, that the simple reversal of the normal phosphorolytic action of phosphorylase is not necessarily the most important aspect of the biosynthesis of branched polysaccharides, of which glycogen is now recognized to be one, but there is no doubt that these experiments of 1939 were a great stimulus to the application of enzymic methods to the study of polysaccharide structure.

It is rather remarkable to think that it is only a little over 30 years ago that the late Sir Norman Haworth and his colleagues began their now classical chemical investigations into the structure of starch and glycogen. These have been successfully developed in more recent years by his scientific colleagues and descendants, of whom I think Professor E. L. Hirst is the senior present today. The knowledge gained by chemical means aided the identification of enzymes concerned in the breaking down and building up of polysaccharides, and the chemical knowledge thus acquired in turn assisted the development of elegant enzymic methods for the determination of the molecular architecture of glycogen and of other polysaccharides on remarkably small samples of material. The understanding of the multiple causes of glycogenoses which