The Cell in Medical Science

Volume 4

Cellular Control Mechanisms
Cellular Responses to Environment

edited by

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and

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Preface

The increasing importance of cell biology in medical science is becoming clear to clinicians and laboratory scientists alike. It is the meeting ground of many traditional disciplines and forms a central theme for many others. Its impact on subjects as diverse as immunology and neurobiology is already very great and one cannot but appreciate the potential that the application of its techniques and discipline must have for the future.

Many excellent introductory books of cell biology are available but beyond these one has in general to pass either to reviews or to original articles in order to probe more deeply. The present volumes are designed for readers who already have an elementary knowledge of cell biology; they present various aspects of the subject in depth and try to indicate some of the directions in which contemporary cell biology is moving and the methods it uses. No attempt is made to provide a comprehensive cover of cell biology, but the topics are chosen so as to produce a coherent work rather than a series of unconnected essays. We are greatly indebted to our contributors for their willingness to work within a number of constraints and for their patience with a multitude of editorial requests made to help us achieve our aims.

Volume 1 of this book is concerned with the generalized cell unit, and its chapters deal with the biophysical and biochemical basis of the structure and function of the chief subcellular organelles. Volume 2 contains a series of chapters on the relationship of the cell to developmental processes both within the cell itself and in the organism as a whole. There follow chapters on specific cellular specializations, particularly within the neuromuscular system. Here morphological adaptation for specific functional purposes is described in detail. This theme is again followed in Volume 3 where connective tissues, various endocrines, absorptive and secretory cells are dealt with. Volume 4 begins with three chapters on metabolic control mechanisms, and these are followed by chapters on the relationship between the cell and its environment in various pathological states; immunological processes, inflammation, wound healing and carcinogenesis are treated within this framework.

We believe this book will be of value to senior undergraduate students and to research workers looking for summaries on a variety of related topics concerned with cell structure and function. The contributors have been asked to provide only brief bibliographies which enable the reader to develop his own interest; the chapters do not attempt to include an extensive review of the literature.

Like many before us, we are indebted to Academic Press for the patience, forbearance and unfailing courtesy of numerous members of their staff.

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I. Introduction

Perhaps the best way to appreciate the importance of intracellular control mechanisms is to imagine a state of affairs in which no such control existed. The myriad chemical transformations constituting metabolism would proceed in disordered fashion and the operation of biosynthetic and degradation reaction sequences would be divorced from the needs of the cell. The capacity to respond to altered conditions would be lost and the entire organism would suffer because the metabolic activities of individual cells would not be geared to co-operation. In short, the absence of intracellular control phenomena would result in metabolic chaos followed by cell and organism death.

This disastrous series of events does not occur because the organism functions as an integrated unit with the ability to adapt to altered conditions. For the maintenance of homeostatic balance, co-ordination and regulation of metabolic reactions is required and a number of control mechanisms have evolved to achieve these ends.

Much is now known about the devices used to create and maintain a controlled ordered state and this chapter is devoted to a discussion of these devices.

Although the control of metabolic processes encompasses a large and complex field one principle is fundamental to all regulation devices, viz., the capacity of the organism to control its own metabolism is due to the ability to increase or decrease the rates of various reactions. At the molecular level, this ability is mediated principally through regulation of the activities of enzyme systems and as far as we know at present, all control mechanisms can be explained on the basis of the control of enzymes. Considerations of the control of enzyme systems can be discussed under two general headings: I. *The Control of Enzyme Activity* in which control mechanisms result in modification of activity of a pre-existing population of enzyme molecules. II. *The Control of Enzyme Concentration* in which the concern is with the absolute number of enzyme molecules and those factors and mechanisms that regulate the size of each enzyme population. Although it is theoretically possible to consider separately the control of enzyme activity and the control of enzyme concentration the two mechanisms do not operate independently of each other. On the contrary, they support each other and their concerted operation is central to regulation. Mechanisms that control enzyme activity may be considered as the first line of defence in the face of altered environmental conditions because they allow the cell to adjust quickly. In comparison, the ability to modify the concentrations of enzymes is a slower process involving protein synthesis or degradation and in this way cells are able to adjust to protracted changes in the pattern of metabolism.

The capacity for self-regulation is inherent in all living organisms from the simplest unicellular organism to man and, by studying control mechanisms in vastly different cells, it has become apparent that substantially the same devices are used throughout Nature. However, in the multicellular, differentiated state the metabolism of a particular cell must be directed not only in terms of the economy and well-being of that cell alone but also to the requirements of the whole organism. In order to achieve integration and control of cells separated by physical distance and by metabolic differentiation the nervous and endocrine systems have been evolved. Metabolic co-operation is achieved by the transmission of nerve impulses and the circulation of hormone molecules. The mechanisms that the cells employ to respond to these signals are essentially those previously referred to, that is, modulation of enzyme activity and alteration of enzyme concentration. However, the cell machinery must be capable of identifying and acting in accordance with the signal and intracellular control devices have been developed for these purposes.

It is clear that an overall view of intracellular control mechanisms can be achieved by considering the controls imposed on enzyme activity and enzyme concentration, together with the controls imposed by nerve impulses and hormone molecules. In the following pages these regulatory mechanisms are discussed in sequence as far as is possible. Inevitably there is a good deal of overlap, illustrating the fundamental truth that, by definition, control mechanisms themselves function in an integrated fashion.

II. Control of Enzyme Activity

A. MULTI-ENZYME SYSTEMS

In the intact cell, metabolic transformations are usually achieved by a series of linked reactions. Thus, the conversion of A to D is dependent upon the production of two intermediate compounds, B and C.

$$A \xrightarrow{E_1} B \xrightarrow{E_2} C \xrightarrow{E_3} D$$

Each step is catalysed by a specific enzyme and the number of enzymes equals the number of steps in the whole process. Thus it is the operation of a multi-enzyme system that allows the step-wise alteration of molecules.

These multi-enzyme systems cannot be considered in isolation because many of them are linked through common intermediates. For example, the three major food materials of heterotrophic cells, carbohydrates, fatty acids and proteins are eventually oxidized via the tricarboxylic acid cycle. Access to the cycle occurs principally through acetyl coenzyme A, a continuous supply of which is required to maintain the operation of the cycle. Acetyl coenzyme A itself is the starting point for a number of biosynthetic reactions leading to the synthesis of fatty acids and steroids. Common intermediates such as acetyl coenzyme A, glucose-6-phosphate, pyruvate, oxaloacetate and glutamate form metabolic pools of primary importance. They are focal points of metabolism through which various chains of reactions are connected, allowing unification of metabolic processes into one extensive co-ordinated system.

The way in which cells control these integrated pathways, providing the correct substrates in sufficient quantity at the right sites, and at the right time, is necessarily very complex. In general, metabolism is regulated by controlling the rate and direction of movement of materials through the multi-enzyme systems. The overall rate of a