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With a Foreword by K. R. Porter

With 177 Figures

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Prof. Dr. PIERRE DUSTIN

Laboratoires d'Anatomie Pathologique et de Microscopie Electronique, Université Libre de Bruxelles, rue aux Laines 97,
B-1000 Bruxelles

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Foreword

The author of this remarkably comprehensive review, PIERRE DUSTIN, has performed an invaluable service in bringing together in one volume the observations and theory on microtubules that have accumulated over the last fifteen years. He has understood the magnitude of the task from the beginning and has met it thoroughly and, I must say, courageously. From here on, and for many years to come, young investigators, and some not so young, will have a ready reference as they seek to discover what has been done and remains to be done in achieving a better understanding of these important cell components.

Since the early 1960's when it became clear that the filaments (microtubules) making up the 9+2 complex of cilia and flagella were to be found very widely in cells, microtubules have attracted an ever-increasing amount of attention. Now it is known, as reviewed in this volume, that they influence the morphogenesis of anisometry in the shapes of cells and cell extensions; that they function as frames for the intracellular movement of granules and chromosomes; that they are subject to control in their assembly and disassembly by externally applied substances such as colchicine and cyclic AMP; and that they display abnormalities in their numbers and orientations in transformed (malignant) cells, to mention only a few of their several functions. Much less is known about the normal control over their disposition in cells and how they engage and interact with the cytoplasmic matrix to bring about its various translocations. This much is certain, the study of these and other questions of microtubule science will be greatly facilitated by the existence of this volume. It is to be hoped that Professor DUSTIN will find the time and enthusiasm to produce successive editions.

KEITH R. PORTER

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Introduction

Where is the wisdom we have lost in knowledge?
Where is the knowledge we have lost in information?

T. S. Eliot
The Rock.

"There are no authorities left, since only those who have no use for their knowledge can acquire it: doubtless a general predicament in all natural sciences these days."

F. Chargaff
The Sciences 15 : 21 – 26, 1975

It is indispensable to define the purpose and limitations of writing a monograph on a subject as vast as that of microtubule research. The name "microtubule" was coined by Slautterback some 14 years ago [23], and already in 1966 the ubiquity of these structures was mentioned in a fundamental article written by Porter [21]. Microtubules (MT) are present in all eukaryotic cells with the single exception of the anucleated red blood cells of most mammals. They appeared about one billion years ago, at the same time as the nucleus, marking the turning point form pro- to eukaryotes. They have maintained since that period of time a remarkable constancy of structure and of chemical composition. Their discovery was a result of electron microscopy and of the advent of better fixation and embedding procedures. They had however been suspected by microscopists since the end of last century, in the form of the marginal bundle of erythrocytes, the neurofibrils, the mitotic spindle fibers, and the complex structures of cilia and flagella.

The study of MT is closely linked with that of a few drugs which are known to combine specifically to some sites of their constitutive molecules—the tubulins. The first of these is colchicine, known since 1889 as a poison of mitosis [20], rediscovered as such in 1934, and which was the subject of a monograph in collaboration with O. J. Eigsti, published in 1955 [11]. At that time colchicine, apart from its very ancient use as a treatment in acute crises of gout, was mainly studied for its destructive and specific action on the mitotic spindle, leading to the arrest of cell divisions at metaphase—the so-called "stathmokinetic" effect [7]. This had numerous applications in various biological fields, the most notable being the use of colchicine for the production of artificial polyploid or amphidiploid species of plants (such as *Triticale*), and for the amplification of the mitotic index in the germinative zones of animals—the "colchicine method", which has been supplanted by the use of tritiated thymidine. Another important consequence of these studies was the demonstration in 1956 [31] of the exact number of chromosomes in man, and the subsequent use of colchicine in most studies of modern cytogenetics. In 1955, only a small number of actions of colchicine on non-dividing cells were mentioned, and mainly considered as non-specific toxic side-effects.

The high degree of specificity of colchicine was emphasized, as no other chemical appeared to be able to destroy the spindle filaments at such low concentrations. It was mentioned that ". . . any work which helps to solve the problem of spindle inactivation by this complex molecule may throw more light on the physiology of the peculiar fibrous protein which constitutes the spindle". We know now that this protein, called *tubulin* since 1968 [1], is present in all cells, and that its participation in the movements of chromosomes at mitosis is only one of the large

number of its activities, linked with the determinism of cell shape, cell movements, secretion, and growth.

Other powerful poisons of tubulin were discovered in the early sixties, and the alkaloids extracted from *Catharanthus roseus* (*Vinca rosea*) [29] have demonstrated an equally specific action on tubulins, and moreover have proved, contrary to colchicine, to be most useful in the treatment of cancer (vinblastine, vincristine). The greatest change in perspective since twenty years ago has however been the demonstration that the tubulin poisons not only affect mitosis, but are remarkable tools for the analysis of many cellular activities. This has been the consequence of the discovery of MT, and this discovery is closely linked with colchicine, as the use of tritiated colchicine, in the hands of Taylor and his collaborators, between 1965 and 1968, was to provide the tool necessary for the isolation and purification of the receptor protein, *tubulin* [1, 4, 28, 29].

The growth of research in this field has been and remains momentous, and papers by the hundred have been published each year in the last decade. It may appear unsound to attempt to write a monograph on the subject of MT, especially if it is planned to cover most aspects of these structures. The problem of dealing with the flow of information is considerable, but some kind of synthesis should be attempted.

Having covered twenty years ago the literature on colchicine, which was at that time already extensive, and having written several reviews on this subject and on MT [8, 9, 10], I felt that a synthesis of the works scattered in many periodicals was possible. It was also a help to have lived all the modern history of the subject, from the early work of A. P. Dustin and F. Lits, to the recent progress of MT chemistry and physiology. All these developments have shown that MT are fundamental organelles and that their importance for cell biology is at least as great as that of structures such as mitochondria or lysosomes. Their multitudinous functions show, in all eukaryotes, some constant features which become more apparent when all aspects of their activity are compared. This study must comprize the complex structures made of assembled MT—with other specific proteins—such as the centrioles, the cilia and flagella, the axonemes and other specialized organelles.

The ubiquity of MT demands that cells of all types be considered. The limitations of space, and the trends of recent work, will put more stress on animal than on plant cells. Unicellulars will be studied in several chapters, for they provide a wealth of information on the possibilities of MT assemblies, which were already suspected by protistologists long before the term microtubule was coined [12].

The history of MT research began with medicine, as *Colchicum* had been known since the end of the 18th century—and probably already in antiquity—as a cure for articular pain and in particular for gout, a position it still holds today. The discovery of the properties of the alkaloids of *Catharanthus* has brought to medicine at least two remarkable drugs, vinblastine and vincristine. Their action is closely related to their fixation on specific receptor sites of the tubulin molecule. More recently, many studies on the action of colchicine and on the medical uses of the *Vinca* alkaloids and some other MT poisons in gout and also in other inflammatory diseases, have been published, and Chapter 11 will be devoted to some medical problems related to MT functions.

In the last few years, several conferences and symposia have been devoted to MT and problems related with MT activity: the most important are the conference organized by the New York Academy of Sciences in 1974 [25] and the symposium which took place in Belgium in 1975 [3]. This was followed by a most important conference, held at Cold Spring Harbor in September 1975, and which covered in detail all the aspects of cell motility, comprising the role of MT in cell structure and movement [13]. This contribution completes the book edited in 1975 by Inoué and Stephens, and devoted mainly to cell motility [16]. Several other reviews of problems related to MT have been published since 1970, and should be mentioned here [2, 3, 5, 6, 14, 15, 17, 18, 19, 22, 23, 24, 26, 27, 30, 32].

Considering this wealth of information, one may wonder whether one more book was necessary. However, few reviewers have attempted to cover the whole field of MT research, from fundamental data to medical applications. The New York meeting neglected cilia and flagella, while Cold Spring Harbor was not concerned with the role of MT either in secretion or in neuroplasmic flow. These subjects may seem far apart, but the MT provide the link which leads to a synthetic understanding of all these problems. It is hoped that this may indicate which functions of MT are constant and which are not, and lead to a clear definition of the role, in all cells, of these organelles.

The literature covered, which numbers several thousand references, is mainly that of the last ten years. It extends to the end of 1976, with a few exceptions for 1977.

Although the tempo of new publications on this subject remains high, many important problems related to tubulins, their assembly, their control, their action, still await a solution. It is thought however that the time is ripe for an overall review. This will aim, as far as possible, to emphasize the unity of life through the variety of the structures made of tubulins and of cell functions which depend on their integrity.

The decision to write this book alone was reached with the purpose of giving the greatest unity to the text, and with the hope of completing a manuscript in the shortest time necessary, when the subject is moving fast and new papers are published each day. The author is well aware of the great dangers of this decision, and takes full responsibility for the errors which may slip into a book covering so many aspects of cell biology. He hopes that through descriptions of complicated facts and events, some idea of the marvellous adaptations of the living cell may become apparent.

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