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(Second Edition)

CANCER OF THE UTERUS

From
Gross Appearances
to
Ultrastructure

By

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CARLO ERBA FOUNDATION

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The object of the Carlo Erba Foundation is to promote international contacts between biologists, physicians, surgeons and others concerned with scientific and technical problems in the whole field of medicine. This is done by organizing meetings and lectures and by sponsoring the publication of works of wide interest. The offices of the Foundation are at Via Cerva 44 (Palazzo Visconti), Milan, Italy.

In 1960-62 the Carlo Erba Foundation organized the following symposia: Malignant lymphogranuloma; Cell morphology and biochemistry; Medicine and hygiene in schools; Surgery of the newborn; Psychosomatic influences in women; Athletic medicine; Allergology; Photography as an aid to medical and biological researches; Pathology of the lungs; Hygiene in modern life; Genes and chromosomes; Gerontology; Proliferative hemopathies; Electron microscopy; Parodontopathies; Building and hygiene; Physiopathology of operated and injured patients; Biological investigations in occupational medicine; Course of medical hypnosis; Feeding of the newborn; Enzyme deficiency and enzymopathies during childhood; Liver and bile diseases; Cell changes induced by physical, chemical and viral agents; Biopsy of the kidney; Psychology of the Child; Virus of the Nervous System; Arthrosis; Myocardial Infarction; Poliomyelitis; Human Chromosomes; Clinical Cytology; Melanin; Climatotherapy; Road Accidents; Air pollution; Radioactivity, and Atherosclerosis.

The Carlo Erba Foundation has sponsored the publication of the following works:

Il Cancro Dell'Utero—Dalla macroscopia all'ultrastruttura: Sirtori C. e Morano E.

Cea Editore—Milano, 1960 (I edition)

Gerontologia, Aspetti Metabolici: Bertolini A. M., Mas-sari N., Quarto di Palo F.

Cea Editore—Milano, 1962

La Patologia Del Progresso: Campanacci D., Gögler, E., Mallet L., Margaria R., Oselladore G., Polvani C., Serruys M., Sirtori C., Vollmar J., etc.

Feltrinelli Editore—Milano (in press)

DEDICATION

WE DEDICATE THIS BOOK to the masters of Italian Gynecology. To them we owe the stimulus to do research in this field of pathology, which in addition to its scientific importance, is of great humanitarian interest.

Some desire knowledge for its own sake, and this is ugly curiosity; others in order to sell their knowledge, and this is vile gain; others for love of fame, and this is foul vanity; but there are also those who seek knowledge to edify others, and this is great merit, or to edify themselves, and this is a sign of wisdom.

(ST. BERNARD)

FOREWORD

IT WAS MY PRIVILEGE and pleasure to be invited to assume the responsibility of translating into English this classic work of Carlo Sirtori and Ettore Morano. The first edition which appeared in 1960 was so well received by students of the cancer problem around the world that an English edition was considered desirable to broaden the circle of readers.

The authors have undertaken to carry out a meticulous study of cancer of the uterus, exploring every facet by means of both time-honored sources and the most modern tools available to the researcher. To accomplish their ends they had available an unlimited number of patients exhibiting every clinical variation of the neoplasm in the uterus and adjacent organs. Their studies were largely at the cellular level beginning with the life cycle of the normal cell in the ectocervix, endocervix and the endometrium, extending to the progressive changes exhibited in developing neoplasia and finally to the detailed characteristics of the cancer cell locally, environmentally and systematically.

The authors and their associates made use of exfoliative cytology, light microscopy and histochemistry. However, their most promising tool is the electron microscope which broadened their horizon tremendously. With it they have been able to demonstrate anatomically minutia not apparent to previous scholars. Histochemical changes have been studied to ascertain disturbances in cellular function. Irradiation effects on carcinoma cells have been investigated to provide new clues toward the improvement in the use of this our most important therapeutic agent. The effects of other procedures such as endocrine surgery, hypophysectomy, oophorectomy and adrenalectomy on cellular growth and development have been explored.

This book presents an exhaustive review of our fundamental knowledge about uterine cancer. It pinpoints areas where well directed research may prove exceedingly fruitful. The enthusiasm and interest of Sirtori and his colleagues in human cancer is reflected throughout the book, which should be of interest to every student of cancer, to the research scholar in the basic sciences and to the physician whose primary concern is the diagnosis and successful therapy of this major medical complication.

I should like to thank Dr. Julia D. Dawkins of England whose literary

talents as well as her medical knowledge are responsible for the fluent English. Dr. George L. Wied, the Director of our cytological laboratories at The Chicago Lying-in Hospital, helped tremendously in providing modern and correct nomenclature.

Lastly, I appreciate the Foreword by my friend and colleague, Charles Huggins, one of the world's outstanding scholars in cancer research.

M. EDWARD DAVIS, M.D.

FOREWORD

*Se tu segui tua stella,
Non puoi fallire a glorioso porto
Inferno CANTO XV*

THE TRANSLATION INTO ENGLISH of this work by Carlo Sirtori is an event of magnitude in the world of Medicine since it makes IL CANCRO DELL'UTERO available to a wider circle of readers. Since its original publication in 1960, this volume has attained the rank of a classic in science which is mandatory reading for wide circles of scholars.

Professor Sirtori exhibits his profound learning by considering uterine cancers exhaustively. In this he follows the great tradition of Science that advances can only be made by deep study of a restricted area and not by superficial examination of a broad field. From a study in depth of this kind, the great generalizations follow.

The present work is Leonardesque in scope. The beautiful electron microscopic representations evoke high esthetic emotions while contributing uniquely to scientific knowledge. da Vinci would be the first to applaud the results. Nor would Leonardo be alone in this. Carlo Sirtori has earned the thanks and applause of all cancerologists and gynecologists. Not only these—the women whose tragic lot will be alleviated through his efforts will count the name of Sirtori blessed.

CHARLES HUGGINS, M.D.

PREFACE TO SECOND EDITION

IT IS THANKS to the great kindness of Mr. Charles C Thomas that this book is now available in English. It will contribute to the spread of the prophylactic concepts which have inspired it and will strengthen the efforts of those engaged in the fight against cancer of the uterus.

This edition published by Mr. Thomas contains more material than the first Italian edition, including a larger ultrastructural and biochemical discussion of subcellular bodies; a fuller study of the endometrium by the electron microscope; an analysis of the ultrastructural changes induced by irradiation, in the cells of carcinoma of the ectocervix; a more detailed investigation of the osmiophilic bodies observed in carcinomas of the uterus; a more extensive coverage of carcinoma in situ; a study of carcinoma recurrences; observations on hypophysectomy and ovariadrenalectomy and finally an original chapter on changes in the senile cells, observed through the optical and electron microscopes. Other additions relate to Arias Stella cells; the cytological diagnosis of lung, peritoneal, and bladder metastases from carcinoma of the uterus; the detection of tumor cells in the peripheral blood and a study of alterations in the bladder, ovaries and pelvic lymph nodes induced by radium, radioactive isotopes and high voltage therapies.

I should like to thank here Professor M. Edward Davis, Director of the Department of Obstetrics and Gynecology of the University of Chicago, who took on the onerous task of revising and correcting the English text and presenting it to his American colleagues. I wish to express my most heartfelt gratitude to him. I wish to convey my special thanks to my great friend Professor Charles Huggins, who most ably supported me in my work and contributed to its happy outcome. Huggins, gifted with an introverted fanaticism for science, inspires me to paraphrase a fragment from Machiavelli's letters: "sembra giochi a tricke-trac coi villani, ma è sempre vestito di panni curiali e chiuso nel tempio della scienza per la quale è nato" ("even though he seems to be playing tricke-trac with peasants, he is always clothed in curial cloth and closed in the temple of science for which he was born").

Finally, I should like to express my gratitude to Dr. Zavanella, Dr. Meriggi and Dr. Severini for their intelligent collaboration in the study of senile cells. I should also like to record my appreciation of the reviews

written by Dr. Ruth M. Graham, Dr. Clarice do Amaral Ferreira, Dr. Paul Pundel and Dr. George L. Wied on the first edition of this book.

CARLO SIRTORI

Milano

N.B.: The text of this book has been prepared in accordance with the recommendations of the Cytological Terminology Committee (Chairman, George L. Wied) at the meeting held in Vienna from August 31st to September 2nd, 1961. We have, therefore, used, among others, the terms eosinophilic and cyanophilic instead of acidophilic and basophilic, and the symbol E.I. (Eosinophilic Index) instead of A.I. (Acidophilic Index).

PREFACE TO THE FIRST EDITION

EVERY YEAR cancer of the uterus kills about half a million women throughout the world. Yet a little foresight, better prophylaxis and more care and attention, could reduce this figure to a level which would be more acceptable, though still sad.

It is our hope that the enthusiasm and experience that have gone into the writing of this book, will leave some impression on even the most casual reader, and that it will be of real benefit to those who are engaged in the fight against uterine cancer.

In Dr. Morano I have found a careful and conscientious collaborator, imbued with a sincere enthusiasm for applied research. With his profound knowledge of methods of investigation; his clear thinking; exact, penetrating analysis and skillful synthesis, my young colleague will certainly be making further contributions to Italian pathological anatomy.

I should like to feel that this work will be useful to cytologists, histologists, pathologists, gynecologists, radiologists, surgeons, physicians and all those who are concerned with the problem of cancer. I say "the problem of cancer" because, although this work is confined to the neoplasms of a single organ, it may be relevant to all types of neoplasm.

Our experience is based on thousands of cases of uterine pathology and on a thorough reading of the immense literature on the subject.

We have discussed the various diagnostic methods, stressing the application and advantages of each. We have also devoted much space to histochemistry, histophysics, radiobiology, hormone studies and electron microscopy. We have attacked electron microscopy with the enthusiasm of a neophyte.

Electron microscopy is, in effect, only six years old. It is fascinating whether seen as a metaphysical, philosophical or a spatial problem. Our observations in this field are examined in detail, in the final chapter of this book, because they form the backbone of a new system of knowledge whose future developments can already be foreseen. We have sufficient grounds for expecting much from future investigations in this field of cancer research. By this method, we have observed that desmosomes are present in the endometrium. We have shown that there is a specific alteration of the cell surface in carcinoma of the ectocervix and of the

endometrium. We have suggested a rational explanation of the differing tendencies of endometrial and ectocervical cells, to exfoliation. We have demonstrated a new ultrastructural pattern called "close mesh material," which is correlated with the accumulation of glycogen in the cytoplasm. We have demonstrated the prelethal state of the endometrial cells during the luteal phase.

The material has been divided into four parts for the sake of the didactic method. The first section is devoted to the pathology of the ectocervix, the second to the pathology of the cervical canal and the endometrium, the third to electron microscopy and the fourth to final conclusions.

The frequent quotation of aphorisms is the only concession to literary leavening we have allowed ourselves in a work which is intended to be formal and synthetic in presentation.

At this point, I should like to express my thanks and Dr. Morano's to all those who contributed to making this book possible. They include the Carlo Erba Foundation, which, with enlightened generosity, sponsored the publication. We wish to thank Professors Giordani and Califano of the National Research Council, who approved our research topics and helped and encouraged us in our work. We also wish to thank Professors Dellepiane, Ingiulla, Massazza, Vozza, Natale, Vecchiotti, Barigozzi and Lanza-vecchia, and our colleagues Candiani, Remotti and D'Incerti Bonini, who kindly allowed us to reproduce illustrations of their work. We wish to thank Professor Pizzetti for working up the histological material, and our collaborators Zavanella and Pignataro for their contributions to the histochemical and hormonal investigations.

We also thank Professors Bernhard, De Brux, Dmochowski, Foote, Gey, Huggins, Oberling, Papanicolaou, Porter, H. Stewart and TeLinde, for lending the weight of their authority to the interpretation of our observations. Finally, we are indebted to Professor Bozza of the Milan Polytechnic, and to Professor Ranzi, director of the Zoology Institute of the University of Milan, who received us in their electron microscopy research centers with exquisite courtesy.

We would like to express our special gratitude to Dr. Mara Ricci for her help with the colposcopic examinations, to Miss Marita Lanza for her care in preparing the text, the bibliography and the analytical index, and to Mr. Nizza for his arrangement of the text and the illustrations.

CARLO SIRTORI

Milano

MATERIAL STUDIED

CASES STUDIED through cytologic examination, colposcopy and Schiller's test: 4,816 divided as follows:

Normal Portio Vaginalis of the Cervix	586
Erosion (Ectopy)	970
Squamous Metaplasia	1,499
Polyp	441
Atrophy	216
Vaginal Trichomoniasis	216
Epidermization	45
Leukoplakia	68
"Base" of Leukoplakia	89
Red Zone	30
"Mosaic" Leukoplakia	180
Papillary Base	68
Iodine-Negative Zone	213
Erosio Vera	90
Carcinoma	105

Cases studied through cytologic examination only: 6,430 cases divided as follows:

Classes I and II	4,500
Class III	80
Classes IV and V	350
Cytohormonal Investigation	1,500

Cases studied through colpomicroscopy: 105

Cases studied through electron microscope: 131 divided as follows:

Normal Ectocervix	10
Carcinoma of the Ectocervix	19
Normal Endometrium	75
Adenoacanthoma of the Endometrium	3
Adenocarcinoma of the Endometrium	24

Cases studied through histological examination only:

Ectocervix: 4,811 divided as follows:

Squamous Carcinoma	3,452
Undifferentiated Carcinoma	269
Polymorphic Cell Carcinoma	110
Microcarcinoma	21
Carcinoma In Situ	32
Sarcoma	2

Hyperdysplasia: 118; hyperplasia: 32; epidermization and squamous metaplasia: 53; leukoplakia: 6; true ulcer: 24; polyp: 98; atrophy: 480; radiation induced alterations: 73; tuberculosis: 9; syphilis: 2; miscellaneous: 28.

Endocervix: 651 divided as follows:

Adenocarcinoma	303
Polymorphic Cell Carcinoma	2
Undifferentiated Carcinoma	81
Microcarcinoma	2
Carcinoma In Situ	6
Sarcoma	4

Epidermization: 36; polyp: 61; decidual changes: 4; inflammation: 114; tuberculosis: 2; miscellaneous: 36.

Uterine Body: 2,697 divided as follows:

Adenocarcinoma	485
Adenoacanthoma	52
Microcarcinoma	13
Carcinoma In Situ	4
Carcinosarcoma	12
Sarcoma	4

Hyperdysplasia: 147; hormonal hyperplasia: 1,079; epidermization: 60; endometriosis: 28; hypoplasia: 15; inflammation: 274; polyp: 187; myoma: 150; decidual changes: 61; post-abortion inflammation: 55; hydatidiform mole: 8; chorionepithelioma: 5; tuberculosis: 4; miscellaneous: 54.

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