CANCER CHEMOTHERAPY

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PREFACE

The present volume contains the complete series of lectures delivered at the Boerhaave Course on Cancer Chemotherapy held at Leiden, The Netherlands, from September 2 through September 5, 1970.

The introductions to the discussions have been included but the panel discussions themselves had to be omitted for lack of space. The lack of uniformity in the nomenclature of cancer chemotherapeutics and in the dosages still constitutes a problem. The editors were of the opinion that in the original text no alterations were to be made, but in the appendix a table of synonyms in nomenclature and a nomogram of dosages has been included.

The editors are indebted to Dr. N. Lubsen, Egmond aan Zee, and to Miss S. E. Oudgenoeg for their help with the preparation of this book, and to Miss G. Hulsman for the translation of some of the manuscripts.

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INTRODUCTION

R. J. H. KRUISINGA

Although writings of the ancient Egyptians already speak of the use of medicaments to treat ulcerating skin tumours, the modern era of cancer chemotherapy is barely 30 years old. It starts just before the Second World War with the application by C. B. Huggins of castration on prostate carcinomas.

At almost the same time it was discovered that a group of chemical compounds derived from mustard gas had a strongly cytotoxic effect. The blood cells, especially the leucocytes, lymphatic tissue, bone marrow and the mucous membrane of the gastro-intestinal tract all were highly sensitive to these compounds.

Immediately after the war it was disclosed that favourable results had been obtained with nitrogen mustard on patients with Hodgkin's disease. At the end of 1947 S. Farber reported favourable results with chemotherapeutics in treatment of acute leukaemias in children. New drugs proved capable of effecting clinical remission.

These chemotherapeutics are, as you know, antagonists of folic acid, an essential metabolite for the development of red and white blood cells. They were later followed by the development of mercaptopurine and fluoruracil.

In 1954 the Cancer Chemotherapy National Service Centre was founded in the United States of America and the Groupe Européenne de Chimiothérapie Anticancéreuse was founded in Europe. The objective of these institutes was the growth and concentration of chemical, biological and clinical research. A marked acceleration in development resulted.

The group of nitrogen mustard chemotherapeutics was expanded. Other alkylating substances like thio-tepa and busulfan appeared on the scene. ACTH and corticosteroids were found to be effective against acute leukaemia, lymphosarcoma and Hodgkin's disease. The derivates of vinca-rosea, inhibitors of the metaphase of cell mitosis, were devel-

oped. Some antibiotics, such as dactinomycin, could also be used as cytostatics.

In the sixties the conviction grew that these chemotherapeutics were capable of effecting long remissions if not a cure especially among patients with rapidly growing malignant processes spread throughout the body. This remarkable progress was noted most clearly with acute lymphatic leukaemia, the other leukaemias, Hodgkin's disease, Burkitt's tumour, choriocarcinoma, Wilm's tumour and testicular carcinoma.

In addition to its application as primary therapeutic in malignant systemic diseases or general disseminations, chemotherapy has also shown its value in combination with surgical or radiological treatment.

The malignant neoplasms or cancers offer a great variety of syndromes. But all have in common an unbridled infiltrative growth of cells capable of metastasis. Neither the efforts in the epidemiological and clinical field nor laboratory experiments, nor cytobiological investigations of genetic material, have been able to inform us fully about the fundamental cause of this abnormal cell growth.

The cancer chemotherapeutics influence cell metabolism most by disturbing the biosynthesis of nucleic acids. In principle their effect on the ordinary dividing cell and the cancer cell is the same. Their selective action is therefore small and is based chiefly on differences in activity with respect to cell division.

The limited therapeutical breadth of these aggressive agents is also the cause of many undesirable side-effects. Normal tissue whose cells divide actively, such as bone marrow, lymph, gonade, foetus, etc., is inhibited. The inhibiting influence on resting, not generating cancer cells is on the other hand normally negligible.

In contrast to the chemotherapeutics against infectious diseases, a cytostatic action is not enough. In infectious diseases the immunological reaction of the host can help to further liquidation of the microorganism. Cancer chemotherapeutics receive hardly any such support and should possibly remain active right down to the last malignant cell.

In essence the difference goes still further, for cancer therapeutics are immunosuppressives, a phenomenon which should also receive attention during this course.

Although admirable progress has been made in experience and application, these and other fundamental facets do clearly show that

cancer chemotherapeutics can now at most be regarded as being in their early stages. A clinical investigation cannot take place until the new drug has been thoroughly screened in the animal test. Then the tolerance of the patient towards the agent has to be tested. The influence of the substance on tumour growth naturally calls for good criteria with regard to objectively measurable improvements. In addition to the evaluation of the ultimate result of the therapy, every attention should be paid to the evaluation of alternatives.

The rapid development of chemotherapeutics in recent decades and the many important unanswered questions regarding malignant growth, and the great problems of the cancer therapeutics, such as their limited action – often no cure, but a temporary improvement – their toxicity, their resistance, all these require the greatest expertise in many fields. This calls for cooperation between laboratory and clinic, between biochemist, pharmacologist and doctor. It requires an international exchange of data.

It also requires that all who are active in this field are informed as widely and as up to date as possible. That is why we consider this postgraduate course in the dissemination and exchange of information so important. The programme of this course we hope will contribute to its success.

Of course, chemotherapy, the heart of this course, must be placed within the totality of possibilities of cancer control. Of course, we must also continue to realize that our chemotherapeutic action with respect to malignant processes is ultimately determined by the patient in his entity as a human being.

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PART ONE