THE MORPHOLOGICAL PRECURSORS OF CANCER

Proceedings of an International Conference
held at the University of Perugia,
26th to 30th June, 1961

EDITED BY

LUCIO SEVERI

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DIVISION OF CANCER RESEARCH
PERUGIA
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EDITOR'S ACKNOWLEDGEMENT

On the occasion of the centenary celebrations of the Chair of Morbid Anatomy, an International Conference on the Morphological Precursors of Cancer was held at the Institute of Morbid Anatomy and Division of Cancer Research, of the University of Perugia Medical School, 26th to 30th June, 1961.

This Conference — with the sponsorship of Farmitalia Società Farmaceutici Italia — was attended by research workers from 26 countries, representing five continents.

Contributions to the support of the centenary celebrations, including this Conference, were made by the Ministero della Pubblica Istruzione, Ministero della Sanità, Farmitalia Società Farmaceutici Italia, Università degli Studi Perugia, Accademia Anatomico-Chirurgica Perugia, Amministrazione Provinciale Perugia, Comune di Perugia, Cassa di Risparmio Perugia, Ente Provinciale per il Turismo Perugia, Azienda Autonoma di Turismo Perugia, Istituto Nazionale Assicurazione contro le Malattie, Soc Philips sezione Metalix, Officine Galileo di Milano, Ing. A. Rastelli & C. Roma, Soc. Perugina Perugia, and Banca Popolare di Spoleto.

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The organizing committee is indebted to Drs. *G. Andreassi, J. Baló, C. Berman, J.J. Bittner, G.M. Bonser, P. Bucalossi, P.F. Denoix, K.B. DeOme, T.B. Dunn, V. Famiani, A. Haddow, L. Haranghy, J.R. Heller, V.R. Khanolkar, N.A. Kraevsky, C. Krauspe, L. Kreyberg, J.G. Kidd, D. Merlini, O. Mühlbock, J.W. Orr, P.R. Peacock, H.E. Rawlinson, R.W. Scarff, K. Setälä, W.L. Simpson,* and *L.C. Strong,* who acted with vigour and tact as chairmen at the various sessions, and moderators of the various panel and group discussions.

Further, the Editor would like to remember very particularly his senior co-workers, *C. Biancifiori,* M.D., *M. Barbieri Olivi,* M.D., and *F. Squartini,* M.D., who did a tremendous job on that occasion.

The Editor cannot fail to specially point out that these Proceedings have been almost wholly prepared in Perugia — Fotoincisione Perugia made the blocks for the black and white photographs, Unione Artistica Industrie Grafiche Milano, whose owner is a fine old character of Umbrian birth, made those for the coloured photographs, and Stab. Tipogr. Grafica di G. Salvi & C. Perugia printed the book — all this under the artistic supervision of the painter *Enzo Rossi*, who also took care of the covers of the « red » and « green » booklets regarding the programme. Miss *Hazel Riseborough* of the University of New Zealand was most helpful as Secretary of the edition and endeared herself to the Editor by coping with some of the language difficulties. The Editor's thanks are also due to *G. Rossi*, M.D. who patiently checked the manuscripts, figures and tables.

Authors were made responsible for their papers, and the Editor thanks them for their help in correcting the proofs.

L.S.

Perugia, March 4th 1962.

PREFACE

In this latter part of the twentieth century in which the field of cancer research has been flooded with the literature of reviews, progress reports, advances, proceedings of symposia, etc., unfortunately with many of the topics duplicated and many of the reviews of a non-critical nature, it is refreshing to have presented a series of studies concerning the histopathologic evaluations of carcinogenesis, particularly of the changes leading up to a morphologically distinguishable neoplasm.

Much is to be gained from histopathologic studies which are not strictly of a perfunctory nature. In the experimental field a beginning to the understanding of recognizable, reproducible changes preceding cancer has been made in the papilloma-to-carcinoma sequence studies with the Shope papilloma-system, in the studies of the relationship of the Bittner milk agent to hyperplastic nodules in the mammary gland and of the relationship of these to mammary neoplasia, and in a study of those early changes preceding the development of lymphocytic neoplasms following introduction of a leukemogenic virus. The lack of correlation of structure of neoplasms with their clinical behavior most likely indicates serious deficiencies in our understanding of the biology of neoplasia. The recent attempts to revaluate histologic structure of mammary tumors in mice in terms of cellular origins of tumors, their progressions through development and their responsiveness to extrinsic stimuli appear to be rewarding efforts.

An awareness is developing of the need for histopathologic study and evaluation and of correlation of these findings with biochemical, immunologic, virologic and genetic data in those systems involving tumor virus and host cell relationships *in vivo*, carcinogenesis in tissue culture with the new agents, and in organ-culture studies designed to study carcinogenesis.

At the clinical level it is important to know what, if any, specific precancerous changes occur in different tissues and the predictive values of such histopathologic changes, the time relationships between precancerous and cancerous changes and whether or not it is possible to alter or change the direction or behavior of such patterns.

Through a Conference such as this it is possible to attain a closer integration of clinical and experimental findings and to establish and stabilize the present knowledge in the field.

The Conference was inaugurated on June 26, 1961 by *L. Severi*, Chairman of the Conference. Investigators from 23 countries participated in the conference and the scientific sessions covered many aspects of the problem including the characteristics of chemical-, viral-, and hormone-induced precursors of cancer and their cytochemical aspects, the description and significance of premalignant precursors of liver, hematopoietic tissue, breast, bladder, uterus, skin, digestive tract, lung and endocrine glands. The panel discussions concerned the possible relationships of observed experimental and clinical premalignant changes to cancer, particularly of the lung and liver. Finally the group discussions were concerned with a specific topic « The Significance of Uterine Carcinoma *in situ* » and the summarizing general topic of the prospects for further research.

It is hoped that the information presented by individuals and developed through the panel and group discussions will come to represent a landmark of the state of knowledge of « The Morphological Precursors of Cancer ».

LLOYD W. LAW

Bethesda, Maryland, November 30, 1961.

FOREWORD

One hundred years of teaching of a medical subject to successive generations of students is no mean achievement. To this may be added the inspiration which has been given to young pathologists and the establishment of a new and vigorous research centre. These are the facets of the Department of Morbid Anatomy in the University of Perugia around which we are gathered in order to mark the centenary of the founding of the Chair in that subject. We desire to express our hopes and good wishes for the welfare of the department in the succeeding hundred years.

The University of Perugia itself has added to the feelings of jubilation which we have all experienced by conferring its highest honour on five scientists to whom has been granted the degree of Doctor of Medicine, *honoris causa.*

Congratulations and good wishes have their place in science, but the centenary celebrations would have lacked purpose without the opportunity to discuss and exchange ideas regarding the scientific work in which we are all engaged. Therefore the organisation of a CIBA Foundation Symposium on « Tumour Viruses of Murine Origin », followed by a more general symposium on the « Morphological Precursors of Cancer » was especially apt. These took place in the buildings of the Division of Cancer Research, the new extension of which was opened during the time of the symposia by Dr. *Thelma B. Dunn,* of the National Cancer Institute, Bethesda, U.S.A.

The long latent period between the moment of application of a carcinogen to a tissue and the subsequent appearance of cancer has occasioned speculation and experiment for at least half a century. During the latent period tissue changes which can be seen with the microscope take place and at some particular moment cancer emerges. The time of this latter occurrence cannot be predicted and the moment can rarely be determined with more precision than a period of a few days. It was natural that pathologists should seek to find in human tissues already the seat of cancer concomitant microscopical changes which resemble those seen in animal tissues *before* the stage of cancer is reached and should regard such changes, when present, as precancerous. It is reasonable to believe that when similar changes are already

present in human non-cancerous tissue a prediction that cancer will supervene may be made. What is lacking is knowledge concerning the length of time which must elapse between precancer and cancer, the proportion of lesions in which cancer can be expected to supervene within the lifetime of the subject and whether microscopical precancerous changes are *essential* to the development of all cancers.

The experimentalist can vary the conditions of his experiments at will, but the clinical pathologist must give an opinion on a lesion in a particular patient, the future treatment of whom depends upon his decision as to whether the changes seen are immediately or remotely precancerous. From the deliberations of the conference emerged the idea that the microscope will continue to be a useful tool with which to detect the presence of precancerous lesions, but that means must be found to submit the subsequent behaviour of these lesions to experimental analysis. A start in this direction has been made in the discovery that the hyperplastic nodules of the mouse breast, when transplanted into the breast fat pad of related animals, have a variety of fixed growth patterns. The next step is to find out by what means these growth patterns can be modified, and to extend such studies to other tissues.

For some members of the Conference a return to Perugia was almost a return home. For others it was the first visit. For all it was a pleasure to enjoy for a brief period this ancient and beautiful city, full of architectural, artistic and historic interest of the highest order, and to receive the generous hospitality of town and gown, especially that of the Division of Cancer Research.

GEORGIANA M. BONSER

Leeds, July 20th, 1961.

Part I

INTRODUCTORY REMARKS

Addresses of Welcome

LUCIO SEVERI

ALEXANDER HADDOW

Opening Lecture

TOMIZO YOSHIDA

Magnifico Rettore,

Since 1951 — when we dedicated the 11th volume of « Lavori dell' Istituto di Anatomia e Istologia Patologica di Perugia » (*Lav. Anat. Pat. Perugia*) in honour of the 90th anniversary of the inauguration of the official teaching of Morbid Anatomy in the University of Perugia — we have had in mind to celebrate, this year, the centenary of the founding of the chair of Morbid Anatomy in our University, by means of two conferences which would be concerned with some present-day topics.

Because of our increasing interest in the study of cancer, we decided that the problems to be approached were those connected in various ways with the main problem of cancer. And thus the problems of aetiology and pathogenesis were gradually outlined as subjects for this occasion.

The precise subject of the Conference which we are now about to open, namely, « The Morphological Precursors of Cancer », was chosen in May 1959, and I wish to acknowledge the help and advice which were given by my colleague, who is Reader in Cancer Research at the University of Leeds, and has for some years been a collabortor in the work of our laboratories in Perugia.

This subject had already been discussed between the old walls of the Institute, which are today scarcely recognizable. In April 1937, in fact, during a refresher course on tumours, organized by the « Lega Italiana per la Lotta contro i Tumori » (Perugia Section), the then Director of this Institute of Morbid Anatomy delivered a lecture entitled « On the General Morphology of Precancerous States ».

In the period 1946-1955 we were actively concerned with the study of dysplasias of the breast and now, from time to time, we like to consider and recall attention to this disease. Later we became interested in metaplasia, hyperplasia, and carcinoma *in situ* of the human uterine cervix, and have reproduced similar lesions in the mouse. In addition we are studying the relation between benign and malignant tumours of the thyroid.

More recently, since our activities have widened into the Division of Cancer Research, we have turned our attention by means of experimental pathology to hyperplastic lesions of the breast in mice, and lastly, we have in progress the study of experimentally induced hyperplasia and benign and malignant tumours of the lung.

At this point it seems opportune to say what we propose by this conference, which we thought ought to cover the specific topics indicated by the meetings as an introduction to the general problem.

To achieve this we had to fix some limits, otherwise the topics presented, and their discussion, would inevitably have led us into too wide a field.

We will discuss cancer in the light of its morphological precursors, being well aware that this will soon become difficult because we must come to some agreement on what is meant by precancerous lesions. Not only this, but perhaps we have prejudiced the preliminary question, since we have already admitted the existence of precancerous lesions. We have done this because we believe that there are few, if any, who would dispute such a contention.

The steady discovery of carcinogens, in which term I include the viruses, which were discussed here last week, has perhaps reduced interest, in some ways, in the aetiology of cancer, since we can say, not without a certain pride, that we can now produce cancer at will, and this after but few decades of study.

But we do not know how carcinogens act, and here lies the present-day interest in pathogenesis, for the morphological precursors of cancer are a pathogenic, rather than a histogenic problem.

It is possible that cancer develops directly from a healthy tissue (that one is dealing with a drama in one act, as has been stated), but every day new evidence accumulates that cancer develops in diseased or already prepared tissue. We still have to establish whether the disordered tissue is a true precancerous lesion, or is an occasional precursor of cancer, as for example gastric ulcer in relation to cancer of the stomach. When cancer supervenes on a precancerous state, the process is slow, and can be divided into two phases.

The first, the biological precancerous phase, we cannot detect with the means at present at our disposal. The second, the morphological precancerous phase, we can see with the microscope. It seems clear to us that this second phase is a fascinating subject to study if we wish to comprehend cancerogenesis as a whole. Gradually exploring the dark area which comprises the biological precancerous phase, we could, we must one day — a day which in truth still seems far off — understand

the initial invisible changes which lead to cancer, and therefore verify existing theories, such as those of somatic cell mutation and viruses, or discover some new factor still beyond our ken.

Clearly we are looking far ahead, perhaps too far with respect to our present possibilities, but although they may be fantastic today, these prospects are no less attractive.

The papers as set out in the programme follow the line which we have just clarified. We start with a consideration of the relationship between benign and malignant tumours, a subject with which we could not end the conference, since it serves to crystallize the premises from which we start, and from which we will continue to the general problem.

Later there will be a series of papers on the morphological precursors of cancer in various systems. These papers, the results of long and tiring work by specialists in their fields, will be for us all a source of valuable information.

On Tuesday and Wednesday precancerous lesions of the breast of humans and animals will be considered. This subject occupies a primary place not only on account of the interest which it holds for my coworkers and me, but because of its importance in all cancer research. A well-known cancer research worker, who is here with us today, has said « the study of tumours of the breast has thrown more light on the fundamental problems of malignancy than any other aspect of tumour pathology ». Many of us will remember that in 1957, here in Perugia, a Doctor *honoris causa* of our Medical School who is also here with us today, called the breast « the fountain of cancer lore ».

In addition we will study precancerous lesions of the liver, haematopoietic tissue, urinary bladder, uterus, skin, digestive tract, lungs, endocrine glands, and miscellaneous (rare) premalignant changes. Each day we will attend conference lectures from 12.15 to 1.00 pm, so that we will always return to the general problem. We will hear « panel » discussions on the clinical and experimental significance of precancerous lesions, on the relation between liver cirrhosis and liver cancer, and on the relation between tobacco smoking and cancer of the lung. In a conference on cancerogenesis we cannot fail to discuss the latter problem as it has such great interest for all mankind. There will also be « group » discussions: one on the significance of carcinoma *in situ* of collum uteri, and the other a summary of the conference and prospects for further research.

These ideas and this programme have been devised by our staff, who welcome the opportunity to discuss common problems with you, our guests who have accepted our invitation to be here. The Magnifico Rettore of Perugia University approving our plan, has, as always, given us

his patronage, and this in turn, has made it possible for us to have the patronage of the Minister of Public Instruction. Experience has taught us to turn to Farmitalia for help, and once again they have come to our aid. Thus we find ourselves together in this building today, amidst leading representatives of the world's most important pathological societies and of the world cancer organisation.

Ladies and gentlemen, you are taking part in this « International Conference on the Morphological Precursors of Cancer » as representatives of the five continents: I wish you every success in your study and appraisal of the problems on your programme, and your conclusions in the different specific fields pertaining to your particular competence. We are embarking upon our task on this hill of Monteluce — the Hill of Light — which, as Dante wrote,* looks to the East in two senses, and is the first to escape from darkness.

Let us pray God it will no longer be true, as Claudio said to Vincentio, that «the miserable will have no other medicine but only hope»**.

LUCIO SEVERI

* Di questa costa, là dov'ella frange
più sua rattezza, nacque al mondo un sole
come fa questo tal volta di Gange.
Però chi d'esso loco fa parole,
non dica Ascesi, ché direbbe corto,
ma Oriente, se proprio dir vuole.

DANTE ALIGHIERI: *La Divina Commedia*, « Il Paradiso », Canto XI, 48-53.

(The hill of Monteluce looks to the East, and rises exactly opposite the western slopes of Monte Subasio, on which stands St. Francis' town of Assisi.)

***Claudio.* The miserable have no other medicine but only hope:
I have hope to live, and am prepar'd to die.

WILLIAM SHAKESPEARE: *Measure for Measure*, Act III, Scene 1-2.

Rector Magnifice,

Clarissime Severi,

Socii,

I regard it as a signal honour to have been asked to speak in these opening proceedings, on behalf of the doctoral graduates *honoris causa* of the University of Perugia Medical School.

We do not work for honour — at least we should not — but nevertheless the graduation ceremony of yesterday, in the Aula delle Lauree of San Pietro, must have been a source of gratification and encouragement to those so honoured, and of utmost pleasure to their many friends.

I vividly recall being the recipient of the same distinction in 1957, when in my case the honour was greatly enhanced through my being in the company of *J.J. Bittner* and *L.C. Strong*, than whom no two men have done more to advance our knowledge of the natural history of cancer. Their contribution was specially marked in the one case by early and pioneer genetical studies which led to the establishment of some of the first pure lines, now maintained the world over as basic weapons in cancer research, and in the other, by elucidation of the role of extra-chromosomal transmission, and of the Bittner virus, in the aetiology of murine cancer of the breast.

In speaking for the graduates *honoris causa*, I do so also in the name of *J.J. Bittner* and *L.C. Strong*.

The most recent graduates are five in number, from the United States, India, Germany, England and Japan.

J.R. Heller is a product of South Carolina at its best. A graduate of Emory in 1929, he has ever since pursued a distinguished career in medicine, as public health clinician and administrator, in the United States Public Health Service, as Chief of its Division of Venereal Diseases, and later as Director of the National Cancer Institute of the National Institutes of Health, and Assistant Surgeon General and a Director of the American Cancer Society. More recently he has undertaken fresh and great responsibilities as President of the Memorial-Sloan Kettering Centre in New York. But apart from his life-long

technical service, he deserves special recognition for his human qualities, being an example of that rare species, namely the human administrator, capable of operating vast organisations not merely with efficiency, but also with concord and amity.

V.R. Khanolkar I am very proud to say received his early professional training in University College Medical School in London, and graduated from London University, where he was Graham Research Scholar. Later Professor of Pathology and Bacteriology in Bombay and Director of the Laboratories of the Tata Memorial Hospital, he is now Director of the Indian Cancer Research Centre, President of the Union international contre le cancer, and also, Vice-Chancellor of the University of Bombay. Dr. *Khanolkar* has carried out pioneer work on leprosy, and on cancer in India associated with the habits and customs of the Indian people. For his meritorious service in these fields, he was awarded the title of Padma Bhushan by the Indian Government in 1955. He is an outstanding figure in our subject, and we are all delighted that the University of Perugia has seen fit to honour him in this way.

After graduating in 1920, *C. Krauspe* became Assistant in the Institute of Pathology of the Albertus University in Königsberg, later of the microbiology division of the Institute of Hygiene in the same University, still later joined the staff of the Institute of Pathology in Leipzig, and subsequently became Professor and Director in Königsberg, and, in 1948, Director of the Institute of Pathology in the University of Hamburg.

The honour done to him by the University of Perugia, recognises his numerous contributions in the fields of immune biology, infectious diseases with special reference to paediatrics, diseases of bone, and wound infection, and of bacterial mutation under the influence of chemotherapeutic agents.

J.W. Orr is a graduate of the Queens University of Belfast, in science with first-class honours in pathology, and in medicine with a gold medal for his doctorate thesis. A Fellow of the Royal College of Physicians in London, Member of the British National Committee on Cancer, an Editor of the Journal of Pathology and Bacteriology, and since 1948, Professor of Pathology and Director of Cancer Research in the University of Birmingham, he is the author of many original experiments and new ideas in the field of carcinogenesis, and it is these which have so happily been acknowledged by the University of Perugia.

In *T. Yoshida* we have an outstanding representative of cancer research in Japan. Now Dean of the Faculty of Medicine and Professor of Pathology in the University of Tokyo, and Director of the Medical

Institute of the Sasaki Foundation, he is famed for his initiation, with Dr. *T. Sasaki*, of the experimental production of hepatoma with the azo-dyestuffs, and for the conversion of such tumours into the ascitic form, especially in the Yoshida ascites sarcoma.

These and other achievements have been recognised by the award to him of the Yamagiwa Prize of the Japanese Cancer Association, the Hattori and Asahi Prizes. and the Scheele Medal of the Chemical Society in Stockholm, and on two occasions of the Imperial Prize, and in 1959 of the Order of Merit, from the Japanese Emperor. We rejoice in his latest honour accorded him by the University of Perugia.

Together with the older and the new graduates *honoris causa*, I wish to express to you, Dr. *Ermini*, not only as Rector but *our* Rector, and also to Professor *Severi*, most grateful appreciation of the honours so conferred.

Of all the reasons which compel our gratitude, not least is the opportunity which you have given to us to participate in an academic ritual and experience dating from the twelfth century, and linking the academic and humane traditions of the Middle Ages and the Renaissance, with that of modern science.

At any time such an experience must be at once salutary, inspiring and agreeable. I venture however to suggest that it may also possess another kind of significance for all of us, of the most practical kind.

A dominant feature of our present day science lies in the immensity and complexity of its world literature, still increasing at the fantastic rate of ten per cent each year. It is a matter of the most simple arithmetic, to show that no man can now hope to follow developments in his own subject, let alone in related fields, in proper detail, without the most prodigious and, indeed, impossible efforts.

In writing a paper on this subject some time ago, a member of my own staff put forward the intriguing notion, that in the latter part of the 20th century the role of the travelling scholar might resume something of the importance which it held in the Middle Ages and later, and that correspondence between individual scientists may again assume the essential importance which it held in the early days of the Royal Society of London.

It may not therefore be altogether too fanciful, to imagine that our present meeting in the historical precincts and confines of the University of Perugia, of scientists from every Continent and corner of the globe, may presage and symbolize a mode of scientific communication, very old but at the same time new, and holding implications most profound, not only for the spread of science but also, if it were to extend on a scale sufficiently wide, for the growth of that international knowledge and trust, which is too much lacking, and which

well may be the only secure foundation, for the comity of nations in the future.

Magnifico Rettore,

a nome dei laureati « honoris causa » ed anche, in vero, di tutti i presenti, noi desideriamo esprimere, per mezzo di Voi, alla Università degli Studi di Perugia, la riconoscenza più profonda per l'onore che è stato accordato e per l'occasione che ci è stata offerta attraverso la nostra permanenza nella Vostra Città tanto ricca di storia quanto ricca di bellezza, di portare il nostro contributo non soltanto alla scienza ed alla medicina, ma anche a quanto di meglio i popoli aspirano.

A. HADDOW