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Normal and Neoplastic Hematopoiesis

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NORMAL AND NEOPLASTIC HEMATOPOIESIS

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Preface

It has been five years since the UCLA Symposium on Hematopoietic Cell Differentiation was held and in the interval there has been an explosion of new knowledge concerning normal and neoplastic hematopoiesis. Modern immunology, molecular biology, virology, biochemistry, and cell biology have impacted on the field of hematopoiesis in a manner that has led to startling scientific advances. Great excitement was generated by the studies of expression of cellular oncogenes in hematopoietic cells and the correlation with specific cytogenetic abnormalities. The impact of virology and molecular biology has been felt most prominently in the isolation and molecular characterization of the human T-leukemia viruses (HTLV). This appears to be the first demonstration of a retrovirus causing human neoplasia. We also are beginning to understand the detailed molecular changes associated with the transition from inactive to actively expressed genes during hematopoietic cell differentiation. Many of the hematopoietic regulatory factors have been purified to homogeneity and some of these will be available as potential therapeutic agents in the not too distant future. The clinical impact of the basic science advances in hematopoiesis has already been substantial and is likely to increase dramatically in the next few years.

The participants were unanimous in their enthusiasm for this conference on Normal and Neoplastic Hematopoiesis. The discussions were animated, the atmosphere exciting, and the poster sessions of unusually high quality. The conference came at a critical time with regard to recent progress in the field. The developments in molecular biology, virology, immunology, and cell biology were updated and the clinical implications discussed at length. The spring skiing also was outstanding!

The present volume contains papers summarizing works presented at the plenary sessions and some of the poster sessions. They reflect the content and hopefully, the spirit of the scientific exchange.

The conference organizers thank Sandy Malone, Betty Handy, and the UCLA Symposia staff for the efficient planning and running of the conference. We also thank Hoffman-La Roche, Inc., Pfizer, Inc., the National Cancer Institute (USPHS CA 1 R13 CA34190-01), Adria Laboratories, Inc., Abbott Diagnostics Division, Eli Lilly and Company, Schering Corporation, and Shell Oil Company for their generous support of this meeting.

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INTRODUCTION

Over twenty years ago, Julian Huxley published The Biological Aspects of Cancer. I purchased and first read this book as a third year medical student at Harvard University, at a time when oncology was ill-regarded and little-mentioned in the Harvard curriculum. From Huxley's book, I quickly learned (for yet another time) that Harvard was negligent. "...cancer, far from being a field of purely medical concern, is a key subject for general biology.... It involves questions of genetics, infection, epigenetics, biochemistry, immunology, endocrinology, virology, pathology, clinical medicine, public health and human ecology, and poses in arresting form the problem of their due interrelation." (1)

Above all else, Huxley's book is suffused with the principle that differentiation and cancer are intertwined. It is mainly this principle that has brought us together for the week (snow may also have had something to do with it), and it is surely this principle that has brought me to this lectern (snow had nothing to do with that).

I am a virologist who has been led to the study of cancer and development by properties of the the tumor viruses with which I work. For the interrelationship

[1]Work in the author's laboratory is supported by grants from the National Cancer Institute, the American Cancer Society and the Hooper Research Foundation.

between cancer and development is stamped indelibly on the face of tumor virology, particularly on the face of tumorigenesis by retroviruses. Consider the following:

1) Neoplastic transformation by Rous sarcoma virus has wide-ranging effects on cellular phenotype which rarely spare the differentiated properties of the cells (2). The changes approximate chaos rather than any orderly scheme, but loss of tissue-specific properties is a common theme.

2) Two groups of avian retroviruses, represented by avian myeloblastosis virus (AMV) and myelocytomatosis virus (MCV, or MC29 virus), meddle in provocative ways with the development of myelomonocytic hemopoietic cells (2,3). The leukemic cells induced by these viruses display a hodge-podge of phenotypic markers representing developmental compartments that run the gamut from the most primitive to the most mature stages in the cellular lineage. How this kaleidoscopic phenotype arises is a matter of some controversy at the moment. All agree that, when a stem cell for the lineage is infected, transformation/leukemia arises only after some cellular maturation has occurred. It may also be true (herein lies the controversy) that infection of a differentiated member of the lineage can elicit the mixed phenotype, evoking a confused sort of dedifferentiation.

3) Perhaps the most incisive example now extant is avian erythroblastosis virus (AEV), masterfully studied by Graf, Beug, Samarut and their colleagues (3). Here is displayed what is likely to be leukemogenesis by developmental arrest, so dear to the heart of hematological oncologists. As we presently understand the scheme, the virus infects a BFU-E cell, which then matures to the CFU-E form from which the leukemia actually arises.

Who among you could look on these schemes and not recognize the purchase they represent, on oncogenesis and on cellular development. Moreover, there is genetic purchase here, that most hallowed leverage for the contemporary biochemist. There is genetic purchase because the events I have outlined can all be traced to the actions of single viral genes, and each of these genes has its counterpart in normal cells. My task here is to essay how we have been lead to this remarkable purchase, how firm it

may be, and where the future may lie.

CANCER GENES CONCEIVED

In 1866, Paul Broca sketched the pedigree of his wife's family. Since the motive to publish was as great then as it is now, we still have that pedigree, and from it, we can see why Broca believed he had discovered an hereditary diathesis to cancer. The insight seems to have attracted little attention in Broca's time. During the century that followed, however, biologists began to seek genetic explanations for tumorigenesis. Now the quest has reached fruition: the long-imagined cancer genes have been brought to view. They were unearthed first by a simplification, the use of viruses that cause cancers in animals.

The harvest from this simplification has been abundant beyond all expectation. Tumor viruses have revealed to us a set of genes whose activities may lie at the heart of every cancer, no matter what its cause. We view these genes as the keyboard on which many different carcinogens can play, whether they be chemicals, X-rays, the ravages of aging, or even viruses themselves. An enemy has been found; it is part of us; and we have begun to understand its lines of attack.

There is a subtlety here that deserves emphasis. The revelations of which I speak do not address the issue of whether viruses may cause some human cancers: that is another pursuit with its own challenges and recent flourish. I speak instead of how viruses have been used as experimental tools to ferret out universal processes that may cause a cell to run amok.

RETROVIRUSES: THE WAY IN

We owe much of our recent progress in cancer research to the retroviruses, whose genes are carried in RNA but are copied into DNA by reverse transcriptase during viral growth. The outlines of this process provide a microcosm of carcinogenesis. Once the viral genes have been copied into DNA, the viral DNA is inserted (or "integrated") into the chromosomal DNA of the host cell. Then, in a foolhardy act, the cell uses its own machinery to express the