

**MYELOYDYSPLASTIC SYNDROMES &
SECONDARY ACUTE MYELOGENOUS LEUKEMIA**

Cancer Treatment and Research

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**MYELODYSPLASTIC
SYNDROMES & SECONDARY
ACUTE MYELOGENOUS
LEUKEMIA:**
*Directions for the New
Millennium*

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*For my mother, Zaheer Fatima, and my father, Syed Ali Raza,
the most inspiring role models in my life.
For Harvey and Sheherzad who are my two biggest strengths &
paradoxically, my two biggest weaknesses
-Azra Raza*

*For my Guru Dr. Nandini Sheth
-Suneel D. Mundle*

*“Surely, you have been made to see if (only) you care to see;
surely, you have been guided if (only) you care to take guidance;
& surely, you have been made to hear if (only) you care to lend your ears”*
-- *Ali Ibn Abu Talib*
“Nahjul Balagha”

“Power Rests on Knowledge”
--*Thomas Sprat*

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PREFACE

Cytopenias in older individuals are becoming almost like what prostate cancer is in older men; if you live long enough, you have a high likelihood of experiencing it. Clonality studies in disease free women have already demonstrated an age-matched increase in the incidence of monoclonal hemopoiesis. More recently, dysplastic features in the marrows of otherwise healthy older individuals without cytopenias have been identified as well. Taken together, these two findings would suggest that as the absolute number of hematopoietic stem cells decrease with increasing age, and the marrow becomes oligoclonal, the likelihood of dysplastic morphology increases. How this translates into the pernicious and potentially lethal disease called *myelodysplastic syndromes* (MDS) is a challenge requiring our immediate attention since the incidence of MDS appears to be on the rise. Limited advances in the treatment of both MDS and secondary acute myeloid leukemia (sAML) in the last two decades also add urgency to improving our understanding of the stepwise pathology involved in the evolution of these diseases. Given the enormous scope of our subject and the page limitations imposed by our publishers, this book is not meant to be the comprehensive last word on MDS and sAML. Rather, by focusing upon recent developments in intramedullary proliferation and apoptosis of hematopoietic cells, role of cytokines in the production of ineffective hematoipoiesis, reasons for the poor in vitro colony growth of MDS cells, non-random cytogenetic abnormalities and sequential accumulation of molecular events leading to eventual leukemic transformation, as well as newer hypotheses regarding the etiology of MDS, we hope to provide thought-provoking suggestions to researchers in the field in this latest book on MDS and sAML.

A good example is the unique and interesting suggestion made by Dr. Harvey Preisler in the chapter on the evolution of secondary hematologic disorders. In order to dissect the sequence of events involved in the evolution of de novo MDS and/or AML in previously healthy subjects, one would have to follow thousands of individuals for years. Dr. Preisler suggests that one should be able to access an already established tissue bank maintained by the Women's Health Initiative where >100,000 women have been clinically followed for >10 years. Their blood and tissue samples have been stored at regular intervals. One can selectively examine serial blood samples for clonality studies/genetic mutations in women who were completely well at the time of enrollment on the study, but who during the course of periodic follow-up were found to have MDS and/or AML. Age-matched control samples from unaffected women would also be available in such a cohort. This study

population would be different than those examined previously and composed of patients heavily pre-treated for a prior malignancy. Undeniably, access to such samples will require an extra-ordinary level of cooperation amongst investigators belonging to various disciplines, but the dividends will be far greater also.

In many ways, the pre-leukemic disorders pose a greater biologic challenge than AML. The bone marrow contains a very heterogeneous population of cells in MDS, all of which are the descendants of a transformed parent, as opposed to a monotonous population of blasts in AML. No satisfactory animal model for MDS exists, and since the hallmark of the disease is excessive intramedullary apoptosis of hematopoietic cells, immortalized tissue culture cell lines can only be considered as being partially representative of the actual pathology. But, like President Kennedy once said, America should go into space not because it is easy, but because it is hard. When one is faced with a particularly difficult challenge, paradoxically, one brings to bear both intellectual and emotional faculties.

The good news is that there appears to be a surge of interest in MDS recently. Rather than being considered an appendage of AML worth no more than a sentence or two as an aside, MDS has finally acquired the credentials and status of a full-fledged, unique disease demanding the undivided attention of its students, with a dramatic increase in the number of researchers. Several Societies and Working Groups have appeared in the last decade and International symposia solely devoted to MDS are being regularly organized. No reputable hematologic oncology meeting is considered complete without a discussion of MDS nowadays, and an unprecedented proliferation in the number of publications entirely dedicated to the study and treatment of MDS is noted. Minds, once catechized with dogmatic nonsense are beginning to dispute established tenets, weighing in with contrary views to re-think and re-examine some cherished ideas. We hope that this timely publication will add to the lively, burgeoning, rapidly expanding field by precisely locating areas ripe for translational research so that our patients can finally benefit tangibly. We apologize to those colleagues in advance who feel that their works have either not received sufficient attention in this book, or whose ideas have been challenged. It is purely the result of focusing on selected aspects of highly complex diseases, and with malice towards none. Finally we hope to invigorate our colleagues by challenging them to reconsider some of their deep-seated beliefs. Remember what the author Frank Burgess said; If in the last few years, you have not discarded a major opinion or acquired a new one, check your pulse.

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March 6th, 2001