Millennium review

The myelodysplastic syndrome(s): a perspective and review highlighting current controversies

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Abstract

The myelodysplastic syndrome (MDS) includes a diverse group of clonal and potentially malignant bone marrow disorders characterized by ineffective and inadequate hematopoiesis. The presumed source of MDS is a genetically injured early marrow progenitor cell or pluripotential hematopoietic stem cell. The blood dyscrasias that fall under the broad diagnostic rubric of MDS appear to be quite heterogeneous, which has made it very difficult to construct a coherent, universally applicable MDS classification scheme. A recent re-classification proposal sponsored by the World Health Organization (WHO) has engendered considerable controversy.

Although the precise incidence of MDS is uncertain, it has become clear that MDS is at least as common as acute myelogenous leukemia (AML). There is considerable overlap between these two conditions, and the former often segues into the latter; indeed, the distinction between AML and MDS can be murky, and some have argued that the current definitions are arbitrary. Despite the discovery of several tantalizing pathophysiological clues, the basic biology of MDS is incompletely understood. Treatment at present is generally frustrating and ineffective, and except for the small subset of patients who exhibit mild marrow dysfunction and low-risk cytogenetic lesions, the overall prognosis remains rather grim. In this narrative review, we highlight recent developments and controversies within the context of current knowledge about this mysterious and fascinating cluster of bone marrow failure states.

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1. Introduction

Almost every journal article reporting research on the myelodysplastic syndrome (MDS) or reviewing these disorders includes an introductory statement similar to the following.

The myelodysplastic syndrome(s) include(s) a heterogeneous group of clonal bone marrow disorders characterized by ineffective hematopoiesis and a variable risk of transformation to acute myelogenous leukemia.

This broad definition, refined and supported by ample reports over several decades, is a statement with which almost all contemporary MDS investigators can wholeheartedly agree. But when it comes time to debate more specific details, this harmony quickly dissolves. This is because a number of important questions about MDS currently lack the definitive answers that all investigators crave: answers grounded in unambiguous data from rigorously reviewed scientific reports. As is the case in many other areas of medicine and science, in the absence of convincing evidence to answer the tough questions, strong and contrary opinions can flourish and vigorous discussion results.

How should MDS be defined—what minimal criteria must individual cases meet in order to be labeled “MDS”? What are the most useful ways to classify the various subgroups of patients? There are many reports describing potential pathophysiological clues; which avenues of biological exploration are most likely to yield results? Of more immediate interest to suffering patients: what are the best therapeutic approaches to the various subtypes of MDS, and which patient and disease features allow the most accurate prognostication of future events?

Complex questions like these have no easy solutions, and many dedicated investigators across the globe are working diligently to try to burn away the fog that enshrouds MDS. The authors of this review certainly do not presume to have the answers to any of these challenging questions. Instead, we share in the excitement of those who are fortunate enough to be pursuing their research quarry with increasingly sophisticated laboratory techniques in this present era of rapid scientific advancements.
bicellular progress. We confidently look forward to develop-
ments in the near future that will lead to more certain
diagnoses and better treatments.

This article is not meant to be comprehensive overview
of MDS. More than 4800 manuscripts about “myelodys-
plastic syndromes” have been published since the National
Library of Medicine began indexing this term in 1986, and
1151 articles on “preleukemia” appeared between 1977 and
1985. It would take a large volume indeed to do justice
to each critical topic and each major area of investiga-
tion. In lieu of being all-inclusive, we hope to highlight
here some of the most active, controversial, or interesting
areas.

2. Terminology: the power of language

Challenges with respect to MDS begin at the most
fundamental level: the language used to define and de-
scribe the condition. The importance of accurate and un-
ambiguous disease terminology extends far beyond the
development of communication tools to aid researchers
and clinicians. Writing in the neoplasia-nosology tradition
established by literary critic Susan Sontag, the late Profes-
sor Suzanne Fleischman, an exceptionally articulate MDS
patient who was a scholar of French and Romance Philol-
ogy at the University of California at Berkeley, pointed
out that the language of medicine also colors the way
patients think of themselves and their suffering and can
affect the perceptions of their physicians[1–3] . For ex-
ample, “preleukemia”, an older term for MDS that is no
longer widely used [4], cast a darker specter than the cur-
rently favored terms because it included the emotionally
charged word “leukemia”. “Preleukemia” also fell into dis-
favor because some patients died of complications of the
condition even though the dreaded full-blown leukemia
never appeared, while in other instances the “preleukemic”
syndrome behaved so aggressively and evolved so rapidly
that there was never a real distinction from overt leukemia
anyway.

The term “myelodysplastic syndrome(s)” emerged in the
mid 1970s from a long list of potential candidate descriptors
(Table 1) [5] and has become sanctified through international
currency. The ideal terminology remains elusive; although
the term MDS appears to have staying power, it may be
misleading in several respects [6].

2.1. “Myelo-” may be misleading . . .

Although the prefix myelo- accurately designates the site
of origin of MDS in the bone marrow, the term has several
meanings, and myelo- can imply narrow restriction of a dis-
order to non-lymphoid cells, i.e. those of erythroid, granu-
locyte, megakaryocyte, and monocyte/macrophage lineage.
Yet in some cases of MDS, lymphoid cells can also be shown
to be part of the aberrant clone [7–12], albeit infrequently
[13–16], and rarely, cases of MDS will transform to lym-
phoblastic leukemias [17–20]. These phenomena reflect the
fact that the cell of origin in MDS can be a very early multi-
potential hematopoietic progenitor and perhaps even the true
marrow incunabulum, the omnipotent undifferentiated stem
cell [21]. Admittedly, this terminological quibble is minor in

<table>
<thead>
<tr>
<th>Table 1</th>
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<tbody>
<tr>
<td>Some previous terms for the myelodysplastic syndromes, with key references (modified from [370,371])</td>
</tr>
<tr>
<td>Anemia pseudo-aplastica</td>
</tr>
<tr>
<td>Refractory anemia</td>
</tr>
<tr>
<td>Odoleucosis</td>
</tr>
<tr>
<td>Preleukemic anemia</td>
</tr>
<tr>
<td>Preleukemia</td>
</tr>
<tr>
<td>Chronic refractory anemia with sideroblasts</td>
</tr>
<tr>
<td>Refractory normoblastic anemia</td>
</tr>
<tr>
<td>Smoldering acute leukemia</td>
</tr>
<tr>
<td>Subacute myeloid leukemia</td>
</tr>
<tr>
<td>Chronic erythremic myelosis</td>
</tr>
<tr>
<td>Refractory anemia with partial myelofibrosis</td>
</tr>
<tr>
<td>Refractory anemia with excess myeloblasts</td>
</tr>
<tr>
<td>Subacute myelomonocytic leukemia</td>
</tr>
<tr>
<td>Refractory megaglobulastic anemia</td>
</tr>
<tr>
<td>Refractory macrocytic anemia</td>
</tr>
<tr>
<td>Preleukemic syndrome</td>
</tr>
<tr>
<td>Chronic myelomonocytic leukemia</td>
</tr>
<tr>
<td>Hypoplastic acute myelogenous leukemia</td>
</tr>
<tr>
<td>Hemopoietic dysplasia</td>
</tr>
<tr>
<td>Dysmyelopoietic syndrome</td>
</tr>
<tr>
<td>Myelodysplastic syndromes</td>
</tr>
</tbody>
</table>

The most appropriate name for what are now known as the myelodysplastic syndromes was a major topic at a 1975 symposium at Paris; a transcript
of the debate was published in a special 1976 issue of the journal Blood Cells [5]. Terms discussed included preleukemia, preleukemic states, myelodysplasia, myeloid dysplasia, myeloid dysplastic disorders, myelodysplastic syndrome(s), hematopoietic/hemopoietic dysplasia, stem cell dysplasia, and stem cell disease.
and the word myelodysplasia was eventually applied to marrow disorders chiefly affecting myeloid tissue (marrow), usually represents a well-established neoplastic clone and not “dysplasia” in the strictest sense of the word [23]. When MDS was first proposed as a diagnostic term in the 1970s, the word “dysplasia” was evolving to a broader usage that included virtually any pre-cancerous lesion: at that time MDS was considered to be a preliminary stage to acute leukemia [5,24]. Although it was widely suspected in the 1970s that MDS/leukemia was a clonal disorder on the basis of the characteristic chromosomal abnormalities, several years passed before more definitive proof of the clonality of MDS arrived in the form of studies of X-linked gene and gene product polymorphisms [10,25–27]. More recently, MDS has been shown to share some biological features with clonal “dysplasias” in other body sites, such as the dysplasias affecting the uterine cervix and gastrointestinal mucosa, including increased proliferation rates, increased apoptosis, altered telomere dynamics, alterations in levels of cell cycle and apoptotic regulatory proteins, alterations in microenvironmental cytokine levels, and a tendency to undergo genetic devolution [28]. However, MDS differs from these other dysplasias in several critical respects, such as the lack of a proven microbiologic origin and the extreme rarity of spontaneous regression [28,29].

Some investigators have argued that the chronic myeloid disorders are really “myeloneoplasias”—i.e. they do not represent preliminary stages of true clonal disorders but are already fully developed clonal, malignant disorders that tend to have an indolent nature initially but undergo clonal evolution, analogous to the well-known Vogelstein model for the progression of colon cancer [30,31]. The same considerations apply to the myeloproliferative disorders, which are also (almost always) clonal entities and share some overlapping morphological and clinical features with MDS [32,33]. In fact, at one time, the term “myelodysplasia” was proposed as a broad categorical label for all of the chronic myeloid disorders, and could have been the heir to an older, non-specific eponym once used indiscriminately for marrow disorders chiefly affecting the erythroid elements, “DeGuglielmio syndrome” [34,380]. However, this terminology did not catch on, and the word myelodysplasia was eventually applied to the restricted set of disorders that are the subject of this review.

### 2.2. “Dysplasia”: deceptive?

The pathological term dysplasia usually refers to congenital, developmental disorganization of cells; in the context of evolving neoplasia, dysplasia encompasses architectural disruption accompanied by cellular pleomorphism and is classically restricted to epithelial tissues [22]. The term “myelodysplasia” in the former sense is actually used in some medical circles to refer to the congenital neural tube defects, confounding computerized searches of the medical literature. Hematopoietic MDS, which arises in a mesodermal tissue (marrow), usually represents a well-established neoplastic clone and not “dysplasia” in the strictest sense of the word [23].

When MDS was first proposed as a diagnostic term in the 1970s, the word “dysplasia” was evolving to a broader usage that included virtually any pre-cancerous lesion: at that time MDS was considered to be a preliminary stage to acute leukemia [5,24]. Although it was widely suspected in the 1970s that MDS/leukemia was a clonal disorder on the basis of the characteristic chromosomal abnormalities, several years passed before more definitive proof of the clonality of MDS arrived in the form of studies of X-linked gene and gene product polymorphisms [10,25–27]. More recently, MDS has been shown to share some biological features with clonal “dysplasias” in other body sites, such as the dysplasias affecting the uterine cervix and gastrointestinal mucosa, including increased proliferation rates, increased apoptosis, altered telomere dynamics, alterations in levels of cell cycle and apoptotic regulatory proteins, alterations in microenvironmental cytokine levels, and a tendency to undergo genetic devolution [28]. However, MDS differs from these other dysplasias in several critical respects, such as the lack of a proven microbiologic origin and the extreme rarity of spontaneous regression [28,29]. Some investigators have argued that the chronic myeloid disorders are really “myeloneoplasias”—i.e. they do not represent preliminary stages of true clonal disorders but are already fully developed clonal, malignant disorders that tend to have an indolent nature initially but undergo clonal evolution, analogous to the well-known Vogelstein model for the progression of colon cancer [30,31]. The same considerations apply to the myeloproliferative disorders, which are also (almost always) clonal entities and share some overlapping morphological and clinical features with MDS [32,33]. In fact, at one time, the term “myelodysplasia” was proposed as a broad categorical label for all of the chronic myeloid disorders, and could have been the heir to an older, non-specific eponym once used indiscriminately for marrow disorders chiefly affecting the erythroid elements, “DeGuglielmio syndrome” [34,380]. However, this terminology did not catch on, and the word myelodysplasia was eventually applied to the restricted set of disorders that are the subject of this review.

The dysplasia versus neoplasia distinction has important practical consequences. Patients diagnosed with MDS often ask their physicians, “Do I have a form of cancer?”—a question especially relevant for patients who carry one of the increasingly common cancer-specific health insurance policies [35]. Savvy patients with MDS may also ask whether a hematologist or an oncologist should direct their care. It can be unsatisfying to explain to such patients that their disease is felt to reside along a shadowy frontier between malignant and benign disease. It can be equally challenging to persuade research funding agencies dedicated to curing cancer that their money would also be well spent by bankrolling MDS investigations. Improving the terminology of the chronic myeloid disorders might mitigate some of these problems.

### 2.3. “Syndrome” is suspect: should it be superseded?

The nebulous word syndrome reflects the incomplete understanding of MDS when the disorder began to be more widely recognized in the early 1970s [36,37]. Although the pathogenesis and natural history of MDS have become more completely understood in the last 30 years, a great deal of work remains. Still, there has been enough progress that some have argued that the time may now be ripe for MDS to be considered a set of “diseases” with common biological and clinical parameters [37,38]. From classical Greece until the 20th century, the term “syndrome” referred exclusively to a cluster of three or more signs and symptoms often seen together, without reference to etiology. During the 20th century, the term “syndrome” underwent devolution and is now used to describe virtually any characteristic pattern or bizarre occurrence, including some in areas of life far removed from medicine (e.g. Supermom syndrome, Clinton syndrome) [36]. Medical librarians have pointed out that MDS represents an unusual use of the term syndrome as an all-encompassing label for a cluster of possibly related pathologic conditions [36]. Perhaps, only the so-called 5q syndrome [39] fits the former, stricter syndrome definition, because it is always associated with hypolobated micromegakaryocytes and isolated chromosome 5 deletions, while the responsible etiologic agent—presumably a tumor suppressor gene—remains obscure.

In truth, some conditions that currently reside under the banner of MDS have little apparent resemblance to one another. Pure sideroblastic anemia, for example, behaves quite differently from the typical case of chemotherapy-related refractory anemia with excess blasts and a complex karyotype [40,41]. Given this diversity, is the general category of MDS worth keeping at all? At least for the moment, it seems reasonable to do so, although disease “lumpers” and “splitters” may differ intelligently on this point. Although MDS represents a cluster of associations without the imprimatur of a consistent genetic lesion, these conditions retain several hallmarks of “real” disease entities: pathologists...
myeloid disorders are nebulous and there may be considerable challenge, as the frontiers between subsets of chronic similar clonal hematopoietic conditions can present a serious overlap. Hybrid myeloproliferative–myelodysplastic syndromes, for example, are not uncommon [32,60–62]. Diagnosing MDS in the presence of a hypocellular marrow can be particularly difficult [63], as cases of aplastic anemia that are otherwise unremarkable may have detectable cytogenetic lesions, and the etiology of both disorders may be similar [64–66]. Marrow and peripheral blood cells in MDS can have a paroxysmal nocturnal hemoglobinopathy (PNH) phenotype with absence of glycosyl-phosphatidylinositol (GPI) anchored proteins [67–69]. MDS can also be seen in association with T-cell large granular lymphocyte disorders (T-LGL) [70], but the simple presence of a T-cell receptor gene rearrangement does not define a T-LGL, as such gene rearrangements are not lineage specific [71].

Often, only the evolution of a particular patient’s disorder over time can allow clearer distinction between these several overlapping entities. The National Comprehensive Cancer Network (NCCN) recognized this, and NCCN guidelines suggest that if a case lacks classic features, several months of observation should pass before a diagnosis of MDS is assigned [72].

Detailed genetic profiling aided by “gene chips” and related microarray technology promises eventual relief for these difficult diagnostic dilemmas [73]. Eventually, MDS-specific DNA and mRNA transcript patterns may be defined, which will set the diagnosis and classification of these marrow conditions on more solid ground, as genomic profiling is already showing potential to do for other diseases [74,75]. MDS gene and protein expression patterns will become even more relevant when specific and effective therapies are developed based upon them. Until these patterns are ferreted out and the critical genes are defined, the MDS counterparts of highly specific therapies such as STI-571 (imatinib mesylate, GleevecTM) for chronic myeloid leukemia [54,55] for chronic myelogenous leukemia [76] must remain only a distant dream.

4. Disease classification: schemes and controversies

The appropriate classification of the many varieties of MDS has been a contentious topic for many years, and the debate shows no signs of abating. The fundamental problem seems to be that it is simply not possible to classify incompletely understood disorders like MDS with absolute certainty and to the complete satisfaction of all investigators. Yet, paradoxically, further understanding of enigmatic disorders cannot easily be achieved in the absence of the framework of a working classification. Each patient with MDS is unique and presents idiosyncratic clinical problems, yet if every patient were to be considered a “special case” because of their peculiar constellation of clinical and pathological features, the overall syndrome would suffer death by deconstruction. Reproducible patterns of bone marrow behavior are clearly seen; recognition of these can facilitate communication between investigators and allow forecasting of a particular patient’s disease course.
Chronic myelomonocytic leukemia

Refractory anemia with excess blasts in transformation
of 1 monocyte counts fluctuating near the FAB “dividing line”
marrow findings. For this reason, patients with peripheral

The FAB definition of CMML is based primarily on the
arbitrary and may not be useful or reproducible[79–82].
white count and other features have been criticized as ar-
and “myelodysplastic” subtypes based on peripheral blood
counts. Efforts to split CMML into “myeloproliferative
and AML clearly and reproducibly, while the expanded
1982 version also successfully divided MDS into low-risk
groups characterized by relative stability over time and
high-risk groups with rapid progression to marrow failure
and/or acute myelogenous leukemia. FAB terminology is
universally recognized and respected. Yet, in many ways,
this 25-year-old classification is showing its age, as an
increasing number of voices point out its weaknesses.

4.1. Old faithful: the French–American–British (FAB)
classification

The venerable classification scheme of the French–American–British (FAB) Cooperative Group was first pro-
posed in 1976 and expanded in 1982 (Table 2) [77,78]. The
FAB classification represented a major step forward, and
the FAB scheme is still the basic framework from within
which most clinicians think about MDS. The 1976 ver-
sion was the first diagnostic scheme to distinguish MDS
and AML clearly and reproducibly, while the expanded
1982 version also successfully divided MDS into low-risk
groups characterized by relative stability over time and
high-risk groups with rapid progression to marrow failure
and/or acute myelogenous leukemia. FAB terminology is
universally recognized and respected. Yet, in many ways,
this 25-year-old classification is showing its age, as an
increasing number of voices point out its weaknesses.

4.2. Not so FABulous: specific weaknesses of the
FAB classification

In the FAB classification, both the definition of chronic
myelomonocytic leukemia (CMML) and its inclusion in
the scheme at all are problematic. Many patients with CMML
have features more closely resembling a myeloprolifera-
tive disorder than MDS, including hepatosplenomegaly,
heavy marrow fibrosis, and increased peripheral blood
counts. Efforts to split CMML into “myeloproliferative”
and “myelodysplastic” subtypes based on peripheral blood
white count and other features have been criticized as ar-
bitrary and may not be useful or reproducible [79–82].
The FAB definition of CMML is based primarily on the
peripheral blood monocyte count with less consideration
of marrow findings. For this reason, patients with peripheral
monocyte counts fluctuating near the FAB “dividing line”
of $1 \times 10^9$ monocytes/L could fluctuate between two differ-
ent FAB subtypes on a frequent basis (e.g. CMML versus
refractory anemia or refractory anemia with excess blasts).
In addition, some patients with large numbers of marrow
monocytes demonstrable by esterase staining have periph-
eral blood monocyte counts too low to qualify as CMML, yet
can have a disorder dominated by the monocytic component.

Another problem with the FAB classification is that many
cases of MDS cannot easily find a place in the classifica-
tion scheme. MDS with heavy marrow fibrosis, hypocellu-
lar MDS, MDS characterized by thrombocytopenia and/or
neutropenia in the absence of anemia, and childhood MDS
are just a few examples of categorical misfits, as discussed
further later.

The FAB classification predetermined routine marrow cyto-
genetic analysis and therefore does not take cytogenetic
findings into account. It has become clear, however, that
some genetically-defined MDS subtypes such as the 5q–
syndrome are distinct disease entities, while the presence
of other chromosome anomalies such as monosomy 7 may
have a more profound effect on prognosis than the FAB sub-
type [83]. At the very least, the FAB classification needed
to be updated to incorporate 20 years of cytogenetics-related
developments.

Several other objections have been raised against the FAB
classification. First, the term “refractory anemia” has been
considered misleading because some patients with MDS ac-
tually have trilineage dysplasia and pancytopenia. The orig-
inal FAB classification recognized that most MDS cases
have predominantly erythroid involvement with less dra-
matically abnormal features in the other cell lines [78].
More recent data suggest that patients with clear dysplasia
in all three myeloid lineages (erythroid, granulocytic, and
megakaryocytic) have a poorer prognosis than those with
abnormalities restricted to the erythroid lineage (the FAB
categories “refractory anemia” and “refractory anemia with
ringed sideroblasts”) [84].

The FAB distinction between refractory anemia with ex-
cess blasts in transformation (RAEB-T, with $>20\%$ marrow
involvement by leukemic blasts) and AML ($>30\%$ marrow
involvement by blasts) has been criticized as unimportant,
as both disorders are treated similarly and have a similarly poor
prognosis. If MDS in general is characterized by a relatively
indolent behavior, then RAEB-T, which has a median sur-
vival of less than 1 year and typically has a rapidly increas-
ing blast count, is a misfit. Several studies have suggested
that there is little difference between RAEB-T and AML in terms
of prognosis, response to therapy, cytogenetic features, and
presence of the high-risk multidrug-resistance (MDR) phe-
notype [37,85,86].

While RAEB-T is very similar to AML, the category of
RAEB actually includes a fairly heterogeneous case mix. Pa-
tients with a marrow myeloblast count of 6% have a disorder
that usually behaves differently from those with a myeloblast

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Table 2

The 1982 French–American–British (FAB) Cooperative Group classification of the myelodysplastic syndromes

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Myeloblasts in peripheral blood (%)</th>
<th>Myeloblasts in bone marrow (%)</th>
<th>Ringed sideroblasts (%)</th>
<th>Absolute monocytes in peripheral blood</th>
<th>Auer rods present in bone marrow?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Refractory anemia (RA)</td>
<td>&lt;1</td>
<td>&lt;5</td>
<td>&lt;15</td>
<td>–</td>
<td>No</td>
</tr>
<tr>
<td>Refractory anemia with ringed sideroblasts</td>
<td>≥5</td>
<td>21–30</td>
<td>–</td>
<td>–</td>
<td>No</td>
</tr>
<tr>
<td>Refractory anemia with excess blasts</td>
<td>≥5</td>
<td>20–30</td>
<td>–</td>
<td>Yes or no</td>
<td>No</td>
</tr>
<tr>
<td>Refractory anemia with excess blasts in transformation</td>
<td>&lt;5</td>
<td>20–30</td>
<td>–</td>
<td>Yes or no</td>
<td>No</td>
</tr>
<tr>
<td>Chronic myelomonocytic leukemia</td>
<td>&lt;5</td>
<td>&lt;20</td>
<td>–</td>
<td>$&gt;1 \times 10^9$/L</td>
<td>No</td>
</tr>
</tbody>
</table>
The proposed World Health Organization (WHO) classification of neoplastic diseases of the hematopoietic and lymphoid tissues [42]: categories relevant to the myelodysplastic syndromes

Myelodysplastic syndromes

Refractory anemia
With ringed sideroblasts (pure sideroblastic anemia)
Without ringed sideroblasts

Refractory cytopenia with multilineage dysplasia

Refractory anemia with excess blasts
With 5–10% myeloblasts (RAEB-1)
With 11–19% myeloblasts (RAEB-2)

5q– syndrome

Myelodysplastic syndromes, unclassifiable

Myelodysplastic/myeloproliferative syndromes

Chronic myelomonocytic leukemia

Atypical chronic myelogenous leukemia

Juvenile myelomonocytic leukemia

Relevant acute myeloid leukemia (AML) categories

AML with multilineage dysplasia

With prior myelodysplastic syndrome

Without prior myelodysplastic syndrome

AML and myelodysplastic-syndromes, therapy-related

Epidendroptilinoma-related

Other types

+ Like RAEB, CMML can also be subdivided based on myeloblast count. The 5q– syndrome is narrowly defined to include only cases with de novo isolated del(5q) and the characteristic morphologic findings of hypolobated megakaryocytes and less than 5% marrow myeloblasts.

4.3. The World Health Organization (WHO) proposal

In 1997, a working group of more than 100 clinicians and pathologists met at Airlie House in Virginia under the auspices of the World Health Organization (WHO) to discuss a new master classification of hematologic disorders [42]. Included in this classification was a proposal for the re-classification of MDS (Table 3). In 2001, the final version of the classification was published and incorporated into the 10th edition of the WHO International Classification of Diseases (ICD-10), which was first used in 1994 and is the most current ICD classification [87,88]. Clinicians and investigators with an interest in lymphoma were already exposed to a forerunner of the new WHO classification in the form of the 1994 Revised European–American Lymphoma (REAL) classification [89]. This group offered comparatively little resistance to the new WHO classification [92]. Controversy over the subclassification of the myeloid disorders, in contrast, contributed to delays in the final publication of the classification, and several revisions were made between the initial and final WHO proposals. Another comparison between myeloid and lymphoproliferative disorders is revealing. Although MDS appears as clinically diverse as lymphoma, in the original WHO proposal MDS was represented by only six “pure” MDS subtypes and three myelodysplastic–myeloproliferative overlap disorders; the lymphoproliferative disorder classification comprised more than 40 entities [42].

4.4. Single lineage versus multilineage dysplasia: does degree matter?

One major change between the WHO and the FAB classifications is the recognition in the former that there is indeed a difference between cases of MDS with morphologic dysplasia primarily restricted to one cell lineage (usually erythroid) and those with more widespread dysplasia. As mentioned above, the FAB originally defined refractory anemia and refractory anemia with ringed sideroblasts as syndromes with dysplasia largely restricted to the erythroid lineage, rendering cases with marked trilineage dysplasia difficult to classify [93]. One key caveat is that mild dysplasia restricted to the erythroid lineage is sometimes not clonal [50]. Stricter definitions for MDS such as those requiring at least bi-lineage dysplasia avoid inadvertently affixing the label of MDS to cases that are not monoclonal, but also risk excluding genuine MDS cases with minimal dysplasia—a sacrifice of sensitivity at the expense of specificity for which there is no easy solution. Several reports have demonstrated that multilineage dysplasia (e.g. “refractory cytopenia with multilineage dysplasia”) carries a worse prognosis than simple erythroid dysplasia [41,84,94], including cases with ringed sideroblasts [40,95]. Whether this finding is independent of other known prognostic variables for MDS remains unclear [37]. In addition, more severe dysplasia within a given lineage may also portend a worse prognosis [96,97], although further studies are needed to support this claim and the same caveat about independent prognostic value applies. A report by the Vienna group reviewing 431 MDS patients did not validate the prognostic value of the new category of RCMD, but a German group reviewing 1600 patients did support the WHO proposal on this point [41,98]. Several of the architects of the WHO classification pointed out that the Vienna group used a different threshold (50% dysplastic cells versus 10% for other groups) to define whether a lineage exhibited dysplastic features or not [97]. This distinction may turn out to be quite important—dysplasia is unlikely to be a “yes or no” issue—but at present, there are no studies that have published the effect of changes in the value of the “dysplasia differential” on prognosis. Most morphologists who diagnose RCMD appear to operate more by a general gestalt (i.e. is there heavy dysplasia, occasional dysplasia, or none at all?) rather than actually enumerating the dysplastic and normal red cells, white cells, and megakaryocytes. More work is needed in this area.
4.5. Chronic myelomonocytic leukemia (CMML): a syndrome with a new name

The WHO classification removes CMML from MDS proper and puts it in a myeloproliferative–myelodysplastic overlap category, along with two unusual disorders, atypical chronic myelogenous leukemia and juvenile myelomonocytic leukemia. This distinction seems reasonable, as CMML was always an awkward bedfellow in the FAB scheme, as mentioned above (fans of the musical group “The Beatles” might compare CMML’s uncomfortable presence alongside the FAB 4—RA, RARS, RAEB, and RAEB-T—to the awkward coupling of Yoko Ono with John, Paul, Ringo, and George).

Although there is universal agreement on CMML’s heterogeneous [79,82,99], it is unclear at present how one might reproducibly split the disorder into distinct subtypes [81]. Placement of CMML in a separate overlap category is a partial solution to this ambiguity, and dividing CMML into two categories based on the blast count, as the WHO has done in their final proposal, may have more prognostic relevance than attempts to divide CMML based on peripheral white count [97].

But other overlap MDS-myeloproliferative conditions do not easily fit into one of the WHO categories [32,61], and there is currently no appropriate default category for such cases. Otherwise typical cases of MDS may have neutrophilia, monocytosis, thrombocytosis, splenomegaly, or other myeloproliferative features, raising diagnostic angst: are such cases truly MDS with minor variation, or are they actually different enough to require re-designation as a unique overlap syndrome?

4.6. “Secondary” MDS/AML: “secondary” to what?

The WHO classification includes a sub-category for therapy-related MDS and AML. This category reflects the historical distinction between “secondary” and “primary” MDS; the former applies to patients who have previously received chemotherapy or radiotherapy for another disease. Confusing matters is the fact that the term “secondary” AML is used to describe both patients with prior genotoxic therapy exposures as well as patients with leukemia arising out of a prior chronic myeloid disorder. Although pretreated patients generally do more poorly than those without such a history [100–102], the prognosis appears to depend primarily on the cytogenetic profile (frequently abnormal and “high-risk” [83,103]) and not the history of treatment per se [21]. Whether or not such patients represent a distinct subset of MDS deserving of a separate classification is questionable.

Someday it may become clear that all MDS is “secondary”, albeit not always iatrogenic. Although findings have been somewhat inconsistent, there are already considerable data supporting the fact that many cases of MDS and AML may result from toxin exposure in a susceptible host. Some of these susceptible persons may be those with polymorphisms in genes encoding NADP(H) quinone oxidoreductase (NQO1) and glutathione S-transferases (especially GSTT1 and GSTM1), a group of enzymes involved in hydrocarbon detoxification [104–110]. Whether an MDS-inciting agent is encountered in the home or workplace or was instead dispensed by a pharmacist or radiotherapist may turn out to be an unimportant distinction.

4.7. Distinguishing MDS from AML: scratching lines in the shifting sand

In some cases of AML, the diagnosis is obvious, while in other cases making a clear distinction between MDS and AML can be extremely difficult. The FAB classification imposed an arbitrary threshold value of 30% marrow blasts to define AML; the WHO proposal lowers this threshold to 20% and thereby does away with the FAB category of “refractory anemia with excess blasts in transformation” (RAEB-T or RAEBIT). This proposed change has engendered strong criticism. Some have argued that RAEB-T is biologically different from AML and should be retained as a diagnostic category [37,111], while others have emphasized the similar prognosis for the two entities as well as the identical response to treatment [85,86] and certain biological features which are indistinguishable [112]. Both proposals suffer from the limitation that regardless of which blast cut-off for AML is accepted (30 or 20%), such numbers are of course fundamentally arbitrary [37]. The effect of blast percentage on prognosis in MDS appears to be a continuous variable, as is true of most biological systems. Reflecting this, the final WHO proposal separates RAEB into two sub-categories depending on whether the marrow blast percentage is 5–10% or 11–19%, a distinction that has been shown to be prognostically important [37,83,113,114]. This may be the best that can be done given the limited precision of bone marrow differential counts.

One proposed compromise position is to redefine AML in terms of a rate of progression rather than a strict blast percentage; such an assessment would require several measurements over time, with relative stability considered the hallmark of MDS [37,38]. Cytogenetic features are also important; MDS is most often characterized by deletions and (less commonly) gains of chromosomal material, while recurrent translocations are more common in AML [100,115]. Most hematologists would consider a marrow exhibiting a classic AML-associated genetic lesion such as t(8;21)(q22;q22), t(15;17)(q22;q11–12), inv(16)(p13q22), or an anomaly of 11q23 as diagnostic of AML regardless of the blast count, and in fact the WHO scheme does categorize such cases as AML [42]. An MDS phase is observed only rarely with such lesions [116,117]. Yet, there are certainly cases of AML with a high blast count which are characterized more by ineffective hematopoiesis than by blast burden [38], and there have been few calls to reclassify such cases as MDS. In addition, in some cases of AML, the bone marrow
gene expression patterns and other biologic parameters may to fall somewhat short of these goals, emerging data on by research reports. Although the current schemes appear will minimize arbitrary distinctions, and will be fluid and "lump" similar biologic entities and "split" disparate ones, Among other virtues, such a classification scheme will producible, and useful for treatment and prognostication.

4.9. Beyond the FAB 5 and the WHO: rolling toward been proposed[133].

The WHO classification has been validated in a large ret-
differently from more typical MDS cases in large series. enough that they have not clearly been shown to behave

4.8. Unclassifiable MDS: a spacious prison for cases with disorderly conduct?
The inclusion of an "unclassifiable" MDS category in the WHO classification has been criticized [37]. The WHO working group recognized that cases are occasionally seen which do not easily fit into the FAB classification and wanted to have a category for such patients for epidemiologic purposes. However, the number of unclassifiable cases is likely to be very dependent on each individual hematologist or morphologist and the strictness of the standard to which each case is held. Among other difficult cases [60], hypoplastic/hypocellular MDS [63,65]. MDS with fibrosis [124], "refractory thrombocytopenia" and "refractory neutropenia" without anemia [125]. MDS in the presence of a simultaneous untreated lymphoplastic myeloid clone [126,127]. MDS associated with a granulocytic sarcoma [128]. clonal cytogenetic abnormalities characteristic of MDS without clear morphologic changes [129,130], MDS with an associated T-cell clonal gene rearrangement [70], "paraneoplastic" MDS (of uncertain clonality) [131], and miscellaneous MDS myeloproliferative overlap cases [62] could all be considered unclassifiable under the WHO scheme. It is not clear whether these should be considered discrete entities, though, because most of them are rare enough that they have not clearly been shown to behave differently from more typical MDS cases in large series. The WHO classification has been validated in a large ret-

In addition to these criticisms, the pediatric MDS com-

In the 1970s, shortly after MDS was morphologically
demonstrates multi-lineage dysplasia but no preceding MDS was recognized. Although the WHO includes an AML sub-category for such cases, the simple presence of dysplasia in AML has not had consistent prognostic value [118–123].

5. Epidemiology: how trustworthy are the numbers?

Several factors have made true the incidence and preva-
lence of MDS difficult to ascertain. As one epidemiologist complained, "we are put off by the fact that MDS is a heterogeneous, vaguely defined group of conditions with seemingly ever-changing names" [135]. MDS terminology has been somewhat consistent only since the 1982 FAB classification, and as discussed earlier, many MDS cases remain unclassifiable, uncertain, or diagnostically problematic. Compounding the difficulty is the fact that cases of MDS are not routinely reported to cancer registries [136,137], a legacy of the benign vs. malignant murkiness detailed earlier. Standard disease classifications such as the still widely used ICD-9 carry terminology that is not even consistent with the FAB classification, let alone the WHO [135,137]. Additionally, MDS can be confused with other conditions with similar names. It is not uncommon to find death certificates, hospital summaries, and patient database records in which the terms "myeloproliferative disorder" and "myelodysplastic syndrome" and "myeloid leukemia" have been used interchangeably. Such muddle confounds registry-based work. Further, most epidemiologic studies in MDS have been limited to data from small, regional reg-

5.1. How common is MDS?

In the 1970s, shortly after MDS was morphologically defined by the FAB, it was estimated that there would be ap-
proximately 1500 new cases of MDS per year in the United States [138]. More recent estimates suggest that this figure is too small by at least a factor of 10. If the annual incidence in the USA were as high as the crude rate of 9.3–12.6 cases per 100,000 persons per year suggested by two English stud-
ies [139,140], more than 30,000 American cases of MDS would be diagnosed annually. In comparison, the overall age-adjusted incidence rate of acute myeloid leukemia in the USA was estimated at 2.9 cases per 100,000 persons per year in 1998, a figure that has not changed significantly since 1973 [141]. Even if only the more conservative MDS incidence estimates are accepted—crude incidence figures
which generally range between 2 and 4 cases per 100,000 persons per year [136,142–144]—it seems probable that MDS is at least as common as AML. The elderly are particularly vulnerable, as annual MDS incidence rates in patients over 70 years of age have ranged between 15 and 50 cases per 100,000 persons per year [145].

5.2. Rumors of the coming plague: is the incidence of MDS really increasing?

Many hematologists from a variety of locations around the world believe that the incidence of MDS is increasing [44,146–149]. It remains unclear whether this is actually true or whether such observed trends are simply a matter of increasing recognition of the syndromes. Changes in demographics such as the overall aging of the population in industrialized nations can also be misleading [145].

Several investigators have found no evidence for an increase in the incidence of MDS over time [136,143]. Since slight macrocytosis, for example, is not easily recognizable on a peripheral blood smear and since a high red cell mean corpuscular volume (MCV) may be one of earliest signs of MDS [150], it is probable that routine use of automated hematocrit counters has highlighted certain milder cases that might previously have been overlooked [140]. Other factors such as the increasing use of remission-inducing or curative therapies for other disorders that are associated with a subsequent risk of MDS [151,152] may also be making a small contribution to changes in MDS epidemiology [137]. A widely held perception that the general environment is becoming more “toxic” has been suspected of fanning fears of a looming epidemic of exposure-related diseases like MDS and asthma [153].

What will it take to obtain reliable incidence data for MDS? Uniform syndrome definitions, clear and comprehensive record-keeping, and multinational collaboration over a prolonged period of time represent challenging but potentially achievable goals that will greatly clarify the epidemiology of MDS.

6. The mysterious biology of MDS

Among the chief challenges in studying MDS are the paucity of adequate cell lines and the lack of an appropriate animal model of the disease. Most mechanistic studies have been carried out on fresh human tissue, of which there is necessarily a limited supply. The current collection of MDS-related cell lines was recently reviewed [154]. Most of the 10 MDS-specific (i.e. not secondary-AML) cell lines that have been described are not currently available from major cell banks, and several of these are lymphoid lines (of less interest for myeloid mechanistic work) and are poorly validated [154]. The myelomonocytoid P39/Tsugane cell line, an MDS/AML cell line that has been the object of several mechanistic studies of myeloid differentiation, has recently been reported by the Japanese Collection of Research Biosources (JCRB) Cell Bank to be cross-contaminated by HL60 cells [155–158]. Additional well-validated MDS cell lines are clearly needed.

A detailed discussion of the mechanisms that initiate and sustain MDS is beyond the scope of this paper, and only a few insights can be mentioned here.

6.1. MDS causation: the prime mover remains unknown

Oncogenesis is thought to be a multi-step process in which several critical genetic lesions accumulate, eventually resulting in overt cancer. The development and progression of MDS from its earliest stages through more advanced disease and its eventual transformation to AML appear to mesh with this concept [106,137]. Multiple genetic pathways can be involved, and sometimes several distinct clones are present in the same patient [101,110,159–161].

Loss of genetic material from chromosomes 5, 7, 13, 17, and 20 or a sex chromosome and (less commonly) genetic gains such as trisomy 8 are well described in MDS [162]. Several hundred other MDS-associated karyotypes have been described [163], some of which are rare but current, yet the critical genes lost or gained in most of these lesions remain a mystery [164]. The region of chromosome 5 often deleted in MDS, for example, contains multiple hematopoietic growth factors, but attempts to define which genes are the sine qua non of the classic 5q− syndrome have thus far been unrevealing [165,166]. Large cytogenetic lesions detectable by conventional karyotypic analysis are likely to be late developments in the pathogenesis of MDS. Several patients have been described in whom clonality (as assessed by analysis of various X-linked genes) preceded the development of an overt cytogenetic lesion by several years [167].

Almost half of de novo MDS cases have normal metaphase cytogenetic findings. Sorting out the relevant altered gene pathways in such cases remains an active area of investigation. “FISHing expeditions” with multiplex-fluorescent in situ hybridization (M-FISH) and spectral karyotyping techniques in cytogenetically normal MDS cases have been generally unrevealing, although these procedures may be useful in clarifying the karyotype in complex cases, which at present is not often clinically relevant [168–170]. Panel FISH techniques, in which a group of FISH probes are used to search for cryptic expression of common MDS genetic abnormalities, are also of limited value [171].

Two recent microarray studies of gene expression in MDS have shown increased expression of a gene encoding the delta-like (dlk) protein in low-risk MDS patients compared with high-risk MDS, AML, CML, and normal controls [73,134]. The function of this gene is uncertain, but there is now evidence that it may have a role in the cellular growth and differentiation programs, including differentiation of hematopoietic cells. In mice, forced overexpression of dlk was a negative regulator of adipocyte differentiation,
and a soluble dlk-IgG Fc chimeric protein was shown to completely inhibit formation of lineage-marker negative (Lin−) bone marrow cell colonies by colony stimulating factors in the presence of stem cell factor (SCF) [172,173]. These microarray experiments represent a proof of concept, and it can be expected that global genomic work will yield other interesting candidate genes whose pathophysiologic relevance in MDS can then be studied in more detail.

Several MDS investigators have probed specific genes known to be mutated in other forms of cancer and pre-cancerous lesions. Mutations of ras, fms, and p53 have all been described in MDS, although the exact prevalence remains uncertain [174–177]. In contrast, other genes often mutated in AML such as AML1 do not appear to be abnormal in the majority of patients with MDS [178,179].

The root cause of the underlying genetic lesions in MDS is often not known, although various epidemiologic associations suggest the importance of exposure to a genotoxic agent in a susceptible host. Patients treated with alkylating agents, epipodophyllotoxins, and ionizing radiation are at increased risk for MDS. MDS is more common in men, in persons with agricultural or industrial occupations or regular exposure to petroleum products, in smokers, and in persons who use hair dyes [142,180–184]. MDS has also been described after exposure to atomic radiation. A number of cases have appeared in the Chernobyl nuclear accident decontamination workers [185], and although MDS was not yet recognized in the years following the atomic bomb blasts in Hiroshima and Nagasaki, re-review of the marrow specimens from those patients who developed AML revealed dysplastic changes [186]. Atomic bomb survivors were recently found to have a dose-dependent increase in the risk of MDS even many years after exposure, lending yet more support for a multi-step pathogenesis of MDS [187]. The “natural experiments” of familial MDS [188–190] and MDS arising in patients with congenital deletion of a tumor suppressor gene (e.g. neurofibromatosis type 1 [191]) or a DNA repair defect (e.g. Fanconi syndrome [192] and Bloom syndrome [193,194]) underscore the importance of host susceptibility.

6.2. Too much apoptosis?

In the late 1980s, apoptosis-associated morphologic changes such as chromatin condensation and cytoplasmic blebbing were observed in hematopoietic progenitor cells in bone marrow from patients with MDS [195]. These findings suggested a resolution to one of the paradoxes of MDS: the presence of peripheral blood cytopenias despite a typically hypercellular bone marrow [196,197]. Numerous subsequent studies have supported the hypothesis that excessive programmed cell death is a contributing factor to the ineffective hematopoiesis in MDS. The marrow failure is usually not a result of decreased progenitor synthesis, as marrow kinetic studies have determined increased proliferation [198].

Various techniques can be used to measure typical apoptotic changes in MDS marrow, including in situ end-labeling (ISEL) and nick-end labeling (TUNEL) of DNA strand breaks [199–204], detection of phosphatidylserine migration to the outer portion of the cellular phospholipid bilayer using the annexin V binding protein [205,206], and quantification of sub-diploid (sub-G1 phase) DNA [207]. Although there continues to be significant disagreement among investigators regarding the degree and extent of apoptosis in MDS marrow and the culpability of stromal cells, several clear trends have emerged.

Multiple studies have demonstrated that there is an increase in the apoptotic index in the marrow of patients with early MDS compared with normal controls. However, the apoptotic index represents a numerator (the number of apoptotic cells detected) over a denominator (the total number of cells counted), and changes in the apoptotic index can result from changes in either number. If the denominator were CD34-positive cells, for instance, as has been the case in most studies measuring the apoptotic index, alterations in the pool of early hematopoietic progenitor cells might give misleading results. Apoptotic phenomena are also time dependent, and not all studies have described the freshness of studied samples [208].

The increased apoptotic index in MDS is associated with an increased proliferative fraction (as measured by Ki-67 monoclonal antibody staining [206] or bromodeoxyuridine/bromodeoxyuridine labeling indices [198,199,202,209]) and signal antonymy [209]. In contrast, apoptotic indices appear to be decreased in late MDS (refractory anemia with excess blasts and refractory anemia with excess blasts in transformation) and in AML arising from a pre-existing MDS when compared with early MDS. The percentage of apoptotic cells in early MDS also appears to decrease significantly after treatment with erythropoietin and/or G-CSF, suggesting one possible mechanism for the salutary increase in peripheral blood counts in patients treated with these agents [201].

Several investigators (including groups at Stanford University, Rush Medical College, the University of Arizona, King’s in London, and others) have studied the mechanistic changes contributing to excessive apoptosis in MDS, and much progress is being made. There is evidence for involvement of members of the Bcl-2 family, for example. In early MDS, the pro-apoptotic members of the Bcl-2 family (Bad, Bax) are overexpressed relative to the anti-apoptotic members (Bcl-2), but this ratio drops in late MDS and secondary AML [206,210]. The ratio of c-myc (pro-apoptotic) to Bcl-2 (anti-apoptotic) is elevated in cases of early MDS compared to normal controls [207]. Vascular endothelial growth factor (VEGF) appears to be an important cytokine for leukemic cell proliferation and contributes to the morphologic phenomenon of abnormal localization of immature myeloid precursors within the marrow microenvironment [211]. The expression of tumor necrosis factor (TNF), a pro-apoptotic cytokine, also appears to be increased in MDS [212–214],...
and this elevation correlates with increased activity of a key biochemical effector of apoptosis, caspase 3 [215]. In addition, increased expression of another death-inducing protein, Fas/CD95, has been noted in MDS and correlates with ineffective erythropoiesis [216,217]. The degree of expression of this receptor’s partner, Fas ligand, in MDS has been correlated with FAB subtype, degree of anemia, and overall survival [218]. In contrast, in one study granulocytes and CD34+ cells from MDS patients were resistant to Fas, TNF-α, and interferon-induced apoptosis [219]. Not to be outdone, several of the receptors for the other known members of the death ligand/receptor family, TRAIL, have also been shown to be overexpressed in MDS marrow compared to normal controls, and treatment with exogenous TRAIL inhibits myeloid progenitor proliferation [220,221].

The underlying genetic lesions contributing to these changes remain obscure. It is also unclear whether increased apoptosis is a desperate cellular reaction to a rapidly proliferating and genetically disturbed clone, or whether excessive apoptosis is instead an integral part of the pathophysiology of the syndrome.

### 6.3. The enigma of ringed sideroblasts

Ringed sideroblasts are abnormal erythroid precursors in which iron-stuffed mitochondria encircle the nucleus; this iron is unavailable for incorporation into heme, resulting in anemia. The finding of ringed sideroblasts can be associated with a number of congenital syndromes that cause defects in heme synthesis—usually via decreased activity of 5-aminolevulinate (5-ALA) synthase, an X-linked enzyme which has been found to be mutated in a subset of patients with sideroblastic anemia [222]. Treatment with pyridoxine, a precursor for the cofactor of 5-ALA synthase, can improve the anemia in some cases of MDS with ringed sideroblasts. Several polyclonal acquired ringed sideroblastic states also exist, such as lead intoxication and alcohol abuse, which may present a diagnostic challenge [223].

Monoclonal acquired sideroblastic anemia is considered a myelodysplastic syndrome [78]. As mentioned above, “pure” acquired sideroblastic anemia carries a much more benign prognosis than sideroblastic anemia associated with multi-lineage dysplasia; the latter is also much more frequently associated with clonal cytogenetic anomalies [40].

The genetic lesions responsible for most cases of acquired sideroblastic anemia remain uncertain; mitochondrial DNA lesions may play an important role [224–226]. In one small study, substitutional, deletional, and insertional mutations in cytochrome c oxidase subunit genes were detected in 13 of 20 MDS patients but only 2 of 10 normal individuals; the significance of this finding is uncertain at present but mitochondrial cisternae morphologic abnormalities have also been observed [226,227]. Autosomal defects too small to be detected by conventional karyotypic analysis are also possible contributors to sideroblastic anemia. The recent cloning of ABC7, an X-linked gene coding for an iron transporter which localizes to the mitochondrial membrane, is of particular interest because the Xq13 locus where this gene is located has occasionally been associated with acquired myeloid disorders including some cases with ringed sideroblasts [228–230].

### 7. Treatments: too few and often too futile

Effective treatments for MDS are limited, but the long litany of potential treatments to which a few patients will respond also makes therapeutic nihilism untenable. It is often stated that the only potentially curative treatment for most patients is also the riskiest, allogeneic stem cell transplantation, but in fact a few patients (especially younger patients with a normal karyotype) will achieve a prolonged polyclonal remission after high-dose chemotherapy even without transplantation and may turn out to be “cured” [231]. Still, given the older age of most patients, gentle, supportive care remains the treatment standard [232].

A number of conventional and experimental treatments for MDS are briefly reviewed below. Although the list of potential treatments is long, very few are effective in a large number of patients. A major challenge lies in predicting which patient is most likely to respond to which treatment. Since the detailed mechanism of action for many agents is unknown, some of the agents listed later in one category may actually have activity that would make them equally at home in a different category (e.g. the interferons, which have growth, differentiation, cytotoxic, and immunomodulatory effects—or thalidomide, which has many poorly understood biological effects).

7.1. The importance of response criteria: what constitutes success?

For chronic disorders such as MDS, treatment success is almost never a simple question of “yes” or “no”. Treated patients often exhibit gradations of clinical change in multiple organ systems—some insignificant and others of major importance, some salutary and others detrimental. Defining arbitrary criteria for therapeutic success or failure that all investigators can agree upon in the face of this biological continuum represents a major problem. When clinical trials in MDS are submitted to medical journals, disagreement over response criteria may be a cause of manuscript rejection [233].

Recently, an International Working Group (IWG) laboring under the auspices of the National Cancer Institute in Bethesda, MD proposed a set of standardized response criteria for clinical trials in MDS [234]. Although such standardized criteria are desperately needed, the IWG proposal has been criticized by some. Several of these response criteria have been perceived as clinically irrelevant or difficult to apply consistently [235,236]. Using the IWG criteria, for example, independent groups reviewing raw data from clinical trials may come to different conclusions about the number...
of patients responding to treatment [233]. Less meaningful hematologic changes could qualify as a treatment response under the current IWG criteria, while in other situations an overt cure would not technically qualify as a complete response [235]. For now, the IWG criteria may provide a useful communication tool for reporting clinical trials, but minor modifications might help investigators use them with more confidence.

7.2. Flogging a recalcitrant narrow: the role of growth factors in MDS

Recombinant human hematopoietic growth factors can be an effective palliative tool in MDS, but they do not seem to prolong survival. The detailed studies of the Scandinavian group have shown that erythropoietin (EPO) ameliorates anemia in about 20% of MDS patients with a serum EPO level of less than 200 U/L, but only rarely works in patients with RARS or those with higher endogenous EPO levels [236]. Very high doses of rHuEPO (up to 240,000 units per week) have been tolerated well by MDS patients, but using very high doses does not seem to improve the response rate over the more typical dose of 40,000–60,000 units per week [237]. In some patients who do not respond to EPO, the addition of low doses of granulocyte colony stimulating factor (G-CSF) (0.3–1.0 mcg/kg per day) or granulocyte-macrophage colony stimulating factor (GM-CSF) may help recruit erythroid progenitors and thereby improve anemia as well as neutropenia [238–242]. Both G-CSF and GM-CSF can increase neutrophil count and reduce infections in MDS [243–245], but no survival advantage has been demonstrated and there is still concern about a small risk of accelerating transformation to acute leukemia [21]. Results from trials of modified, longer-acting growth factors in MDS (e.g. darbepoetin and pegylated filgrastim) have not yet been reported.

Options are more limited for growth factor-based treatment of thrombocytopenia. Recombinant interleukin-11 is a megakaryocyte growth factor recently FDA approved for the prevention of severe thrombocytopenia and to decrease platelet transfusion needs after myelosuppressive chemotherapy. It appears to have mild efficacy in MDS [246]. Side effects such as atrial arrhythmias and fluid retention are common and troublesome with this agent in standard doses (50 mcg/kg per day), but may be seen less often when very low doses (10 mcg/kg per day) are used [246]. Thrombopoietin (TPO) dynamics in MDS are complex [247,248], and no data are available yet on the therapeutic use of recombinant TPO in this condition.

Other agents with growth factor activity that have undergone or are undergoing clinical evaluation in MDS include interleukin-6, interferon alpha and gamma (which also have differentiation properties in vitro), and interleukin-3. Each has had rather limited efficacy and substantial toxicity [249–260].

Several growth factors have been tried in combination with other biologic agents such as amifostine, with varying but generally unimpressive results [261–264]. The use of all of the hematopoietic growth factors is currently limited by their high cost and the need for parenteral administration.

7.3. The peril and promise of high dose chemotherapy

High-risk MDS has very little distinguishing it from AML, and therefore, AML-like therapy is a reasonable consideration for patients with aggressive MDS such as those with a high blast count. Although elderly patients tolerate AML-type chemotherapy poorly, the median age for MDS patients is not markedly different from that for AML. Studies of patients with high-risk MDS reveal a 40–50% remission rate with high dose AML induction therapy, but patients in trials of such regimens are usually a select group younger and healthier than the typical patient with aggressive MDS. Almost all patients achieving a remission via such therapy will relapse promptly [85,265,266]. In one study, only 5% of patients receiving high-dose therapy were alive at 3 years [231]. Growth factor support following aggressive therapy is tolerated but of uncertain benefit [267]. Several high dose regimens such as the combination of mitoxantrone and intermediate-dose cytosine arabinoside (ARA-C) have shown excessive toxicity with little redeeming characteristics [268]. In an attempt to move beyond these limitations, the MD Anderson group is currently pioneering several combination programs containing newer agents such as topotecan, a topoisomerase inhibitor that has been demonstrated to be useful in a number of solid tumors, and fludarabine, a nucleoside analog designed to treat lymphoproliferative disorders [231,269–272]. These drugs appear to be somewhat toxic but effective in MDS when used in combination with ARA-C and anthracyclines, and the optimal dosing and schedule has yet to be determined.

7.4. Low dose chemotherapy: gentleness rebuffed

For older and sicker patients with MDS in whom high dose cytotoxic therapy is deemed to be too dangerous, it would be beneficial to have a useful low dose chemotherapeutic regimen that might assist in palliation. Unfortunately, no low dose program has been particularly successful, although occasional patients will have salutary results. In CMMML, etoposide has been used palliatively with conflicting results that may be schedule dependent [273–275]. Low dose oral melphalan may also have brief palliative benefit in MDS [276], but all patients described in the original encouraging trial have since relapsed and several developed a new 17p deletion [277]. Low dose ARA-C looked promising when first attempted in the 1980s, but an intergroup trial showed little efficacy and made this agent appear less exciting as monotherapy [278]. Today, there is little enthusiasm for low dose, non-specific cytotoxic agents.
7.5. Differentiation therapy has yet to make a difference

One of the hallmarks of MDS is that the neoplastic clone exhibits a maturation block, a fixed stage of differentiation beyond which the abnormal cells apparently cannot progress. Since the 1980s, multiple attempts have been made to induce maturation of these "stalled" cells. The resounding success with differentiation therapy with all-trans-retinoic acid in acute promyelocytic leukemia (AML M3) greatly encouraged investigators with such aspirations [279]. Thus far, there has not been a resounding success: the litany of unsuccessful or marginally promising MDS trials with differentiation agents was recently reviewed [263].

In addition to the interferons described earlier, other differentiating agents that have been tried in MDS include hexamethylene bisacetamide and its derivatives (the polar-planar compounds [280,281]), homoharringtonine (a plant-derived alkaloid used in traditional Chinese medicine [282]), 5-azacytidine and 5-aza-2′-deoxycytidine (nucleoside analogs which may also be cytotoxic and can modify gene methylation status), butyrates such as butyric acid and sodium phenylbutyrate (histone deacetylase inhibitors which may alleviate histone deacetylation-mediated transcriptional repression [283]), amifostine (an inorganic thiophosphate originally designed to be a radioprotective agent but subsequently found to stimulate hematopoiesis), heme arginase (a promoter of heme biosynthesis [284–286]), brystostatin (a macrocyclic lactone isolated from a microspic sea creature [287]), retinoids such as Vitamin A and its analogs (stimulants of normal erythroid and myeloid progenitor proliferation [262,264,288–292]), and Vitamin D and its analogs (which bind to transcription factors that can induce terminal monocytic differentiation). With a few exceptions, these agents have shown little real benefit, or have been excessively toxic, or have induced only transient improvements in hematopoiesis [263]. Amifostine, a relatively well-tolerated agent, showed considerable promise in an early trial, but subsequent studies have engendered pessimism about the drug’s use in unselected cohorts of MDS patients [293–295].

Advocates of “biological”, differentiation-style therapy recently received a boost when the Cancer and Leukemia Group B (CALGB) reported the results of a 191-patient randomized trial of azacytidine versus supportive care in MDS [296]. In this study, statistically significant benefits in quality of life (i.e. less fatigue and dyspnea with improved mood and overall performance status), rate of leukemic transformation and overall survival were observed when azacytidine was administered subcutaneously at a daily dose of 75 mg/m² for 7 days every 4 weeks, especially among those patients who completed at least four cycles of the drug [296]. Whether these results will translate into broad usefulness in general clinical practice and whether 5-aza-2′-deoxycytidine (decitabine) will prove even more efficacious than its demethylating cousin remains to be seen [297]. Despite the many disappointments, the concept of differentiation therapy is so appealing that considerable work continues in this area, and one can only hope for more successes in the near future.

7.6. Anti-apoptosis therapy: suicide prevention

Since excessive apoptosis seems to contribute to ineffective hematopoiesis in MDS, it seems logical that preventing programmed cell death might improve peripheral blood counts. Whether detrimental cell death can actually be prevented without inadvertently immortalizing a frankly neoplastic clone remains to be seen. Since tumor necrosis factor (TNF) can induce apoptosis, and since some studies have suggested that MDS marrow has higher than normal TNF levels, anti-TNF therapy with etanercept (a soluble TNF-a receptor) and infliximab (a chimeric anti-TNF monoclonal antibody) is currently being attempted and has shown some initial promise [296,299]. In one small study, ciprofloxacin and pentoxifylline down-regulated TNF expression but there was no hematologic effect [300]. Combination therapy with amifostine, pentoxifylline, ciprofloxacin, and dexamethasone is currently in vogue, but the trial introducing this regimen appears somewhat less encouraging when patients who had a neutrophil increment after receiving dexamethasone are excluded from the tally of responders (see later for a discussion of the effects of corticosteroids on neutrophil count) [301]. Inhibitors of the caspases, a family of enzymes that represent the final common pathway in effecting apoptosis, have shown inconsistent results in improving hematopoiesis in vitro and have not yet been tried in vivo [302–304]. Anti-apoptosis therapy has many obstacles to overcome before it becomes reality.

7.7. Immunologic manipulation: suppressing the oppressors

Some patients with MDS may respond to immune suppression directed at potentially auto-reactive T-cells. Because of the success of immune modulating therapy in aplastic anemia, patients with hypoplastic MDS have been assumed to be particularly good candidates for such therapy [21,305]. Agents including antithymocyte globulin and antilymphocyte globulin have shown responses in approximarily 10–20% of patients, but because these agents are derived from horses, goats, or other animals, serum sickness and other toxicities can be problematic [306,307]. Cyclosporin has also been used with some success [308,309]. To the best of our knowledge, there are no data on the use of other immunosuppressive agents such as tacrolimus (FK506) or rapamycin in MDS.

7.8. The disappointing and the untested: miscellaneous standard and novel therapies

There are several novel agents and therapeutic agents of historical importance in MDS that do not clearly fit into one
of the other categories in this section. Since occasional patients with sideroblastic anemia will respond to pyridoxine (Vitamin B6), a brief trial of this agent can be worthwhile in patients who appear to have RARS. Supplementation of MDS patients with other vitamins is not usually worthwhile, including folic acid supplementation, as this group generally has adequate folate stores [310,311]. Androgen therapy is generally ineffective in MDS [312-314]. Danazol, a synthetic androgen, improved thrombocytopenia in occasional patients in some studies but had no effect in other trials [315-317].

Corticosteroids reliably increase the peripheral blood neutrophil count, but this phenomenon is due to not increased neutrophil synthesis but rather to neutrophil release from blood vessel walls and egress of a storage pool from bone marrow [318]. Such increases are not associated with a decreased risk of infection; trials of corticosteroids in MDS have been ineffective and associated with increased infections [319].

Iron chelation therapy with deferoxamine has been advocated for red cell transfusion-dependent patients, in order to prevent iron overload and secondary hemochromatosis [320]. Such therapy is cumbersome, however, since deferoxamine requires prolonged parenteral infusion by a pump. Sadly, most transfusion-dependent patients with MDS will not live long enough to be concerned about iron overload, making such treatment perhaps not worthwhile.

The use of chelation therapy may be justifiable especially in the younger patients such as those with classic 5q− syndrome. More recent data suggesting that iron overload may contribute to ineffective hematopoiesis argues in support of a wider role for chelation therapy [320]. Oral iron chelators are greatly needed, but progress has been slow. Deferipone is a moderately effective oral iron chelator that is currently available, but there is controversy about its ability to prevent iron-related hepatotoxicity [321].

Novel agents currently undergoing clinical trials in MDS include farnesyltransferase inhibitors (which interfere with processing of the ras oncogene, mutated in 10-40% of MDS cases [175,177,322])—one farnesyltransferase inhibitor has shown activity in relapsed AML [323]. Gemtuzumab ozogamicin (a monoclonal antibody against the CD33 epitope conjugated to a toxin; the CD33 epitope is present on early myeloid progenitors, and this agent has been approved for acute myelogenous leukemia), various putative anti-angiogenesis agents including matrix metalloproteinase inhibitors, arsenic trioxide (an ingredient in a traditional Chinese remedy that has shown efficacy in acute promyelocytic leukemia [324,325]), inhibitors of the MDR-1 “drug-resistance” glycoprotein, tricotitabine (a novel nucleoside analog [326]), lenocovin (folinic acid, used because the dihydrofolate reductase gene maps to the long arm of chromosome 5 and may be deleted in 5q− syndrome [327]), STI571 (a targeted tyrosine kinase inhibitor custom-made for chronic myelogenous leukemia [76,328]), flavopiridol (a cyclin-dependent kinase inhibitor), and others. Some clinical trials of novel agents designed for refractory AML are also open to high-risk MDS patients, expanding their options for clinical trial enrollment.

7.9. Thalidomide: a ray of hope from a dark remedy?

Thalidomide, the tragic teratogen that in 1961 catapulted the Food and Drug Administration (FDA) into the modern era, was recently approved by the FDA for the rare clinical situation of leprosy-associated erythema nodosum [329]. The drug is now enjoying extensive "off-label" use in hematologic diseases use because of its proven success in refractory multiple myeloma [330], and it is currently being tested in a wide range of other disorders. Its biologic mechanism remains mysterious, as it has both immunomodulatory and anti-angiogenic actions, and dozens of associated cytokine changes have been described [329,331]. Several reports have described responses to thalidomide in MDS [332-335]. Many institutions are currently studying the drug alone and in combination with other agents, which should more clearly define its role in MDS [301,336]. Unfortunately, the drug can be difficult to tolerate, especially for the older age group typical of MDS, because of its common side effects such as drowsiness, rash, postural hypotension, peripheral neuropathy, bradycardia, constipation, and erectile dysfunction. Thalidomide embryopathy still occurs in leprosy-plagued areas of South America [337], and careful safeguards have been introduced in North America to limit the possibility of the drug falling into the hands of anyone who might become pregnant [336].

7.10. Flavors of stem cell transplantation: auto, allo, mini, cord

The role of stem cell transplantation in MDS has recently been reviewed [338,339]. Overall, approximately 30-40% of MDS patients can be cured with allogeneic transplantation, but many of those will suffer scars such as chronic graft-versus-host disease, which can be so disabling that some "successfully" transplanted patients have committed suicide [340]. The best outlook with transplant is for patients with early MDS who receive stem cells from fully HLA matched donors; in this subgroup more than 75% will be long-term disease free survivors. The major limitation to allogeneic transplantation is the older age of MDS patients, whose median age is approximately 65 years [144]. Older patients tolerate allogeneic transplantation poorly (although some success was recently achieved in a cohort of 55-66-year-old MDS patients, with a 3-year disease free survival of 33-53%, depending on disease subtype [341]) and have a higher risk of disease relapse after the procedure [342]. Registry data have shown that patients who receive stem cells from an unrelated donor have a 2-year disease-free survival of only 29% and a treatment-related mortality of 54% [343]. No superior marrow ablation regimen has been defined [344], and the appropriate timing...
of transplant in MDS remains unclear [345]. Some have suggested that patients transplanted early in their disease course may do better long-term [346].

Autologous stem cell transplantation for MDS at first blush would seem a futile proposition—why transplant marrow that potentially contains corrupt stem cells? The success of this endeavor hinges on the ability to selectively harvest and transplant polyclonal stem cells that are not part of the neoplastic process, which can be accomplished in some cases [347,348]. Some patients with MDS retain significant polyclonal hematopoiesis [349,350], and others who receive high-dose chemotherapy can achieve a remission with restoration of polyclonal hematopoiesis [351,352]. Stem cell collection is occasionally successful in such patients [353]. The European Group for Blood and Marrow Transplantation has led the way in this area [346]. Although autologous transplant was well tolerated in the small trials that have been reported [354,355], it is still too early to know just what role autologous transplantation will have in MDS, and the results of randomized trials are awaited.

Novel transplantation methods include non-myeloablative (“mini-allogeneic”) transplantation, in which an attempt is made to harness the immunologic activity of donor cells to purge the recipient’s malignant clone and re-establish healthy hematopoiesis [356,357]. This treatment modality at present is attempted primarily in patients felt to be too old or too sick to proceed with standard allogeneic transplantation, or in those whose disease has returned after conventional allogeneic transplant.

Allogeneic transplantation using umbilical cord blood offers distinct advantages such as a decrease in graft-versus-host disease [358]. Although cord blood transplantation can be successful in adults [359], fetal blood often does not contain enough stem cells to re-establish hematopoiesis in a large adult. Efforts to expand the stem cell population in cord blood in order to allow more frequent transplantation options for larger individuals are ongoing [360].

8. Prognosis: the improving science of forecasting

Since the development of the Bournemouth index in 1985 [361], multiple prognostic scoring systems have been proposed for use in forecasting the natural history of patients’ illnesses, thereby allowing appropriate treatment decisions or ensuring equivalent patient assignments in clinical trials [362]. At present, the most widely used MDS prognostic index is the 1997 International Prognostic Scoring System (IPSS), developed after multivariate analysis of 816 patients with de novo MDS who primarily received supportive care [83] (Table 4). Although its applicability to groups not included in the primary analysis remains uncertain, the IPSS has many advantages. It is relatively simple, the prognostic groups it classifies clearly have different outcomes, and multiple groups have validated it.

A number of other biological prognostic markers are now recognized that were not included in the IPSS. The methylation status of the p15(INK4B) gene [363], telomere length [364], degree of marrow apoptosis [365], presence of abnormally localized immature precursor cells in the marrow (a marker for vascular endothelial growth factor expression) [211,366,367], and mutational status of various genes (including ras, fms, and p53 [175,177]) may all have prognostic value, but they have not yet been subject to a multivariate analysis and tests for these factors are not available in routine clinical practice. The IPSS clearly separates high, intermediate, and low-risk cytogenetic categories, but the heterogeneous group of “other” cytogenetic lesions classified in the intermediate risk category could be refined further. Trisomy 8 and deletions of the long arm of chromosome 1, have been demonstrated to be adverse markers by several groups [162,368], while anomalies of chromosome 12 may be relatively benign. Patient gender may also be important [369]. The IPSS will be of most value if it is periodically revised incorporating any newer factors that retain independent prognostic relevance in multivariate analysis.

![Table 4](image)

<table>
<thead>
<tr>
<th>Score</th>
<th>0</th>
<th>0.5</th>
<th>1</th>
<th>1.5</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marrow myeloblast percentage</td>
<td>&lt;5</td>
<td>5–10</td>
<td>11–20</td>
<td>21–30</td>
<td></td>
</tr>
<tr>
<td>Karyotype</td>
<td>Good</td>
<td>Intermediate</td>
<td>Poor</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Peripheral blood cytopenias</td>
<td>0 or 1</td>
<td>2 or 3</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Risk groups</td>
<td>Total score</td>
<td>Median survival</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low-risk</td>
<td>0 points</td>
<td>5.7</td>
<td></td>
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<td></td>
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<tr>
<td>Intermediate-2 risk</td>
<td>1.5–2 points</td>
<td>1.2</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>High risk</td>
<td>2.5 or more points</td>
<td>0.4</td>
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Karyotype: good—normal karyotype; –Y, del(5p), del(20q); intermediate—all karyotypes not good or poor risk; poor—abnormal chromosome 7; complex karyotype (three or more anomalies). Peripheral blood cytopenias: hemoglobin, <10 g/dl; absolute neutrophil count, <1500/mm³; platelet count, <100,000/mm³.
9. Conclusion

Much has been accomplished in the last 10 years, but many challenges remain in understanding the myelodysplastic syndromes. As the biology of these disparate disorders becomes better understood, more appropriate classification schemes and more appropriate prognostic indices will be achieved. Hopefully, improved treatments will also become available to brighten the outlook for patients with what at present can only be described as dismal diseases. Clinical trials will carefully selected novel therapeutic agents deserve widespread and enthusiastic support. Even as new agents become available, excellent supportive care by conscientious physicians will remain the best that medicine has to offer.

References

[30] Fleischman S. I am . . . I have . . . I suffer from . . . a linguist ...


