The French-American-British classification system for acute myeloid leukemia

Daniel A. Pollyea

Division of Hematology, University of Colorado, Aurora, CO, USA

E-mail: daniel.pollyea@cuanschutz.edu

https://doi.org/10.3324/haematol.2025.288546

TITLE	Proposals for the classification of the acute leukaemias. French-American-British (FAB) Co-operative Group.
AUTHORS	Bennett JM, Catovsky D, Daniel MT, *et al.*
JOURNAL	British Journal of Haematology. 1976;33(4):451-458. doi: 10.1111/j.1365-2141.1976.tb03563.x.

In 1974, 150 stained peripheral blood and bone marrow biopsy slides from patients with acute leukemia and other disorders were shared among a group of seven expert hematologists from France, America and Britain (FAB). Their task was to independently diagnose and assess each specimen. For 5 days in Paris in the fall of 1974, they gathered to discuss and debate their findings, with a charge to reach a consensus on a new way to categorize acute leukemias using morphology. Nine months later the group assembled once again, this time in London, to apply the diagnostic criteria they had adjudicated using an independent set of specimens. Successful in their task, they published the seminal paper on the "FAB classification system" in 1976 in the *British Journal of Haematology* (Figure 1).[1] Notably, this was one of the first efforts to distinguish acute myeloid leukemia (AML) from acute lymphoblastic leukemia, which was of emerging importance due to inklings that these different diseases might respond to different treatments. What their work has become mainly remembered for, however, is the sub-grouping of AML into six types: M1, M2, M3, M4, M5 and M6 (later efforts would expand this well-known system to include M0[2] and M7[3]). The FAB classification system became the predominant system utilized by the field. The definitive t(15;17) lesion characterizing acute promyelocytic leukemia overlapped nicely with M3, as did later discoveries of the core-binding factor leukemias with respective morphological subtypes. However, with

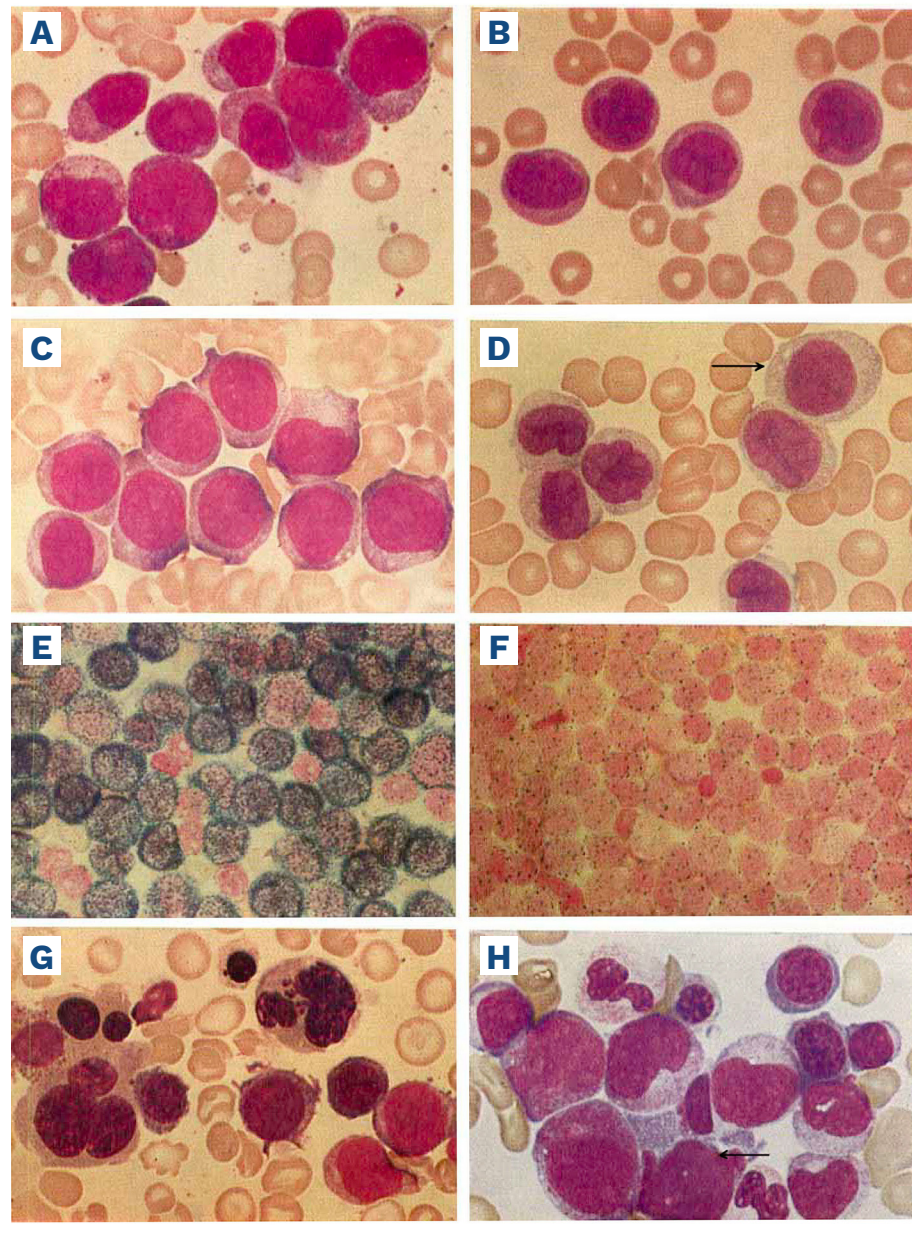

Figure 1. Exemplary blood and bone marrow findings. (A, B) Myelomonocytic leukemia (M4); bone marrow (A) and peripheral blood (B) of the same case. Magnification x 800. (C, D) Monocytic leukemia (M5): bone marrow. (C) Poorly differentiated type. (D) Differentiated type; note promonocyte (arrow). Magnification x 800. (E, F) Naphthol-AS-acetate esterase reaction in M5: bone marrow. (E) Strong reaction. (F) Reaction almost completely inhibited in the presence of sodium fluoride. Magnification x 640. (G) Erythroleukemia (M6): bone marrow. Magnification x 800. (H) Refractory anemia with excess of blasts: bone marrow; note micromegakaryocyte (arrow). Magnification x 800. Figure reproduced, with permission, from Bennet JM *et al.*[1]

the widespread use of cytogenetic testing, these biological features were found to hold greater prognostic importance. Ultimately, once extensive genomic testing became widely available, the morphological FAB classification system was relegated. Clinicians did not request its use, as the various subgroups were not treated differently. A new generation of pathologists were not trained to use it, and some of the necessary stains became limited in availability.

That might have been the end of the story, except for the development of a new therapy for AML, the BCL-2 inhibitor venetoclax. In searching for factors that could predict outcomes with this therapy, our group and another nearly simultaneously reported that monocytic disease features, as defined by morphology or immunophenotypic markers, were adverse in the setting of this novel agent.[4,5] Suddenly, the morphological classification of AML was relevant again. What had been discarded for being archaic was newly appreciated, providing novel insights into this well-studied disease that even the most extensive genomic probing could not reveal.

It is said that one can learn a lot about the underpinnings of a human disease by its classification system. When clinical features, as opposed to more sophisticated genomic and cytogenetic markers, are used to classify a disease and its subtypes, this has been interpreted as an indictment of the sophistication with which the field knows its disease. Let the work of those seven expert hematologists, who over 50 years ago labored to classify AML using only their two eyes and a microscope, stand as evidence that we cast aside such efforts at our peril. In the dynamic field of AML, everything old is new again.

Disclosures

DAP has served as a consultant or advisor for Ryvu, Bristol Myers Squibb, Servier, Oncoverity, AbbVie, Taiho, Astellas, Sumitomo, and Johnson and Johnson.

References

1. Bennett JM, Catovsky D, Daniel MT, et al. Proposals for the classification of the acute leukaemias. French-American-British (FAB) Co-operative Group. Br J Haematol 1976;33(4):451-458.
2. Bennett JM, Catovsky D, Daniel MT, et al. Proposal for the recognition of minimally differentiated acute myeloid leukaemia (AML-MO). Br J Haematol. 1991;78(3):325-329.
3. Bennett JM, Catovsky D, Daniel MT, et al. Criteria for the diagnosis of acute leukemia of megakaryocyte lineage (M7). A report of the French-American-British Cooperative Group. Ann Intern Med. 1985;103(3):460-462.
4. Kuusanmaki H, Leppa AM, Polonen P, et al. Phenotype-based drug screening reveals association between venetoclax response and differentiation stage in acute myeloid leukemia. Haematologica. 2020;105(3):708-720.
5. Pei S, Pollyea DA, Gustafson A, et al. Monocytic subclones confer resistance to venetoclax-based therapy in patients with acute myeloid leukemia. Cancer Discov. 2020;10(4):536-551.