Editorial

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A brief history of hematology analyzers and recent advancements: the available testing wealth

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In this issue of the Turkish Journal of Biochemistry (TJB), three articles are related to hematology analysis systems. One of these pertains to the test utilization in two major hospital laboratories, indicating that complete blood count (CBC) tests are most frequently requested [1]. In the second issue of the TJB, there were six articles directly related to CBC systems. Two of these were focused on the comparison and verification of hematology analyzers [2, 3]. The remaining four investigated the role of relatively new parameters used in hematology analyzers as biomarkers in various clinical conditions [4–7]. Indeed, articles on new parameters in hematology analyzers are increasingly emerging. This is somewhat expected, as hematology analyses, particularly complete blood counts (CBC), are among the most requested tests in medical laboratories. Clinicians almost always want to see and monitor the CBC results of their patients in nearly every disease. Additionally, CBC is included in the emergency testing menu. Moreover, new technological advancements are expanding the range of tests that hematology analyzers can perform. Inevitably, these new parameters are investigated in different clinical conditions.

Progress in science and technology proceeds through the accumulation of knowledge over a long period of time, followed by the emergence of scientific revolutions or discoveries in a relatively short period of time. The emergence of hematology analyzers follows a similar pattern. Blood is a highly complex suspension, the structure of which we still do not fully understand today. Research on its structure dates back to the microscopic discoveries of Dutch scientist van Leeuwenhoek (1,632–1,723) in the 17th century. For instance, van Leeuwenhoek identified in 1,674 that erythrocytes (RBCs) are disc-shaped cells. Throughout the first half of the 20th century, CBC analyses were performed manually. However, manual testing was both time-consuming and lacked precision. The most significant step in the development of hematology analyzers came with the work of Wallace Coulter (1913–1998) in the late 1940s, culminating in his discovery in the early 1950s. Coulter, an electrical engineer and businessman by profession, was attempting to measure the number of microscopic particles in various suspensions using optical systems. Observing that technicians spent approximately 30 min counting RBCs in hospitals, he sought solutions to automate this process. Initially attempting to count cells passing through a capillary using optical systems, he found that the signals obtained were not stable, leading to poor measurement reproducibility [8]. He wondered whether there would be a change in electric current if cells passed one by one through a narrow aperture (at that time, it was not yet known that blood cells were insulators). He discovered that when a blood cell passes through the aperture, it displaces an equal volume of surrounding fluid, resulting in a proportional change in electrical voltage. Thus, the Coulter principle, the electrical resistance or impedance method, was discovered in 1947: the electrical resistance exhibited by cells suspended in a conductive liquid passing through a narrow aperture is proportional to their size, resulting in a voltage pulse [9, 10].

This invention formed the basis of modern blood counting analyzers. It was later combined with the flow cytometry technique based on optical method developed by Moldavan in 1934 [10]. Modern hematology analyzers utilize various techniques such as impedance, conductivity, light scattering/fluorescence scattering, and cytochemistry for cellular and morphological analyses. For example, some hematology analyzers, in addition to impedance technique, incorporate conductivity measurements with high-frequency electromagnetic current and optical light scattering (Abbott, Coulter, Sysmex) or fluorescence light scattering (Mindray), while others use only light scattering and cytochemistry techniques (ABX, Sysmex) (Table 1).

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Table 1: CBC parameters available from selected instruments [10].

Instrument (manufacturer)	Cell- dyn sapphire (Abbott)	DxH 900 (Beckman Coulter)	BC 6800 (Mindray)	Advia (Siemens)	XN (Sysmex)
Available parameters	WBC and 5-part differential	WBC and 5-part differential	WBC and 5-part differential	WBC and 5-part differential	WBC and 5-part differential
	IG	NRBC	IG	RBC	IG
	NRBC	RBC	RBC	Hb	NRBC
	RBC	Hb	Hb	HCT	RBC
	Hb	HCT	HCT	MCV	Hb
	HCT	MCV	MCV	MCH	HCT
	MCV	MCH	MCH	MCHC	MCV
	MCH	MCHC	MCHC	RDW	MCH
	MCHC	RDW	RDW	MCVr	MCHC
	RDW	PLT	NRBC	PLT	RDW
	MCVr	MPV	PLT	MPV	PLT
	CHr	RET	RET	Mean PLT component	MPV
	CHCr	Immature RET	Immature RET	PDW	IPF
	PLT	CPD	Infected RBCs	RET	RET
	MPV rPT	Early sepsis indicator		LUC	IRF
	Leukocyte viability			CHr	RET-He
	RET			CHCr	
	Flow cytometry assays[a]				

CBC, complete blood count; CHr, mean cellular hemoglobin content of reticulocytes; CHCr, mean cellular hemoglobin concentration of reticulocytes; CPD, cell population data; Hb, hemoglobin; HCT, hematocrit; IG, immature granulocytes; IRF, immature reticulocyte fraction; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume; MCVr, mean cellular volume of reticulocytes; MPV, mean platelet volume; NRBC, nucleated red blood cells; PDW, platelet distribution width; PLT, platelet count; RBC, red blood cell count; RDW, red cell distribution width; RET, reticulocyte count; RET-He, reticulocyte hemoglobin; rPT, reticulated platelet fraction; WBC, white blood cell count; [a]options exist for CD3/CD4/CD8 T-cell subsets and monoclonal antibody-based flow cytometry assays.

The primary purpose of hematology analyzers is cell counting [RBC, white blood cell (WBC), and platelets] and differential leukocyte analysis. In modern hematology analyzers, differential WBC analysis may be 5-part (neutrophils, basophils, eosinophils, lymphocytes, and monocytes) or 7-part (additionally immature granulocytes and blasts). Additionally, reticulocyte counting is available on current hematology analyzers. These analyzers are multichannel analyzers, and these measurements are usually performed on different channels: one channel for RBC and platelet measurement, one for WBC and hemoglobin measurement, one for WBC differential counting, and one for reticulocyte counting. In recent years, many new parameters have been added to the test menu of modern hematology analyzers, such as nucleated RBC, RBC fragments such as schistocytes, immature reticulocytes fraction, and reticulocyte hemoglobin content; in addition to platelet count, mean platelet volume, platelet distribution width, immature platelet (reticulated platelets) fraction; immature granulocytes, large unstained cells, granularity index, and lymphocyte index. Furthermore, although the classic cyanmethemoglobin method for hemoglobin measurement has been recommended by the International Committee for Standardization in Haematology (ICSH), there is a trend towards methods that do not contain cyanide for environmental protection. This is because cyanide is a well-known cytotoxic compound that inhibits mitochondrial cytochrome *c* oxidase (Complex IV) in the electron transport chain. Therefore, methods using sodium lauryl sulfate instead of cyanide, where hemoglobin is converted to sodium lauryl sulfate-methemoglobin complex and measured photometrically, are becoming widespread.

On the other hand, information technology profoundly impacts medical laboratories, as in almost every field. Advanced flagging systems facilitate autoverification of hematology analyzer results. Currently, the easiest area for autoverification in medical laboratories is CBC. Furthermore, applications such as artificial intelligence and machine learning are applied in areas with easy imaging in medical laboratories. CBC and its complement, blood smear, are included as significant parameters in clinical decision support systems, including interpretation.

In conclusion, hematology analyzers primarily rely on flow cytometric particle counting and imaging. In flow cytometry, potentially every particle can be analyzed, making it highly flexible. Therefore, with the inclusion of new technologies, the enrichment of hematology analyzers will continue. Thus, hematology analyzers may help clinicians and patients by improving diagnosis and contributing to timely management of disease states.

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