PERSPECTIVE ARTICLE

The evolution of the complete blood count: have we gone too far?

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Abstract

The complete blood count (CBC) began its evolution at the end of the 19th century with the development of the hemacytometer to count blood cells. Soon thereafter, the hematocrit, a method to determine the packed red cell volume, was described in Sweden. Subsequently, the mean volume and hemoglobin content of red cells were added. Stains that distinguished individual leukocyte types permitted differential white cell counts: the product of the total white cell count and the fraction of each white cell type. A reliable means to count platelets rounded out the manual CBC. In 1954, Wallace Coulter introduced the Model A electronic particle counter. Modifications and advancements evolved into the Model S, a rapid, accurate, electronic method to determine the standard variables in the CBC and an array of additional measurements. Electronic particle counting has undergone numerous further developments including the application of florescence technology, such that approximately 30 variables can be measured as part of a CBC. This evolution has led to a chaotic situation; a recent study showed that the CBC ranged from 12 to over 24 variables when measured in either a community or academic hospital hematology laboratory. Out-of-range values, frequent and often trivial, have to be reconciled for patient and physician. Redundant and very low value variables have accrued in the CBC. We propose a major change in the CBC depending on the reason for its measurement. These recommendations markedly decrease the variables measured and make the results more impactful, which will enhance the physician's focus on the use of this key laboratory test to the benefit of the patient's care.

The development of the manual complete blood count

Progress in hematologic diagnosis is a history of the laboratory examination of blood cells. In 1852, Karl von Vierordt (1818-1884), a German physiologist, introduced counting of red cells, which, eventually, through a series of improvements in the precision of the counting chamber, led to the hemacytometer. This device enabled quantification of deviations from normal in red or white cell counts for over 100 years into the mid-20th century.[1] In 1879, Paul Ehrlich (1854-1915) developed and applied dyes that discriminated leukocytes by their staining properties. This led to the white cell differential count.[2] It became standard to multiply the fraction of the specific white cell type by the total white cell count to determine the absolute count of individual leukocyte types. The identification of the reticulocyte by Ehrlich resulted in the later realization by subsequent observers of its usefulness in the evaluation of erythropoietic marrow function.[3] It allowed differentiation of the pathogenesis of anemia: impaired red cell production *versus* accelerated red cell removal (hemolysis).

In 1885, the Swedish physiologist, Magnus Blix (1849-1904) invented, and Sven Gustaf Hedin (1859–1933), both at the University of Lund, further developed the "hämatokrit" device. This was an instrument to determine the packed red cell volume of human blood by using a small glass tube and centrifugal force.[4,5] The Swedish term "hämatokrit" (syn. "hematocrit" in American English) is derived from the Greek *haima* (αἷμα, "blood") and *kritēs* (κριτής , "judge"). This usage represented a means to judge (measure) the solid (cellular) fraction of blood, principally red cells.

Blix was incentivized to measure the heavier "solids" (cells) in blood by the Swedish dairy farmers' use of the "laktokrit", a technique to measure the fat content in cow's milk. The fat content reflects the cream content, which

in turn dictates what products, such as cheeses, could be made from the milk. Thus, the lactocrit directed the breeding of cows. The fluid portion of cow's milk formed the lower layer and was sometimes referred to as plasma or serum, in Blix's "hämatokrit" the plasma of blood was the upper layer.

Hedin continued and advanced this work by using the hematocrit in demographic studies. Normal values of packed red cell volume values in healthy men and women and young and old were explored by Hedin using the hematocrit method.[6]

Thirty-seven years later, Maxwell Wintrobe (1901-1986) improved the hematocrit tube, which led to its use to measure the sedimentation rate and, after centrifugation, the packed red cell volume and plasma coloration (e.g., presence and severity of jaundice or the icteric index). Wintrobe also proposed estimation of the size of the buffy coat as a crude first assessment of the white cell count. The buffy coat is the layer between red cells and plasma in centrifuged blood and contains platelets and white cells; they separate with centrifugation but their densities are not sufficiently different to get complete separation of the two layers. Nevertheless, in the extreme, one may discern severe leukopenia or exaggerated leukocytosis. The narrow Wintrobe tube measured 110 mm long and had graduations from 0 to 100 mm in ascending and descending order.[7,8] This method was replaced, later, by the microhematocrit method, which used a small capillary tube, often filled directly from the blood of a finger prick, requiring less blood and a small high-speed centrifuge with a rack to hold the capillary tubes. In time, the meaning of the term "hematocrit" was changed by popular usage from the instrument of measure to the measure itself, the packed red cell volume, which designation has been largely supplanted by the term "hematocrit".

Wintrobe also used the mean red cell volume to provide a classification and an algorithm for the diagnosis of anemia.[9,10] The evolution of the measurement of red cell size (*né* mean corpuscular volume) and hemoglobin content (*né* mean corpuscular hemoglobin and mean corpuscular hemoglobin concentration), which began in 1863, became the tripartite red cell indices as amplified by Wintrobe and reviewed by Haden.[11]

The introduction of the cyanmethemoglobin method, using spectrometry, resulted in an accurate and reproducible measurement of blood hemoglobin concentration.[12] The development of the platelet count permitted more insightful and accurate assessment of thrombocyte disorders.[13] However, manual cell counting of blood cells was tedious, slow and subject to error. Enter Wallace H. Coulter (1913-1998).

Electronic cell counting

Coulter became familiar with the inefficiency and lack of high reproducibility of manual blood cell counting when he was a salesperson visiting hospitals in the Far East before World War II. Later, the effect of the atomic bomb detonations in Japan and the need to count blood cells accurately as an index of the severity of radiation injury and recovery from exposure in a large population captured his interest. He became aware of the hours spent by technologists doing hemacytometer chamber counts of blood cells and of the method's tedium and variability.[14-16]

In April 1947, Wallace Coulter, with a background in electrical engineering, and his brother, Joseph R. Coulter, Jr. (1924-1995), began experimenting with photoelectrical counting of red cells flowing through a capillary tube. This eventually led to the Coulter Principle, first articulated in 1948. This principle holds that particles pulled through an orifice, coincident with an electric current, produce a change in impedance proportional to the volume of the particle traversing the orifice.[17] An application filed on August 27, 1949 and awarded on October 20, 1953 as US Patent 2,656,508 was entitled "Means for counting particles suspended in a fluid".

This new approach and instrumentation was more accurate and efficient than manual methods. In 1956, the groundbreaking Model A Coulter Counter was introduced at Wallace Coulter's presentation at the National Electronics Conference (Figure 1A). The Proceedings of this conference contained his sole scientific publication.[18] Sales of this initial device began to increase. In 1958, Wallace and his brother incorporated Coulter Electronics. The Model A went through progressive improvements designated by a letter, Model B, C, etc., resulting in the Model S, which profoundly advanced the ease and accuracy and speed of blood cell enumeration and sizing in the complete blood count (CBC) (Figure 1B).

Advances in the technology and the entry of other players in the market eventually allowed the measurement or calculation of a host of other variables beside those in the traditional CBC. These include red cell and platelet distribution width, platelet volume, the absolute reticulocyte count, the reticulocyte index, immature granulocyte cell count, nucleated red cell count, the immature reticulocyte fraction and reticulocyte hemoglobin content. Other variables and derivative variables may also be measured as a function of the specific instruments used.

The initial application of the Coulter Principle led to flow cytometric techniques that later incorporated fluorescence detection and additional advances by others. These have been integrated into some advanced versions of electronic particle counters.[19]

Wallace Coulter's progress from his appreciation of the need for accurate, reproducible and rapid blood cell counting to the design, implementation, commercialization and progressive improvement of his cell count and volume analyzer resulted in a revolution in particle enumeration and sizing, cytometry, laboratory medicine and healthcare. Many additional innovations have expanded his original concept.

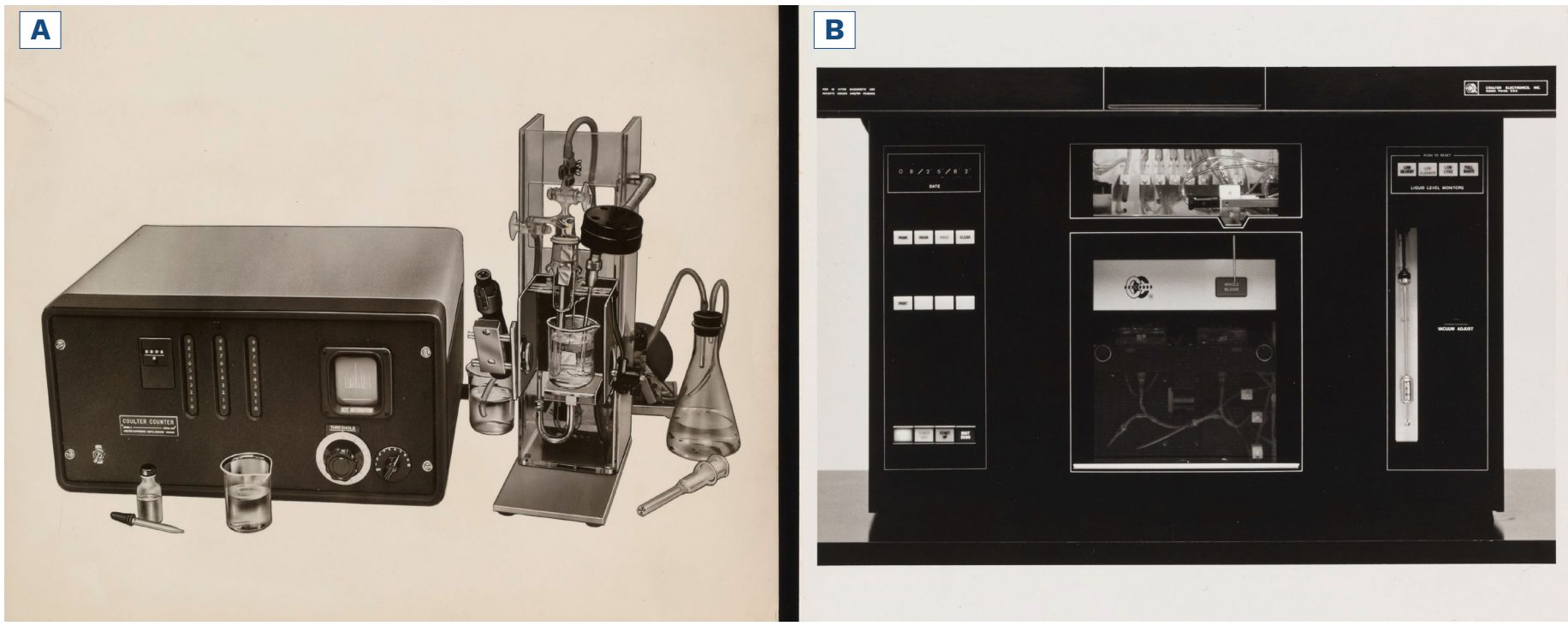

Figure 1. The evolution of the Coulter cell counter. (A) The Model A Coulter Counter introduced in 1954. (B) After a series of improvements over 14 years, the Model S Coulter Counter was released in 1968. Many further advancements have accrued in the ensuing years. Images courtesy of the Science History Institute.

The effect of the expanded complete blood count

It is estimated that over 500 million CBC are performed every year in the USA. Out-of-range values, which may represent a trivial divergence from the normal 95% confidence interval, are reported to the patient and need to be reconciled. Thus, questions are being raised about the need for redundant values in the CBC, such as the red cell count, hemoglobin concentration and the packed red cell volume (hematocrit), and obsolete values, such as the total white cell count and the percent of each leukocyte type, when the absolute count of each white cell type is provided.[20,21] This common practice results in eight unnecessary and uninformative variables in the CBC.

A recent study of hospital laboratory practices found a range from 12 to 24 variables in the CBC in hospital laboratories.[22] Most CBC contained 20 or more variables. There was little difference between community and academic medical centers. The UCLA Medical Center has 23 variables in its CBC of which we would consider nine as very useful. Others are redundant, non-physiological or of low impact. This situation is very common in many medical centers.[22] In contrast, the Mayo Clinic CBC contains 12 variables.[23] These findings indicate that a reappraisal of the content of the CBC is overdue. In such a reappraisal, one should consider that most CBC are measured in someone in whom the diagnosis is known and are not measured to diagnose a hematologic abnormality.[24] An enhanced focus on the essential components of the CBC without redundant, non-physiological, unneeded or very low impact components would improve its utility for physicians of all stirpes.

Our proposal for modernization

In cases such as the annual physical examination of an ostensibly well individual, screening CBC could be omitted or reduced to three variables. Clinical guidelines and initiatives like the “Choosing Wisely” campaign discourage unnecessary laboratory testing, including the CBC, in well patients. Our limited CBC, which we propose here, comprises only three variables, decreases the likelihood of false positive variables and may be more impactful as it focuses on three key screening measurements: blood hemoglobin concentration, white cell count and platelet count (Table 1). The screening CBC (three variables) may be more efficient in the annual, periodic or pre-employment medical examination than the current version (often >20 variables). As to eliminating the CBC in such instances, a screening CBC may be justified in subjects over a given age, such as 50 years, or when some minor variation from expected is found in the periodic or screening medical history or physical examination. Further study of this question would be useful.

Moreover, a significant fraction of CBC are measured in people with a known diagnosis and the information is required to follow a patient’s blood cell counts, periodically, to measure the response to therapy or the tolerance of the marrow to therapy. Here, we estimate the need is for a CBC containing seven variables (Table 1). In most settings, the CBC for these purposes currently includes 20 or more variables, cluttering the electronic medical record with unneeded data.[22]

We also propose that a CBC in a patient with new undiagnosed findings, be they hematologic or not, but requiring comprehensive evaluation, should contain ten numerical variables and the examination of a blood film[20] (Table 1).

The reasoning behind the elimination of rarely informative variables, such as the mean corpuscular hemoglobin and mean corpuscular hemoglobin concentration, redundant variables, such as the red cell count and hematocrit, when the hemoglobin is reported, and non-physiological variables, such as the white blood cell count and the five individual white cell percentages in the presence of absolute individual white cell counts, is discussed elsewhere.[21-23]

Surveys have found that physicians focus on a very few variables in the CBC. A 2020 study in Pakistan found that 80% of respondents indicated that only three variables (hemoglobin, white cell count, and platelet count) were considered frequently or always useful.[25] Similarly, in a study conducted in Cleveland, Ohio, four variables (hemoglobin, hematocrit, white cell count, and platelet count) were considered useful for screening by more than 90% of physicians. Of course, hemoglobin and hematocrit provide the same information. A fifth value, the mean corpuscular volume – but not the red cell count, mean corpuscular hemoglobin or mean corpuscular hemoglobin concentration – was deemed useful in the evaluation of anemia.[26] Thus from Asia to the USA, only three variables, hemoglobin concentration, white cell count and platelet count, are the focus of many physicians evaluating patients.

The current CBC evolved erratically over many years by accretion with a more-is-better mindset, often driven by technology, not evidence–based, without consideration of the negative consequences of numerous low impact variables, redundant variables or variables that might be useful in a highly specific circumstance but represent clutter when used indiscriminately.

Let us consider increasing the specificity and, thus, impact and utility of the CBC.

Table 1. Three blood counts for specific purposes.

Variable	Screening	Follow-up	Diagnostic
Hemoglobin	X	X	X
Mean cell volume			X
Red cell distribution width			X
White cell count	X		
Absolute neutrophil count		X	X
Absolute lymphocyte count		X	X
Absolute monocyte count		X	X
Absolute eosinophil count		X	X
Absolute basophil count		X	X
Platelet count	X	X	X
Absolute reticulocyte count			X
Examination of the blood film			X
Total quantitative variables	3	7	10

Disclosures

No conflicts of interest to disclose.

Contributions

MAL and WRB contributed equally to the literature review and preparation of the manuscript.

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