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The Automated Blood Count: Its History, Utility and Need for Change

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Abstract

An automated complete blood cell count (CBC) is one of the most frequently ordered laboratory tests. The clinical utility of its 20 to 25 parameters, however, is variable depending, for example, upon the physician's age, education and specialty. Likewise, the information value of some CBC indices differs in populations with, for example, a high prevalence of benign (ethnic) neutropenia or thalassemia trait compared with other populations. Whereas modern blood cell analyzers count reticulocytes they do not include this important count in a 'standard' CBC report. In this article, we review the history of blood cell counting, the clinical utility of some parameters as well as the logic and information processing costs of their use in clinical practice. We conclude that the CBC as currently reported is an unnecessarily complex yet incomplete test, and suggest that blood analyzers be reprogramed to offer physicians a Short CBC with 11 clinically relevant parameters i.e. red cell count, reticulocyte count, hemoglobin, mean corpuscular volume, red blood cell distribution width, platelet count, and five absolute leukocyte differential counts.

Keywords: Public health; History of medicine; Differential leucocyte count; Reticulocyte count; Red cell indices; Clinical laboratory technique

Introduction

The automated complete blood cell count (CBC) is one of the most frequently utilized laboratory tests. We estimate that it is requested between one and seven million times per day worldwide. Automated blood cell counters produce results rapidly, precisely, and at low cost. They are a marvel of modern medicine and technology and are used throughout the world [1-3].

The automated CBC is a complex investigation reporting 20 to 25 parameters that define eight (and sometimes more) types of blood cells from three hematopoietic cell lines. The parameters, however, differ in their diagnostic usefulness. For example, mean corpuscular volume (MCV) is more useful than mean corpuscular hemoglobin concentration (MCHC) and internists use MCV more often than surgeons [4,5]. Despite its name, the standard CBC is an incomplete investigation since it does not include the reticulocyte count.

Automated blood cell counters have created novel challenges in medical practice. In societies with a high prevalence of a low neutrophil count due to benign ethnic neutropenia or of small red cells due to thalassemia trait, CBC results have increased uncertainty in the differential diagnosis of neutropenia, microcytosis, and anemia thereby producing diagnostic confusion and adding to the cost of health care [6-9]. When interpreting results, the doctor needs to use his/her intelligence and avoid requesting unnecessary work ups and consultations, which result in extra cost. There should be a penalty for such a behavior. In an attempt to curb such practices in the United States, the CMS (Center for Medicaid and Medicare services) recently introduced a rule whereby a physician needs to present a reason for requesting an MRI or a CT scan. Furthermore, Medicare reimburses services with a fixed amount as per DRG (diagnostic related group) regardless of the expense incurred for investigations, consultations and length of patient stay. In North America, reviews of large databases have disclosed substantial age, sex, and race-related variations in the value of erythrocyte parameters that are not well covered with reference ranges currently in use [10]. These and other factors complicate the interpretation of CBC results for physicians who themselves differ widely in their education, specialty, type of clinical experience and years of practice. In this article, we review the history of blood cell counting, the clinical utility of CBC parameters, and the logic behind their use together with the associated costs. We conclude that the automated CBC is an incomplete and unnecessarily complex test in need of modification.

A short history of the CBC

All ideas and methods have a lifespan. The ancient Greeks believed that at the beginning of the World Chaos ruled, and then came the Titans, Olympians, and other gods in whose veins circulated blue and oily Ichor, a concoction of nectar and ambrosia that was poisonous to mortals [11]. The latter portion of this model may still be seen as valid in view of the unhappy outcome from a transfusion of incompatible blood. There is a rule which states that the older an idea, the greater are the odds for its future survival. This is called the Lindy effect and, restated, indicates that, in contrast to that which is perishable such as human life, robust ideas "age" in reverse and with time gain "antifragility" [12]. The Greeks expanded the concept of blood by adding three additional humors and stipulated that their balance in the body determined the state of an individual's health and disease. The anointed father of humoral theory, Hypocrites, is also the forefather of 'rational' medicine. Before him diseases were explained by supernatural causes [13]. The humoral theory appeared sound because the existence of the four humors provided a sufficient number of combinations of imbalance to explain every possible malady; it thrived

for two millennia till the turn of 20th century. Treatment by bloodletting was its logical extension. Its lifespan was even longer since the Greeks inherited it from the Egyptians [14]. Both theory and treatment had broad acceptance and acquired mythical proportions in the practice of medicine before being replaced by more credible ideas and methods. In support of the validity of the Lindy effect, treatment by venesection was resurrected in the 20th century and is still used today in treating disorders such as polycythemia and hemochromatosis.

A switch from the humoral to the 'cellular' theory of disease together with emergence of the 'corpuscular' model of blood proceeded in stages in which the longevity of novel ideas and methods varied widely [15]. Transition to the 'corpuscular' model of blood was initiated in the 17th century with the invention of the microscope by Antoni van Leeuwenhoek who was first to observe and draw sanguineous globules, later known as red blood cells [16]. In practice, the model was virtually useless for two hundred years because of the rare availability of microscopes and the poor quality of their optics. Nevertheless, after initially small improvements in microscopy optics, many physicians enthusiastically embraced this technological advance only to be admonished not to lose themselves in a micro-world of cells and forget the patient [17].

In the second part of 19th century, the diluting pipet and hemocytometer were invented which made cell counting possible and led to the discovery of white cells in the blood. Blood cell counting, however, was tedious and results were unreliable until the next step-up in methodology was made possible by Paul Ehrlich. He introduced dyes into the field of hematology and stained the otherwise colorless globules. Ones that stained "red" became red blood cells (RBCs) and those that were "white" became white blood cells (WBC). But the latter turned out to be a composite of five different cells, which led to the creation of the concepts of total leucocyte count and leucocyte differential [18]. The manual counting of leucocytes (still performed as a teaching aid in some medical schools and occasionally in laboratories) is important to remember here for the purpose of comparison with direct counting in modern analyzers. With manual counting the total leucocyte count was obtained from a hemocytometer and the differential counts from microscopic examination of colored blood film [1]. In the blood film, each type of leucocyte is counted separately until their sum total is 100 in this way their numbers became the percent differential. The goal of such counting is to determine the absolute count for each of five types of leucocyte in the blood: this is done by multiplying the total leucocyte count (obtained in a hemocytometer) by the fractional differential of each leucocyte type (obtained from the blood film). In the early 20th century, this was a remarkable success for medical practice although at that time it was much in the shadow of momentous achievements in physics and may have suffered from 'physics envy'. The latter premise is supported by the fact that once automated blood analyzers began to count all types of leucocytes directly, the total WBC and it's percent differential were recalculated (in reverse) almost as if to recall this historical achievement.

The history of the reticulocyte count follows that for leucocytes in many respects. Reticulocytes were discovered at the time of Paul Ehrlich's experiments with the coloring of blood cells but their use in practice began only in the second part of the 20th century [19]. Reticulocyte counting proved even more tedious than that of leucocytes and involved: i) Counting RBCs in a hemocytometer, ii) counting reticulocytes and 1,000 erythrocytes in a colored blood film, iii) calculation of the reticulocyte percent, and iv) calculation of the absolute number of reticulocytes from the RBC count and reticulocyte percent [1,19]. In practice, the last step was often omitted and perhaps left to famously busy physicians to perform. As a result, the established way of reporting reticulocyte counts was as a percent. Nonetheless, in a drive to improve the efficiency of diagnosing anemia, the 'corrected reticulocyte count' and 'reticulocyte (production) index' were devised. They required additional parameters (sex and age of the patient, standard hematocrit values, and a reticulocyte maturation table) for calculation, were more difficult to interpret, and were infrequently used in practice [1]. In the last decade of 20th century fully automated reticulocyte counts became available and both tests became obsolete [19,20].

The measurement of hemoglobin (HB) began at the turn of the 20th century and was initially difficult, the units were confusing and the reference standards were non-existent for decades. In a drive to improve diagnostic efficiency, however, the hemoglobin level and RBC count were used to calculate 'color index' and 'saturation index'. Both derivatives were of a limited practical value and survived only a few decades [17].

In the 1930s, Maxwell Wintrobe quantified the volume of red cells packed in a glass tube (hematocrit) after centrifugation [21]. In contrast to hemoglobin, this measurement of hematocrit (HT) was technically simple and the results were reliable. The use of HT became popular and overshadowed the use of hemoglobin for many decades. Today, it is a more frequently used than HB in clinical guidelines. For example, in Polycythemia Vera patients are phlebotomized until the HT is less than 45%. The equivalent HB level is less than 15 g/dL, but is rarely noted in the current literature.

Wintrobe's importance to hematology and the practice of medicine at large comes also from his description of the relations between HB, HT, and the RBC count. This is summarized in definitions of the erythrocyte indices MCV, MCH, and MCHC. In contrast to HB, HT, and RBC count, which at the time were products of direct measurements, MCV, MCH and MCHC were calculated derivatives. Wintrobe used them to create a morphological classification of anemias and revolutionized the approach to their diagnosis [22]. Today, these ideas remain firm and, nearly a century later, all six erythrocyte parameters remain components of the standard automated CBC report. By contrast this is not the case with some of his other ideas whose life span was short. His Icterus Index, used in the diagnosis of hemolytic anemia, survived several decades only. His measurements of packed leucocytes volume and leucocyte indices, calculated in a manner analogously to that for erythrocytes, never entered medical practice [21]. Yet his invention of the erythrocyte sedimentation rate survives till today (in a modified form) albeit with fading popularity. In his 1933 paper discussing sedimentation, he reflected on the relation between the origins of humoral theory and four visible layers of clotted blood: two levels of differently packed red cells, buffy coat, and plasma [21]. It is perhaps appropriate to use that seminal publication to mark the end of the three-century long transition from the humoral to the 'corpuscular' model of blood.

Coulter's era

The most recent chapter in the history of the CBC began in the 1960s with the invention of the automated blood cell counter by Wallace Coulter. He counted cells streaming through a tiny channel using the property of cells to conduct electricity less well than the non-corpuscular component of blood [23]. The technology has improved

over the years and, in addition to counting and sizing the cells, the machines directly measures other cell parameters and the amount of HB released from RBCs. The other important component of the invention of the blood cell counter, however, resides in the computer chip, which, fortuitously, became available at the time of its development. As a result, they are easy to program and can instantly perform a variety of calculations. Indeed, modern cell counters can generate over 70 parameters either by direct measurement or by calculation, in many samples in short time [1,3].

However, in contrast to the pre-Coulter era, some directly measured parameters became calculated and vice versa. Thus, in the routine automated CBC, the RBC, reticulocytes, five types of leucocyte and platelets are directly counted, and directly measured are the HB and MCV. Calculated parameters are the HT (the product of the RBC count and MCV), total WBC and it's percent differential (both derived from five absolute leucocyte counts), percent reticulocytes (derived from reticulocyte and RBC counts), and red blood cell distribution width (RDW). This methodological twist is important because of the way in which the results – obtained manually and by automated machines – are reconciled in the reports of automated CBC results: namely, both are often retained which has increased the total number of parameters presented to the physician. Furthermore, the ease by which cell counters could be programmed to compute the derivatives, on one side, and the tradition of seeking greater diagnostic efficiency through calculation, on the other side, contributes to a large and still growing number of parameters in CBC reports (Figure 1). One meta-analysis, for instance, identified over 40 indices intended to improve differentiation of iron deficiency anemia from thalassemia trait [24]. One must ask is more always better or, could an unnecessarily long list of CBC parameters hinder clinical interpretation of the results?

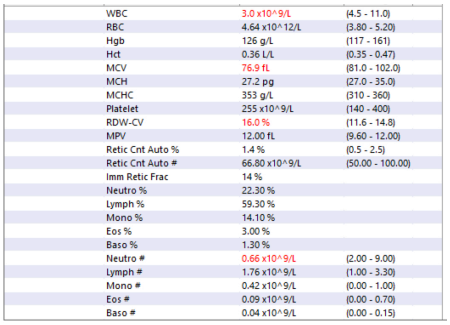
CBC results in the context of information theory

CBC results frequently have an important and often vital bearing on clinical diagnosis and patient management. Interpretation of CBC depends on numerous factors including the clinician's medical education, training, type of practice, and years of experience. Accurate interpretation of the CBC is governed also by the universal laws of information theory according to which the speed at which information is processed is proportional to the bandwidth of the channel and inversely related to the amount of background "noise" [25]. Human cognitive bandwidth is defined by the biological limits of the neocortex [26]. In contrast to the tireless computer, human cognitive bandwidth decreases with fatigue, which is induced by, amongst other factors, information overload. An increase of information density prolongs search time and decreases accuracy of retrieved information [27]. That is why we often have two types of CBC i.e. with differential count and without differential. This helps to minimize unnecessary information. In surveys of hospital physicians, up to one third thinks that the CBC has too much of information [4,5].

In information theory, data have a measurable value called 'content' or 'surprise' value and a component without 'content' is noise. Noise is universal and unavoidable in any information processing channel. In medical practice, noise has many sources and one is laboratory data that have little or no clinical value. The physician who is required to process low 'content' data will likely be less productive per unit of time compared with his/her colleague who is dealing with high "content" data. When information load exceeds processing capacity of the channel, unprocessed information, some of which may be of clinical importance, is wasted. And, when the upper limit of processing capacity is reached, information with low 'surprise value' is likely to become noise. That is one good reason not to recommend to medical students and residents checking labs on a routine daily basis. In the emergency room, a slew of labs are often ordered when patients present with minimal complaints and prior to proper evaluation, which often result in needless consultations and investigations. Indeed, the CBC is a highly abused laboratory test. One measure that could be help is that the information content of its parameters is critically examined, ranked and appropriately presented to clinicians [28].

Information content of CBC parameters

Leucocytes: Automated blood cell counters generate 11 leucocytes parameters: total WBC count, five absolute leucocyte differential counts and their five respective percentage values (Figure 1). The total WBC count is the single most often used CBC parameter by physicians and is closely followed by its differential count. Of the two differential counts, physicians prefer the percent leucocyte differential count [4,5]. This is an anomaly because the percent differential count is generated so that absolute counts for each type of leucocyte can be determined. Therefore, when an automated CBC provides both kinds of leucocyte differentials, the absolute differential provides sufficient information and the total WBC and percent differential counts are unnecessary. In fact the latter two counts should be removed for three additional reasons.



WBC	3.0 x10^9/L	(4.5 - 11.0)
RBC	4.64 x10^12/L	(3.80 - 5.20)
Hgb	126 g/L	(117 - 161)
Hct	0.36 L/L	(0.35 - 0.47)
MCV	76.9 fL	(81.0 - 102.0)
MCH	27.2 pg	(27.0 - 35.0)
MCHC	353 g/L	(310 - 360)
Platelet	255 x10^9/L	(140 - 400)
RDW-CV	16.0 %	(11.6 - 14.8)
MPV	12.00 fL	(9.60 - 12.00)
Retic Cnt Auto %	1.4 %	(0.5 - 2.5)
Retic Cnt Auto #	66.80 x10^9/L	(50.00 - 100.00)
Imm Retic Frac	14 %	
Neutro %	22.30 %	
Lymph %	59.30 %	
Mono %	14.10 %	
Eos %	3.00 %	
Baso %	1.30 %	
Neutro #	0.66 x10^9/L	(2.00 - 9.00)
Lymph #	1.76 x10^9/L	(1.00 - 3.30)
Mono #	0.42 x10^9/L	(0.00 - 1.00)
Eos #	0.09 x10^9/L	(0.00 - 0.70)
Baso #	0.04 x10^9/L	(0.00 - 0.15)

Figure 1: Complete blood cell count (CBC). Computer display of 23 results ordered as CBC with reticulocytes. Normal ranges are in parenthesis and abnormal values are displayed in red.

First, their use is illogical. The total WBC and percent differential are the by-products of manual cell counting and, in automated analyzers, they need to be recreated. This goes against common sense and the principle of parsimony, devaluing a system we want to impart to medical students and physicians in training.

Second, the percent differential count for one or more leucocyte type may be abnormal when the absolute differential count is in fact normal, and vice versa. The confusion between the abnormal and normal total, relative, and absolute leucocyte counts is common among medical students and physicians. This was noted as early as 1903 in the report of eosinophilia in patients infested with parasites who had normal total numbers of leucocytes [29]. More recently, this phenomenon became a serious problem in societies in which the introduction of automated blood cell counters resulted in the discovery of a high prevalence of low neutrophil counts due to benign (ethnic) neutropenia. Such populations, estimated at 1.8 billion people, have a mix of 'low' and 'normal' neutrophil count phenotypes [6]. For

neutropenic patients in these populations, there is much uncertainty about the nature of a low neutrophil count (primary benign versus secondary non-benign) which readily translates into higher costs and lower quality of patient care [30]. One obvious solution to this problem is the removal of the total WBC and percent differential counts from automated CBC reports [31].

Third, when the absolute leucocyte differential count is available, the total WBC and percent differential counts are noise since they contain no additional information. Furthermore, when their reference ranges (12 additional numbers) are provided, they add noise to CBC reports. Moreover, the practice of flagging abnormal result (e.g., in red color) is common and, when total WBC and percent differential counts are marked out-of-range, this could unnecessarily distract physicians (Figure 1).

In short, the total WBC and percent differential counts are vestiges of the past drifting through current medical practice. Sadly, they are strongly preferred by physicians, favored by some of our most prestigious medical journals, and sometimes, when not shown in CBC reports, are re-introduced 'at popular request' [5,32]. We disagree with this practice and believe that the total WBC and percent differential counts could and should be removed from CBC reports without loss of information while speeding up interpretation of the results, decreasing the odds of misinterpretation and clinical misjudgment, and improving communication between physicians and with the laboratory (Figure 2).

RBC	5.02 x10^12/L	(3.80 - 5.10)
Retic Cnt Auto #	48.20 x10^9/L	(50.00 - 100.00)
Hgb	101 g/L	(117 - 155)
MCV	65.7 fL	(81.0 - 100.0)
RDW-CV	16.6 %	(11.6 - 14.8)
Platelet	303 x10^9/L	(140 - 400)
Neutro #	4.57 x10^9/L	(1.80 - 7.70)
Lymph #	2.12 x10^9/L	(1.50 - 4.00)
Mono #	0.36 x10^9/L	(0.20 - 0.95)
Eos #	0.10 x10^9/L	(0.00 - 0.70)
Baso #	0.05 x10^9/L	(0.00 - 0.15)

Figure 2: The Short CBC. Normal ranges are in parenthesis.

Erythrocytes: Standard CBC reports present seven erythrocyte parameters some of which are redundant and therefore unnecessary. Consider hemoglobin and HT which are intimately correlated (HT=hemoglobin × 3) which means that when a HB value is known the information value of HT is negligible, and vice versa. Studies have found that physicians use these two parameters with similar frequency [4,5]. Why use two if one would suffice?

In selecting the better of the two parameters to record, a few factors need to be considered. Hemoglobin measurements by automated blood cell analyzers are marginally more precise than the HT [1,20,33]. Hemoglobin is measured after it is release from lysed RBCs, which adds to the cost of the test whilst HT is calculated and is practically costless. In this area of debate, considerations of physiological/pathophysiological knowledge and human thought processes might be important. For example, hemoglobin is a carrier of oxygen and HT is not. In anemia, we link low hemoglobin (not HT) with the development of tissue hypoxia and its clinical manifestations. Likewise, in polycythemia, we use the high RBC count (not HT) to picture in our mind pathophysiological processes underlying the disease. A final point here is that both hemoglobin and HT are required for calculation of MCHC and only hemoglobin for that of MCH.

The MCH and MCHC correlate with MCV. In two studies, a third of physicians admitted rarely or never using MCH and MCHC [4,5]. In view of the long history of utilization of RBC indices, a lack of physician education is an unlikely explanation. A likely explanation is that MCH and MCHC have poorly defined clinical utility for most physicians. Indeed, an abnormal MCH or MCHC often confuses physicians [5]. Hence, we should ask whether we need all three erythrocyte indices in the CBC. In hereditary spherocytosis, MCHC is elevated and does not correlate with MCV, but this is only in half of patients and it is not important in making the diagnosis [1]. The MCH may dissociate from MCV in some rare combined anemias and can result from inappropriate sample storage [20]. Overall, it is difficult to find sound clinical grounds for including the MCHC and MCH in every CBC for all physicians. Moreover, the availability of tests such as serum ferritin, B12, folate, hemoglobin analysis, and erythropoietin blood level have decreased the practical usefulness of some erythrocyte indices for many physicians [20]. Therefore, for the vast majority of physicians, removing HT, MCH, and MCHC from the routine CBC would not result in loss of useful information but, importantly, would decrease the "noise" in laboratory results (Figure 2). The value these parameters have had in the past has changed and, today, they are more of historical interest than practical use.

Reticulocytes: The reticulocyte count is one of the most underutilized hematology tests, yet it is essential in the investigation of anemias (17 p805). In one third-world country, over half of hospital-based physicians rarely or never used the reticulocyte count [4]. The manual reticulocyte count is performed by staining of red cells with Romanowsky stain and reticulocytes with another supravital dye. This labor-intensive process adds to the cost of the test and was in the past usually ordered by hematologists or upon their approval. This policy was rational because it preserved limited laboratory resources. The first fully automated reticulocyte count became available in mid 1990s. Automated analyzers count 10,000 cells hence reticulocyte counts so obtained are more precise and reliable than manual counts and more expensive than standard CBC. By 2014, at least 15 types of machines from six producers were in the market [19] yet still today the reticulocyte count is not a part of a standard CBC report. Why?

Today, any physician can order a 'reticulocyte count' or 'CBC with reticulocyte count' (Figure 1). In practice however this often means that a CBC test 'with reticulocytes' has to be performed soon after the CBC test results show anemia. Repetition of the test would be unnecessary if a reticulocytes count was, as a routine, part of the standard CBC. This would also reduce the cost of testing and improve the quality of care by facilitating an earlier diagnosis and discharge and sometimes removing the need for a revisit to the physician. Further, any test repetition increases the odds of a chance error in the result which, in the case of the CBC, is compounded by the large number of parameters. Although the CBC with reticulocytes is charged at a higher rate than a standard CBC, we believe that its cost/benefit ratio is low, and it should be used as the new standard. This then is similar to tests with low cost/benefit ratios we already have in the practice such as 'electrolyte' and 'liver function tests' panels.

When an absolute reticulocyte count is available, a percent reticulocyte count is generally preferred by physicians [4,5]. This is an anomaly since percent reticulocyte contains no additional information and further clogs the CBC report thereby slowing the reading and processing of data. An absolute reticulocyte count is needed for a

proper understanding of the result (Figure 1). A normal absolute but 'increased' percent reticulocyte count often confuses medical students and physicians. As with the leucocyte percent differential, reticulocyte percent is an unnecessary relic of the past and should be removed from automated CBC reports (Figure 2). Similarly, many other reticulocyte parameters should not be included in routine CBC reports but for different reasons. The reticulocyte (production) index was rendered obsolete after the automated absolute reticulocyte count became available. The immature reticulocyte fraction is a promising test in the assessment of bone marrow activity, but it is rarely used even by hematologists and oncologist and its inclusion in the CBC is not utilized by the vast majority of physicians. The same applies to reticulocyte indices which, incidentally, are calculated in the same way that Wintrobe utilized for erythrocyte indices nearly a century ago [19,20].

Platelets: In automated CBC, the most often used platelet indices are mean platelet volume (MPV) and platelet distribution width (PDW). Both are poorly standardized tests which are rarely used by physicians and are of small clinical utility [4,5]. We believe that their omission from the routine CBC would decrease the density of information and increase its overall usefulness in general clinical practice (Figure 2).

Who decides what parameters are displayed in the CBC report?

The answer should logically depend upon the appropriateness of each test parameter. However, appropriateness is a complex and elusive concept. In deciding what parameters should go into the automated CBC, there are so many alternatives, consequences and unknowns. It has been suggested that the input of many stakeholders (patients, physicians, laboratory staff, administrators and industry representatives) should be taken into consideration [34]. However, each of these has many of their own interests thus making a consensus extremely difficult. One proposed solution is to proceed with a multidisciplinary and multi-professional team, collect and review all available evidence and select the laboratory tests using the best available methodology. Once such a template is established, it would be necessary to educate physicians (and patients), obtain feedback and conduct audits in order to regularly update the whole process [34]. This proposed solution, however, matches the complexity of the problem itself. We believe that such problems are better tackled with the use of common sense: selection of parameters that have been most useful in the past and removal of those that have been of little or no practical value. This is an old-fashioned heuristic, which has been in use since Hippocrates and is still championed today in studies of decision-making [35,36].

Conclusion

Advances in the technology of blood cell counting have produced an excessively complex yet incomplete CBC. In the current CBC, several parameters have vanishingly small clinical utility and could be removed. On the other hand, the reticulocyte count is an important test that is missing and should be included in every automated CBC report. This inadequacy could be corrected by reprogramming of hematological analyzers so that physicians have the option to request a Short CBC with 11 parameters: RBC, absolute reticulocyte count, HB, MCV, RDW, platelet count and five absolute leukocyte counts. Such a Short CBC would be easier and faster to read and interpret and would better fit the needs of the vast majority of physicians and their patients.

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