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Malaria-Induced Anaemia: A Narrative Review

[1] Chisom Chidera Ekwonu, [2] Sunday Joyce Imbigbu, [3] Chukwuebuka Rufus Maduagwu, [4] Kelechi Immaculate Ezenagu, [5] Samuel Bakel Samuel, [6] Esther Onyinyechi Nchuma, [7] Ahmed Yahia Mohamed Yahia, [8] Innocent Ugochukwu, [9] Agu Ijeoma Thelma, [10] Joseph Okwudili Ugwuoke, [11] Ejiofor Johnson Chidiebere, [12] Charity Chidera Nwosu, [13] Isuajah Chukwuka Emmanuel, [14] Udeh ifunanya Joan, [15] Oku Victoria Chisom

[1, 8, 15] Department of Medical Laboratory Sciences, University of Nigeria, Enugu Campus, Enugu State, Nigeria
[2] Department of Science, Plateau State Polytechnic Academy, Barkin Ladi, Plateau, Nigeria
[3] Department of Microbiology, Imo State University, Owerri, Imo State, Nigeria
[4] Department of Agricultural Economics and Extension, Nnamdi Azikiwe Universsity, Awka, Anambra State, Nigeria
[5] Department of Epidermiology and Evidence-Based Medicine, F. Erishman Institute of Public Health, I.M Sechenov First Moscow State Medical University, Moscow, Russia
[6] Department of Medical Laboratory Science, Abia State University, Uturu, Abia State, Nigeria
[7] Department of Russian Language Learning Program for Students, The Agricultural University, Chiboxari, Russian
[9] Department of Science Laboratory Technology (Microbiology Option), Institute of Management and Technology, Enugu State, Nigeria
[10] Department of Dentistry and Dental Surgery, University of Nigeria Enugu Campus, Enugu State, Nigeria
[11] Department of Nursing, Medical Faculty, People's Friendship University (RUDN) Moscow, Russia
[12] Department of Medical Laboratory Science, Usmanu Danfodiyo University, Sokoto State, Nigeria
[13] Department of Clinical Pathology, College of Medicine, Lead City University Ibadan, Nigeria
[14] Department of Computer and mathematics education, Enugu State University of Science and Technology, Enugu State, Nigeria

Corresponding Author: **Chisom Chidera Ekwonu**

Abstract
Malaria-induced anaemia remains a major contributor to morbidity and mortality in endemic regions, especially among children under five and pregnant women. This narrative review narraretes the multifactorial pathogenesis, clinical manifestations, and management strategies of this condition. We explore the destruction of parasitized and non-parasitized red blood cells, highlighting that approximately 90 % of acute erythrocyte loss stems from non-parasitized cell clearance via hemolysis and splenic phagocytosis. We also discuss host factors such as genetic traits (e.g., G6PD deficiency, hemoglobin variants) and co-infections that modulate severity. Nutritional deficits and reinforcements from concurrent infectious diseases exacerbate anaemia, particularly in low-resource settings. Therapeutic approaches emphasize prompt antimalarial treatment, iron supplementation where appropriate, and emerging immunomodulatory agents targeting cytokine-driven suppression. Drawing from clinical and experimental studies, we highlight gaps in understanding the molecular interplay and advocate for integrated therapeutic strategies combining anti-parasitic, hematologic, and immunologic interventions. Enhanced insights into these mechanisms are critical for developing comprehensive interventions to reduce the global impact of malaria-induced anaemia.

Keywords: Malaria, Anaemia, Parasitized Red Blood Cells, Non-Parasitized Red Blood Cells, Nutritional Deficits

Introduction

Hematopoiesis denotes the series of dedicated and distinct mechanisms responsible for generating all blood cells from hematopoietic stem cells. In grown individuals, the primary site for hematopoiesis is the bone marrow (medullary), although it can additionally take place in alternative organs like the liver, thymus, and spleen (extramedullary). This process involves the complete spectrum of blood cell generation, encompassing their creation, maturation, and specialization. During the prenatal

stage, hematopoiesis initially occurs in the yolk sac, subsequently in the liver, and ultimately in the bone marrow. Hematopoiesis refers to the generation of all cellular constituents found in blood and blood plasma. This process takes place within the hematopoietic system, encompassing organs and tissues such as bone marrow, liver, and spleen. In the adult human body, the bone marrow is responsible for producing the entirety of red blood cells, as well as 60-70 percent of white blood cells (specifically granulocytes) and all platelets. Lymphatic tissues, notably the thymus, spleen, and lymph nodes, contribute to the production of lymphocytes, which make up 20-30 percent of the white blood cells.

Anaemia

Anaemia is a condition in which the number of red blood cells or the hemoglobin concentration within them is lower than normal. Hemoglobin is needed to carry oxygen. If you have too few or abnormal red blood cells, or not enough hemoglobin, there will be a decreased capacity of the blood to carry oxygen to the body's tissues. This results in symptoms such as fatigue, weakness, dizziness, and shortness of breath, amongst others.

The optimal hemoglobin concentration needed to meet physiologic needs varies by age, sex, elevation of residence, smoking habits, and pregnancy status. The most common causes of anemia include nutritional deficiencies, particularly iron deficiency, folate, vitamin B12 and A, hemoglobinopathies, and infectious diseases such as malaria, tuberculosis, HIV, and parasitic infections.

Anemia is a common nutritional deficiency disorder and global public health problem that affects both developing and developed countries, with major consequences for human health and their social and economic development. According to reports, one-third of the global population (over 2 billion) is anemic due to an imbalance in their nutritious food intake.

As the epidemiology of malaria coincides with the epidemiology of inherited red cell abnormalities, nutritional deficiencies, and helminth infections, anemia is often multifactorial, and the distribution of hemoglobin concentrations in healthy people is lower and broader than in temperate countries. Although a wide, and frankly confusing, variety of definitions of anemia in general had been proposed, the most commonly used definitions in malaria studies, based on hemoglobin concentrations, are as follows: mild anemia ≤11 g/dl, moderate anemia ≤8 g/dl, and severe anemia ≤5 g/dl.

Epidemiology of anaemia and malaria

The clinical consequences of malaria, and in particular the prevalence of anemia, depend on the intensity of malaria transmission. The main determinants of malaria transmission intensity are the density, longevity, biting habits, and efficiency of the local mosquito vectors [1]. In high transmission settings, people may receive as much as one infectious bite each day, so the entire population is infected repeatedly, but it is young children who bear the brunt of the disease, and most are anemic [2]. As the child grows, a disease-controlling immunity develops such that by adolescence and adulthood nearly all malaria infections are asymptomatic. The prevalence of anemia declines. Thus, apparently healthy individuals carry malaria parasites in their blood. These infections can persist for many months. This persistent asymptomatic parasite carriage reduces the operational diagnostic specificity of a positive microscopy or rapid test result as febrile illness in a parasitemic individual may be caused by other infections. Meta-analyses of the relationship between malaria and anemia are confounded by the non-specificity of parasitological diagnosis in high transmission settings, widespread self-treatment of febrile illness, inability to characterize preceding infections and thus recurrences in point prevalence surveys, and frequent concomitant hemoglobinopathies, nutritional deficiencies (particularly iron deficiency), and intestinal helminth infections—all of which contribute variably to anemia [3]. Thus, in higher transmission settings malaria increases the risk of anemia in the entire population with the greatest impact in young children, and in particular infants. In lower transmission settings symptomatic malaria and resulting anemia may occur at all ages, although it is children and pregnant women who are more likely to be anemic. At all levels of transmission malaria (all species) is an important contributor to maternal anemia during pregnancy, and poor birth outcomes [4]. Falciparum malaria is a direct cause of maternal mortality in lower transmission settings and an indirect cause by contributing to anemia in higher transmission settings. Anti-malarial drug resistance causing recrudescent infections increases the prevalence and the severity of malaria anemia.

Pathogenesis

The pathogenesis of malarial anemia is multifactorial [5]. Malaria is an intraerythrocytic parasite so there is obligatory destruction of red cells containing parasites at schizont rupture. However, a more important contributor is the accelerated destruction of non-parasitized red cells that parallels disease severity. It has been estimated that loss of unparasitized erythrocytes accounts for approximately 90% of the acute anemia resulting from a single infection. Parasitemias in falciparum malaria commonly exceed 1% (of red cells parasitized), and in severe disease may exceed 10%. Plasmodium knowlesi may also cause hyperparasitaemia, but parasite densities in the other human malarias very rarely exceed 2% [1]. In severe falciparum malaria, there is a heavy parasite burden and anemia develops rapidly. The main contributor to this usually rapid decline in hematocrit is the hemolysis of unparasitized red cells. The ratio of unparasitized red cells to parasitized red cells lost in acute malaria is even higher in P. vivax than in P. falciparum infections [6]. The hemolytic anemia of malaria is compounded by bone marrow dyserythropoiesis during and immediately after the acute illness. Bone marrow dyserythropoiesis persists for days or weeks following the start of malaria treatment in acute malaria. As a consequence, reticulocyte counts are usually low in the acute symptomatic phase of the disease. This accounts for the delayed erythropoietic response in acute malaria in low transmission settings. In such settings, the nadir of hemoglobin concentration in acute falciparum malaria is usually around 1 week after presentation with fever. In acute vivax malaria the nadir in hemoglobin is earlier (usually after a few days) [5]. In contrast in higher transmission settings, in the context of some premunition from repeated previous infections, hemoglobin concentrations usually begin to rise immediately following the start of effective anti-malarial treatment. In acute uncomplicated malaria, the

resultant anemia is worse in younger children and those with protracted infections.

Anemia and outcome of severe malaria

The relationship between hemoglobin concentration at presentation to hospital and outcome in falciparum malaria suggests that mortality rises sharply at levels below 3g/dl (independent of other severe manifestations). Severe anemia is a prominent feature of all severe malaria but in areas of high transmission, where severe disease is confined to the first few years of life, it is the predominant manifestation. Consensus definitions of severe malaria agreed upon for the anemia criterion is hemoglobin below 5g/dl in a patient with at least 10,000 parasites/µl. Patients who fulfill the anemia criterion for severe falciparum malaria, but have no other manifestations of severe malaria (i.e. cerebral, renal, metabolic, or pulmonary dysfunction) have a much better prognosis than patients with one or more of these other manifestations. Although most patients presenting with a parasite density of >10,000 parasites/µL have malaria as the cause of their illness, this parasitemia threshold for the "severe malaria" definition still means that some anemic children with incidental parasitemia and another infectious disease (usually sepsis) may be diagnosed as having severe malaria. Thus, the severe anemia criterion encompasses a broad range of presentations ranging from a fulminant disease with severe hemolytic anemia to a sub-acute illness, often from recurrent or inadequately treated malaria, in which there has been progressive anemia. The prognosis of the subacute presentation is much better as there has been time for physiological adaptation to anemia (right shift of the oxygen dissociation curve) and there is a low risk of other vital organ dysfunction. In addition, the sequestered parasite biomass in these sub-acute presentations is much lower than in patients presenting with acute multiorgan dysfunction [7]. Thus the mortality associated with severe malarial anemia depends on many factors which include the degree of anemia, age, transmission intensity, referral practices, access to and quality of health services, availability of safe cross-matched blood, and delays in transfusion. In published series of children admitted to hospitals with severe malaria anemia (including those with other severity manifestations) mortalities range from 2.6 to 10.3%—while mortalities as low as 0.5% have been reported in children with severe anemia but without any other severity manifestation [8]. Those patients who are admitted with severe anemia and do not survive succumb quickly, nearly half the deaths are within 12 hours of admission. Above a hemoglobin concentration of 5g/dl, other manifestations are required for a diagnosis of "severe falciparum malaria".

Hemoglobin

Hemoglobin is a specialized protein in the cells, which functions to carry oxygen to the tissues and to return carbon IV oxide from the tissues to the lungs. Each red cell contains approximately 270 million hemoglobin molecules [9]. Each molecule of normal adult hemoglobin A (HbA) consists of four polypeptide chains, α2 β2 quantities of each with its own heme group. Normal adult blood also contains small quantities of two other hemoglobins; HbF and HbA2. These also contain α chains but with γ and δ chains respectively instead of β. The major switch from foetal to adult hemoglobin occurs 3-6 months after birth.

Hemoglobin structure and function

The red cells in systemic arterial blood carry oxygen from the lungs to the tissues and return the venous blood with carbon IV oxide to the lungs. As the hemoglobin molecule loads and unloads oxygen, the individual globin chains in the hemoglobin molecule move to each other. The α1β1 and α2β2 contact stabilize the molecule. The β chains slide on the α1β1 and α2β2 contacts during oxygenation and deoxygenation. When oxygen is unloaded, the β chains are pulled apart, permitting entry of the metabolite 2,3-diphosphoglycerate (2,3DPG), resulting in a lower affinity for oxygen (O2). This movement is responsible for the sigmoid form of the hemoglobin – O2 dissociation curve.

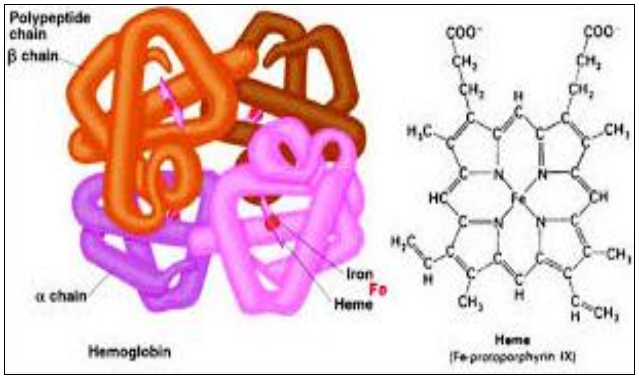

Fig 1: Hemoglobin structure [9]

Hemoglobin concentration: Diagnostic significance

Hemoglobin concentration is a cornerstone of anemia assessment and monitoring. Hemoglobin levels directly reflect the oxygen-carrying capacity of the blood and serve as a reliable indicator of anemia severity. Numerous studies have demonstrated a clear correlation between malaria parasitemia and decreased hemoglobin levels. The extent of parasitic burden often corresponds to the degree of hemoglobin reduction, providing valuable insights into the disease's severity and progression.

Furthermore, hemoglobin levels assist in gauging the effectiveness of antimalarial treatment. Successful treatment outcomes are often characterized by a rise in hemoglobin levels, signaling a reduction in parasitic burden and an improvement in erythropoiesis [10].

Red cell indices and their clinical significance

These are blood tests that provide information about the hemoglobin content and size of the red blood cells. Abnormal values indicate the presence of anemia, and which type of anemia it is. The red cell indices most frequently used in the investigation of anemia are:

- Mean cell hemoglobin concentration (MCHC)
- Mean cell volume (MCV)
- Mean cell hemoglobin (MCH)

MCHC

This gives the concentration of hemoglobin in g/l in 1 litre of packed red cells. It is calculated from the hemoglobin(Hb0 and PCU as follows:

MCHC (g/l) = Hb(g/l)/PCV(l/l)

A guideline reference range for MCHC in health is 315-360 g/l (31.5-36.0 g/dl)

(Monica Cheesbrough, second edition)

Interpretation of MCHC values

- Low MCH values are found in iron deficiency and other conditions in which the red cells are microcytic and hypochromic (MCHC may be normal in the Thalassemia trait).
- An increased MCHC can occur in marked spherocytosis, but this is a rare condition. A raised MCHC is more often due to a calculation error or an incorrect hemoglobin or packed cell volume.

MCV

This provides information on red cell size and volume. It is measured in femolitres(fl) and it is determined from the PCV and electronically obtained RBC count. It can be calculated as follows:

MCV (fl) = PCV(l/l)/RBC x 1012/l

A femolitre(fl) is 10-15 of a litre.

Interpretation of MCV values

There are some variations in reference ranges for MCV, depending on the method used by the manufacturers of blood cell analyzers to obtain the MCV value and how the instrument has been calibrated. A guideline reference range is 80-98 fl.

- Low MCV values are found in microcytic anemia, particularly iron deficiency, anemia of chronic disease, and thalassemia. The MCV is low in infancy (about 70fl at one year of age)
- Raised MCV values are found in macrocytic anemia, marked reticulocytosis, and chronic alcoholism. The MCV is raised in neonates.

MCH

This gives the amount of hemoglobin in picogram(pg0 in an average red cell. It is calculated from the hemoglobin and electronically obtained RBC count.

MCH(pg) = Hb(g/l)/RBC x 1012/l

A picogram(pg) is 10-12 of a gram.

A guideline reference range for MCH in health is 27-32 pg

Interpretation of MCH values

- Low MCH values are found in microcytic hypochromic anemia, and also when red cells are microcytic and normochromic. In thalassemia minor, the MCH is low even when anemia is mild.
- Raised MCH values are found in macrocytic normochromic anemia, which is also raised in neonates.

Role of Red Cell Indices: MCV, MCH, and MCHC

Red cell indices, including Mean Corpuscular Volume (MCV), Mean Corpuscular Hemoglobin (MCH), and Mean Corpuscular Hemoglobin Concentration (MCHC), offer deeper insights into anemia's underlying mechanisms [11]. MCV reflects the average size of red blood cells, with macrocytic or microcytic changes indicating potential underlying causes. In the context of malaria-induced anemia, alterations in MCV can provide insights into disruptions in erythropoiesis caused by the parasitic infection.

MCH and MCHC offer information about the average hemoglobin content within red blood cells and the concentration of hemoglobin within individual cells, respectively [11]. Deviations in these indices can provide clues about variations in hemoglobin content and synthesis, potentially indicating different anemia types or complications.

Diagnosis of malaria

Microscopic examination of blood film

The most economically preferred and reliable diagnosis of malaria is a microscopic examination of blood films because each of the four major malaria parasites (plasmodium falciparum, plasmodium vivax, plasmodium ovale, plasmodium malariae) has distinguishing characteristics. Two sorts of blood films are usually used. Thin films are similar to usual blood films and allow species identification because the parasite's appearance is best preserved in this preparation. Thick films allow the microscopist to screen a larger volume of blood and are about eleven times more sensitive than the thin film, so picking up low levels of infection is easier on the thick films. However the appearance of the parasite is much more distorted, and therefore distinguishing between the different species can be much more difficult. With the pros and cons of both thick and thin smears taken into consideration, it is imperative to utilize both smears while attempting to make a definitive diagnosis [12].

From the thick film, an experienced microscopist can detect parasite levels (or parasitemia) down to as low as 0.0000001% of red blood cells. Diagnosis of species can be difficult because the early trophozoites(ring form) of all four species look identical and it is never possible to diagnose species on the basis of a single ring form; species identification is always based on several trophozoites. One important thing to note is that *P. malariae* and *P. knowlesi* (which is the most common cause of malaria in Southeast Asia look very similar under the microscope. However, P. knowlesi parasitemia increases very fast and causes more severe disease than P. malariae, so it is important to identify and treat infections quickly. Therefore, modern methods such as PCR or monoclonal antibody panels that can distinguish between the two should be used in this part of the world [13].

Antigen tests

For areas where microscopy is not available, or where laboratory staff are not expected at malaria diagnosis, there are commercial antigen detection tests that require only a drop of blood. Immunochromatographic tests (also called: Malaria Rapid Diagnostic Tests, Antigen-Capture Assay, or "Dipstick") have been developed, distributed, and field-tested. These tests use finger-stick or venous blood. The completed test takes a total of 15-20 minutes, and the results are read visually as the presence or absence of colored stripes on the dipstick, so they are suitable for use in the field. The threshold of detection by these rapid diagnostic tests is in the range of 100 parasites/µl of blood (commercial kits can range from about 0.002% to 0.1% parasitemia) compared to 5, by thick film microscopy.

One disadvantage is that dipstick tests are qualitative but not quantitative – they can determine if parasites are present in the blood, but not how many.

The first rapid diagnostic tests were using P. falciparum glutamate dehydrogenase as antigen PGluDH was soon replaced by P. falciparum lactate dehydrogenase, a 33 kDa oxidoreductase. It is the last enzyme of the glycolytic pathway, essential for ATP generation, and one of the most abundant enzymes expressed by P. falciparum. PLDH does not persist in the blood but clears at about the same time as the parasite following successful treatment. The lack of antigen persistence after treatment makes the PLDH test useful in predicting treatment failure. In this respect, PLDH is similar to the pGluDH. Depending on which monoclonal antibodies are used, this type of assay can distinguish between all four different species of human malaria parasites, because of antigenic differences between their pLDH isoenzymes.

Molecular methods

Molecular methods are available in some clinical laboratories and rapid real-time assays (for example, QT-NASBA based on the polymerase chain reaction) [14] are being developed with the hope of being able to deploy them in endemic areas.

PCR (and other molecular methods) is more accurate than microscopy. However, it is expensive and requires a specialized laboratory. Moreover, levels of parasitemia, are not necessarily correlative with the progression of disease, particularly when the parasite is able to adhere to blood vessel walls. Therefore, more sensitive, low-tech diagnosis tools need to be developed in order to detect low levels of parasitemia in the **Prevention**

Methods used in order to prevent the spread of disease, or to protect individuals in areas where malaria is endemic, include:

- Prophylactic drugs
- Mosquito eradication
- Prevention of mosquito bites

The continued existence of malaria in an area requires a combination of high human population density, high mosquito population density, and high rates of transmission from humans to mosquitoes and from mosquitoes to humans. If any of these is lowered sufficiently, the parasite will sooner or later disappear from that area, as happened in North America, Europe, and much of the Middle East. However, unless the parasite is eliminated from the whole world, it could be re-established if conditions revert to a combination that favors the parasite's reproduction. Many countries are seeing an increasing number of imported malaria cases due to extensive travel and migration.

Vector control

Efforts to eradicate malaria include:

- Eliminating mosquitoes.
- Monitoring and treatment of infected humans.
- Use of the pesticide DDT (dichlorodiphenyltrichloroethane).
- Removing or poisoning the breeding grounds of the mosquitoes or the aquatic habitats of the larva stages by filling or applying oil to places with standing water.

Prophylactic drugs

Several drugs, most of which are also used for the treatment of malaria, can be taken preventively. The choice of which drug to use depends on which drugs the parasites in the area are resistant to, as well as side effects and other considerations. The prophylactic effect does not begin immediately upon starting taking the drugs, so people temporarily visiting malaria-endemic areas usually begin taking the drugs one or two weeks before arriving and must continue taking them for 4 weeks after leaving. Generally, these drugs are taken daily or weekly, at a lower dose than would be used for treatment of a person who had actually contracted the disease. The use of prophylactic drugs is seldom practical for full-time residents of malaria-endemic areas, and their use is usually restricted to short-term visitors and travelers to malarial regions. This is due to the cost of purchasing the drugs, negative side effects from long-term use, and because some effective anti-malaria drugs are difficult to obtain outside of wealthy nations.

Indoor residual spraying (IRS)

Indoor residual spraying (IRS) is the practice of spraying insecticides on the interior walls of homes in malaria-affected areas. After feeding, many mosquito species rest on a nearby surface while digesting the blood meal, so if the walls of dwellings have been coated with insecticides, the resting mosquitoes will be killed before they can bite another victim, transferring the malaria parasite.

One problem with all forms of indoor residual spraying is insecticide resistance via the evolution of mosquitoes. According to a study published on Mosquito Behaviour and Vector Control, mosquito species that are affected by IRS are endophilic species (species that tend to rest and live indoors), and due to the irritation caused by spraying, their evolutionary descendants are trending towards becoming exophilic (species that tend to rest and live out of doors), meaning that they are not as affected-if affected at all-by the IRS, rendering it somewhat useless as a defense mechanism.

Mosquito nets and bedclothes

Mosquito nets help keep mosquitoes away from people and greatly reduce the infection and transmission of malaria. The nets are not a perfect barrier and they are often treated with an insecticide designed to kill the mosquito before it has time to search for a way past the net. Insecticide-treated nets (ITNs) are estimated to be twice as effective as untreated nets and offer greater than 70% protection compared with no net [15].

Diagnostic and prognostic implications

The diagnostic significance of hemoglobin concentration and red cell indices extends beyond anemia assessment. Monitoring these parameters during treatment can aid in evaluating the effectiveness of antimalarial therapies and interventions. Malaria infection typically leads to a decrease in hemoglobin concentration due to the combined effects of hemolysis, decreased erythropoiesis, and increased destruction of infected red blood cells. Red cell indices, such as mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH) and mean corpuscular hemoglobin concentration (MCHC), provide insights into the size and hemoglobin content of individual red blood cells.

Changes in hemoglobin levels and red cell indices often correspond to successful treatment outcomes, offering clinicians valuable tools for guiding patient management decisions. A rise in hemoglobin levels and normalization of red cell indices often correspond to successful treatment outcomes, highlighting the potential of these parameters in guiding clinical decision-making.

Automation in hematology

Diseases are characterized by changes in individual blood parameters, which are more or less, typical for the underlying disease. It is therefore of greatest interest to be able to easily and rapidly measure these parameters at any time with high precision and accuracy to allow for a precise diagnosis.

History of automation

The inspection of blood was a basic principle of diagnosis from ancient times till the 16th century. This is called the hemoscopy or hematoscopy (the investigation of the color and structure of the blood).

A Swiss doctor Paracelsus (1495-1541) developed a procedure that enabled the examination of blood cells for the first time. The first step towards automation was made in 1934, with the Maldavan capillary method where a suspension of blood cells was illuminated in a dark field and counted in an optical chamber, which converted the light impulses into electrical impulses. Wallace Coulter in 1956 developed hematological instruments suitable for routine work (patent high-speed automatic blood cell counter). The principle of this machine was based on impedance measurements and for the first time, enabled to count much higher cell numbers than the known manual method. This instrument invented by Wallace Coulter is a semi-automated instrument. For over 40 years now, there has been the invention of a modern automated system, which determines the hemogram, the differential blood count, and reticulocyte analysis in EDTA whole blood. The instruments are based on various measurement technologies used in different ways:

- Impedance measurement
- High-frequency measurement
- Forward scatter at different angles
- Fluorescence flow through cytometry

Conclusion

Malaria-induced anaemia arises from multifactorial mechanisms, destruction of both parasitized and non-parasitized red blood cells, bone marrow suppression, splenic sequestration, and nutritional deficiencies. It disproportionately affects infants, pregnant women, and individuals in high-transmission settings, often leading to severe anaemia and increased mortality. Effective prevention, vector control, bed nets, prompt diagnosis, and appropriate treatment, significantly reduces anaemia burden. Continued research is needed to optimize transfusion thresholds and refine strategies for iron supplementation and erythropoietic recovery.

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