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Chapter

Perturbations in Generation and Flow of Energy in the Eukaryotic Cell Explain the Chromosomal Instability Syndrome

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Abstract

Chromosomal instability is poorly defined and used inconsistently and imprecisely. It is the increased propensity to chromosome aberrations due to chromosome replication, repair, or segregation. Therefore, acquired genetic changes are central to leukemia development. Fast-growing cells require substantive amount of energy; however, tumor cells take up more glucose, processing it through aerobic glycolysis producing large lactate amounts with lower use of oxidative phosphorylation to generate ATP. The Warburg effect is characterized by reduced use of tricarboxylic acid cycle, so pyruvate made in glycolysis is converted into lactate and expelled, but this metabolic pathway is energetically inefficient. When genes are malfunctioning, both oncogenes and tumor suppressor genes influence negatively the switch between aerobic glycolysis and extensive use of TCA cycle to generate ATP, as the normal gene replication and expression require adequate energy levels. Chromosomal instability is increasingly entangled and unnecessarily complex. So far, researchers focused solely on studying the mass and have forgotten the energy. The intrinsic property of melanin to transform light into chemical energy, through water dissociation, as chlorophyll in plants, opens a new landscape in chromosome biology, highlighting the role of the environment toxics in leukemia pathogenesis, inhalation being the dominant pathway of exposure.

Keywords: energy, chromosome instability, hydrogen, oxygen, melanin, water dissociation, benzene

1. Introduction

Chromosomal instability is characterized by aneuploidy, allelic losses, and the consecutive accumulation of chromosomal abnormalities [1].

Aneuploidy is widely acknowledged as a leading cause of miscarriage and birth defects in humans and is generally known to be deleterious to the survival of individual cells. However, aneuploidy is also ubiquitous in cancer and is thought to arise as an adaptive response in certain contexts given the technical difficulties to study it and the poor understanding of the involved processes. This dichotomy of aneuploidy has attracted the interest of researchers for over a

century, but many studies have reached conflicting conclusions [2] which reflect how difficult it is to understand billions of years of evolution. The emergence of new technology apparently has allowed scientists to revisit the aneuploidy problem and has fueled several recent studies aimed at understanding the effects of aneuploidy on cell physiology with frustrating results. Therefore, the reviewing of those studies, considering previous observations and knowledge, specifically focusing on the effects of aneuploidy on cellular homeostasis, chromosome stability, and adaptation, gives notably fewer useful conclusions than the expected.

Under normal conditions, genomic integrity is given by chromosomes that are assembled by the DNA sequence and proteins, such as histones that play essential structural and functional roles in the transition between active and inactive chromatin states [3]. Histones have a high degree of conservation regarding maintaining the overall structure of the nucleosomal octameric core.

The DNA is hierarchically packed in the nucleus with the aid of proteins forming a complex called chromatin. Histone variants and posttranslational modifications and interactions with chromatin remodeling complexes influence DNA replication, transcription, repair, and recombination.

The study of the chromatin has been focused in the structural aspect only. And even this type of analysis faces, so far, formidable technical challenges. But it's not simple or even possible to find articles about the flow of energy through the nucleus, nor works on the absence of mitochondria and ATP in the cell nucleus.

Despite the progress in structural studies, we cannot yet answer the question of who controls who. Does chromatin control histones or vice versa or both or other genetic or epigenetic factors?

Eukaryotic chromatin is a highly dynamic macromolecular assembly, which means that it requires energy expenditure continuously, not only to carry out its functions but also to preserve the shape of each component, beginning with the covalent bonds and other types in every molecule, and so on until it reaches to the macromolecule. Most eukaryotic organisms have multiple copies of histone gene; thereby, they are highly conserved in evolution.

The highly complex histone interactions with the nucleosomal core particle are processes that happen in amazing accurate way. All histone domains share a similar structural motif; they form interfaces with each other in several unique ways. This interface specificity is consistent across many variant histone sequences, demonstrating the flexible and adaptable architecture of histone complexes. These are extraordinarily complex biochemical processes that repeat in the same way since the beginning of time.

So far, it is not clear if chromatin inactivation is due to an enzymatic activity and/or a steric block that impedes access by transcription factors or the chromatin remodeling machinery [4]. However, there is an unexpected actor that has not been studied at least in detail: the generation and distribution or flow of energy (from melanin) across the cell nucleus.

It is relatively easy to reverse core histone tails, i.e., by acetylation, methylation, ubiquitination, and phosphorylation, among others [5]. So it is interesting the evolution could happen relatively fast. Evolution is not a process of trial and error, because in that way it would have required time lapse greater than the age of the universe.

Thereby it is possible that the generation and distribution of energy coming from melanin not only releases energy but also is giving information.

1.1 Chromosomal instability

CIN is a form of genomic instability in which chromosomes are uneven, such that either whole chromosomes or fractions of chromosomes are duplicated or

deleted. The inadequate distribution of DNA to daughter cells upon mitosis results in a failure to maintain euploidy (the correct number of chromosomes) leading to aneuploidy (incorrect number of chromosomes). The daughter cells do not have the same number of chromosomes as the cell they originated from.

In solid and hematological cancers, chromosomal instability is a common occurrence [6], involving gain or loss of whole chromosomes or fraction of chromosomes [7]. Chromosomal instability is thought to be an early event during tumorigenesis or furthermore is involved in tumor initiation.

Cancers result from the accumulation of inherited and somatic mutations in oncogenes and tumor suppressor genes [8]. Supposedly, these genes encode proteins that function in growth regulatory and differentiation pathways. Mutations in those genes increase the net reproductive rate of cells. Mutations in genes increase the rate at which whole chromosomes or large parts of chromosomes are lost or gained during cell division.

Chromosomal instability causes an imbalance in chromosome number (aneuploidy) and an enhanced rate of loss of heterozygosity, which seems as an important mechanism of inactivating tumor suppressor genes. Thereby, cancer results if normal regulatory mechanisms of cell birth and death are disrupted [9].

Maintenance of chromosomal stability requires a statistically nonsignificant gene mutation. Many cancers, if not all, are characterized by a high degree of aneuploidy, result of chromosomal instability mainly. However, linear analysis of chromosomal instability with mathematical models suggests that it does not arise simply because it allows a faster accumulation of carcinogenic mutations. Instead chromosomal instability must arise because other reasons, such as environmental factors, epigenetic events, or as direct consequence of a tumor suppressor gene inactivation. The increased variability alone is not enough explanation for the presence of chromosomal instability in most cancers [10].

The characteristics of cancer cells as aneuploidy, and multiple chromosomal anomalies including gain or loss of whole chromosomes or transposed chromosomal fragments [11], suggest that many cell processes are failing at the same time. The above is compatible with a generalized failure, which is characteristic of energy problems.

The prior intracellular conditions necessary to induce substantive mutations in the genes as well as aneuploidy, which are considered necessary conditions for neoplastic transformation; they are like widespread chaos inside the cell. And in a biological system as evolved as the eukaryote, cell is difficult to explain, unless we take energy into account.

Maybe, so far, the investigation did not consider the energy flow required by the cell nucleus because it does not have mitochondria or ATP. And perhaps that's why you might think it does not require energy; but the cell nucleus is the largest intracellular organelle, so its energy needs are expected to be substantive; and on the other hand, let us remember that the cell uses energy in many ways, not only to impel each and every one of the amazingly accurate biochemical reactions that make up what we call life, which happen in the same way, with the same sequence, with the same temporality, with the same molecules, with the same location, and in similar proportions since the beginning of the time.

We can think that the eukaryotic cell knows his work perfectly, because he has done it millions of years, millions of times. But the astonishing perfection and characteristic coordination of living entities requires a source of energy that possesses similar characteristics, which are so different from the ATP energy currency prevalent theory.

The cell, therefore, requires energy for many things, not only to carry out the extraordinarily complex biological functions that we are far from understanding but even to preserve the form and stability.

1.2 Hematopoietic stem cell

The biochemical processes involved with the hematopoiesis are extraordinarily complex and surprisingly accurate, since they have been repeated in the same way continually since the beginning of time. They can be disturbed by physicochemical alterations in some of their foremost components, for example, the water viscosity is one of the characteristics that is altered with greatest ease.

The bone marrow produces an average of 2.5 million erythrocytes per second, which requires prodigious amounts of precursors of organic molecules and energy. And the production of such a quantity of blood-forming elements requires great and fast coordination between the different and highly biochemical processes involved, since they must happen with an astonishing exactitude, but their main requirement is, without a doubt, energy.

Hematopoiesis in the bone marrow turns ineffective when the biochemical steps that make up and that happen at a staggering speed suffer some alteration due to the presence of contaminants in water, in the air, or in food such as pesticides, herbicides, fertilizers, metals, plastics, solvents, industrial waste, drugs, anesthetic agents, alcohol, drug addiction, extreme climates (cold, heat) etc.

This perturbed hematopoiesis in the bone marrow can lead to cytopenias in the blood and predisposition to acute myeloid leukemia (AML) [12]. There is a delicate interplay between the hematopoietic stem and progenitor cells, stromal cells, and cytokines or chemokines secreted within the microenvironment that is needed to maintain hematopoiesis. Thereby, this microenvironment is at the same time highly complex and highly dynamic, requiring enough available chemical energy at any moment.

The bone marrow is separated into vascular and nonvascular sections. The vascular section contains blood vessels that supply the bone with nutrients and transport CO₂, blood stem cells, and mature cells away from the bone and into circulation. The nonvascular sections of the bone marrow are where the hematopoiesis or blood cell formation occurs.

It is contradictory that in nonvascular section of bone marrow, hematopoiesis takes place. Supposedly, the current deep-rooted dogma says that our body can get the energy and mass precursors through a single molecule, this is glucose. However, glucose requires to be transported through blood stream, and surprisingly, the bone marrow section with the highest metabolic rate has no blood vessels at all.

Something similar happens in human retina, where the rod and cone layer, with a metabolic rate almost ten times greater than cerebral cortex, under normal conditions, it has no blood vessels at all.

Bone marrow stromal cells are progenitors of skeletal tissue components such as the bone, cartilage, the hematopoiesis-supporting stroma, and adipocytes and possibly can also form neural and myogenic cells [13].

In average, there are 2.5 trillion of red blood cells in your body at any moment. To maintain this number, under normal conditions, about two and a half million new ones need to be produced every second by your bone marrow. Considering all the tissues and cells in our body, 25 million new cells are being produced each second. We give birth to over 200 billion red cells every day.

Hypoxia or low oxygen availability is a prominent molecular feature of the bone marrow that contributes to both normal and malignant hematopoiesis. Relative to most tissues, the bone marrow microenvironment resides in a particularly hypoxic microenvironment. Oxygen tensions within the bone marrow cavity range from 0.6% to 4.2%, whereas oxygen tensions in most other adult tissues range from 2 to 9% O₂ [14]. But because each cell can dissociate the molecule from water, thanks to melanin, then oxygen levels are an indirect indicator of molecular hydrogen levels in tissues.

The purely structural analysis of bone marrow, as it has been to date, confronts, at least two important challenges: (1) substantive technical limitations due to the complex anatomy and biochemistry of the area to study and (2) researchers are trying to decipher 4 billion years of evolution without considering the generation and flow of energy.

1.3 Glucose

Glucose is (supposedly) an important fuel that is used by nearly all organisms through a common set of metabolic pathways. The knowledge of glucose metabolism that is prevalent until today, dates to 1860, with the identification of glycolysis with Louis Pasteur and thereafter in 1937, with the work of Gustav Embden and Otto Fritz Meyerhof [15]. Also, in 1937, the foundations of citric acid cycle were provided by Albert Szent-Gyorgyi, Hans A. Krebs, and William A. Johnson [16]. Two decades later, Peter D. Mitchell hypothesized a chemiosmotic mechanism that supposedly led to the elucidation of the electron transport chain and oxidative phosphorylation [17]. Thereby, at least apparently, the pathway for aerobic glucose metabolism and ATP generation was completed.

However, glucose is the universal precursor of any organic matter in the human body, but it cannot provide the energy that its own metabolism requires. Our circumstantial finding in human retina, during an observational study about the three main worldwide causes of blindness, about the unsuspected intrinsic property of melanin to dissociate the water molecule, like chlorophyll in plants [18], constitutes a disruptive discovery because it destroys existing dogmas deeply rooted and allows to open new ways to knowledge (**Figure 1**).

Glucose and ATP have biological functions related mainly to biomass metabolism and not so much with energy. The unexpected intrinsic property of melanin to transform photon energy into chemical energy through the dissociation of water molecule, a role performed supposedly only by chlorophyll in plants, seriously questions the sacrosanct role of glucose and thereby mitochondria and ATP as the primary source of energy for the cells (**Figure 2**). Furthermore, increased glycosylation has been linked to increased apoptosis [19].

If we accepted by a moment that our body is able to take energy from the light thanks to the melanin, then the absence of blood vessels in anatomical structures with very high metabolic rate such as photoreceptors of the retina and the avascular region of the bone marrow is now explainable, and it is congruent with the fact that the blood vessels are not able to transport energy (**Figures 3 and 4**).

The absence of capillaries in anatomical regions with a high metabolic cup is explained, at least, for two reasons:

- A. Blood cannot carry on energy. The bloodstream only transports metabolites and their intermediaries. Considering the discovery of the unsuspected bioenergetic role of melanin, the main gas that the blood transports is the CO₂. Recall that unknowns about blood are important and numerous, for example, albumin formula is not yet known, and by other side, the similitudes of hemoglobin and chlorophyll molecules are substantive, thereby cannot be discarded that hemoglobin can also dissociate the water molecule, irreversible, like chlorophyll.
- B. If all the capillaries in the human body were lined up in a single file, the line would stretch over 100,000 miles. It's been estimated that there are 40 billion capillaries in the average human body.

The circulatory system has a complex design and is very extensive, and not all capillaries are permeable at the same time, supposedly something less than half is



Figure 1.

Schematic representation of the way in which melanin (center) dissipates the energy it absorbs, dissociating the water molecule, that is, hydrogen and molecular oxygen (H_2 and O_2), which are released in the form of growing spheres of energy that follow the laws of simple diffusion. The difference in color of the spheres is to remark that a sphere contains higher concentration of H_2 and O_2 , result of the dissociation of the water; the next sphere would contain higher quantity of electrons of high energy, as melanin generates four electrons of high energy for every two molecules of water that is reassociated.

Plants:



Humans:

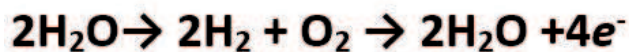


Figure 2.

General outline of the very first step in photosynthesis in plants and humans. In plants the chlorophyll dissociates irreversibly the water molecule by expelling the oxygen to the atmosphere. In humans, melanin dissociates the water molecule in reversible form, and for every two water molecules that are reformed, four high-energy electrons are generated.

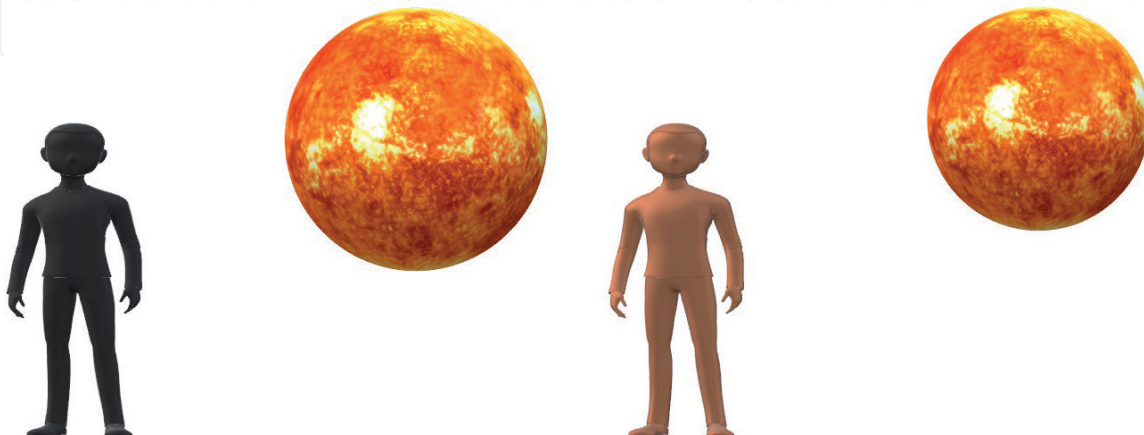


Figure 3.

When the amount of sunlight is abundant, as in the tropics, the amount of melanin in the skin is higher to regulate the quantity of light that must penetrate the inside of the organism, because even the bone marrow requires luminous energy continuously. It is not surprising that leukemia in white people is more frequent than in dark-skinned people.

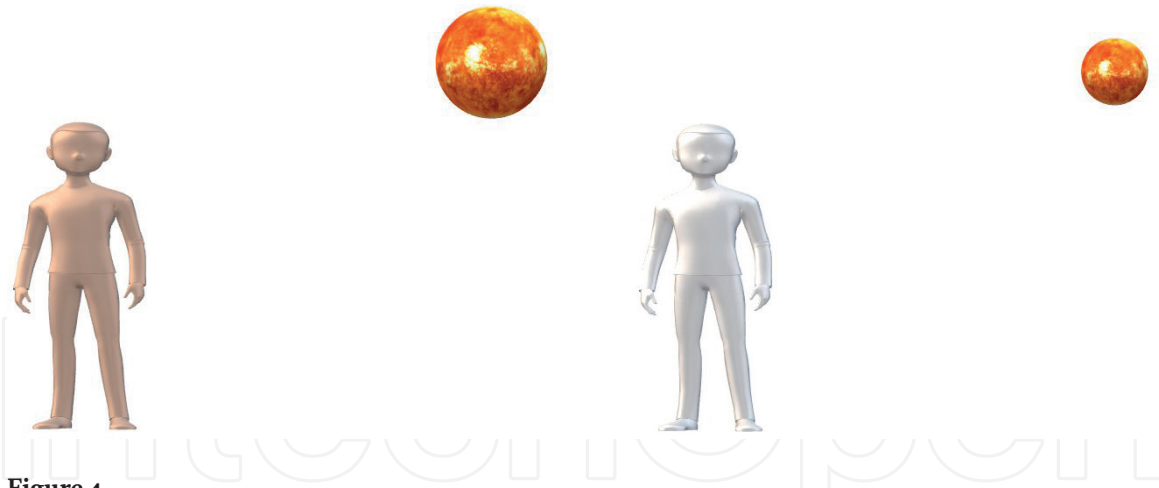


Figure 4.

When the amount of sunlight is lower, as in cold countries, the amount of melanin in the skin decreases to allow for a greater passage of light, and in that way, the final quantity of light that the body inside needs will remain the right one. The amount of melanin in the skin is determined by the amount of light in the environment where people inhabit.

closed at a given time, otherwise, the volume of circulating blood would not reach to fill them all at the same time.

The intricate circulatory system and its highly complex blood content have functions related to the biology of the structure or mass mainly, but anyway energy expenditure is constantly required, thereby, our body or the cell itself, can capture it from visible and invisible light, and it is transduced into chemical energy by melanin, throughout the dissociation of the water molecule, like chlorophyll in plants and hemoglobin in blood.

Melanin absorbs the full electromagnetic spectrum, visible and invisible light, from radio waves to gamma rays; thereby, the process of transduction is quite similar during night and day, the products being molecular hydrogen (H_2) from water dissociation and high-energy electrons (e^-) from reformatted water.

The cells are energetically independent, because melanin is found in every one of them, mainly placed in the perinuclear space; therefore, each cell can generate its own energy by dissociating the water molecule (**Figure 5**).

The fact is surprising that in the different schemes of the cell, melanin passes unnoticed, very seldom or never depicted in the drawings of the eukaryotic cell. It is necessary to add the melanosomes in the perinuclear space, its main location (**Figure 6**).

On the other hand, the rarely noticed absence of mitochondria and ATP in the cell nucleus, the largest organelle of the eukaryotic cell, now has a coherence with the presence of melanosomes in the perinuclear space, which surround the nucleus, while they provide it with the energy necessary for its functions (**Figure 7**).

Hence the importance of water in living beings, because it is the perfect substrate for melanin that must always be available and accessible so that the cell can obtain the energy it requires incessantly through water dissociation.

The water content of the cells is very high, 77% by weight and 94.54% by number of molecules, and the constant need for water (and energy) explains the cerebral caesuras, because in this way the water of the cerebrospinal fluid (CSF) can circulate quickly and deeply, reaching up to the neuron furthest from the ventricles and the subarachnoid space.

Although the discussion of water, so far, is largely focused on its properties as a solvent, it also serves as a ligand. For example, in both hemoglobin and cytochrome oxidase, the binding and subsequent release of water molecules is critical to their proper function and now in ahead with need to add a new possibility: water as substrate to energy production.

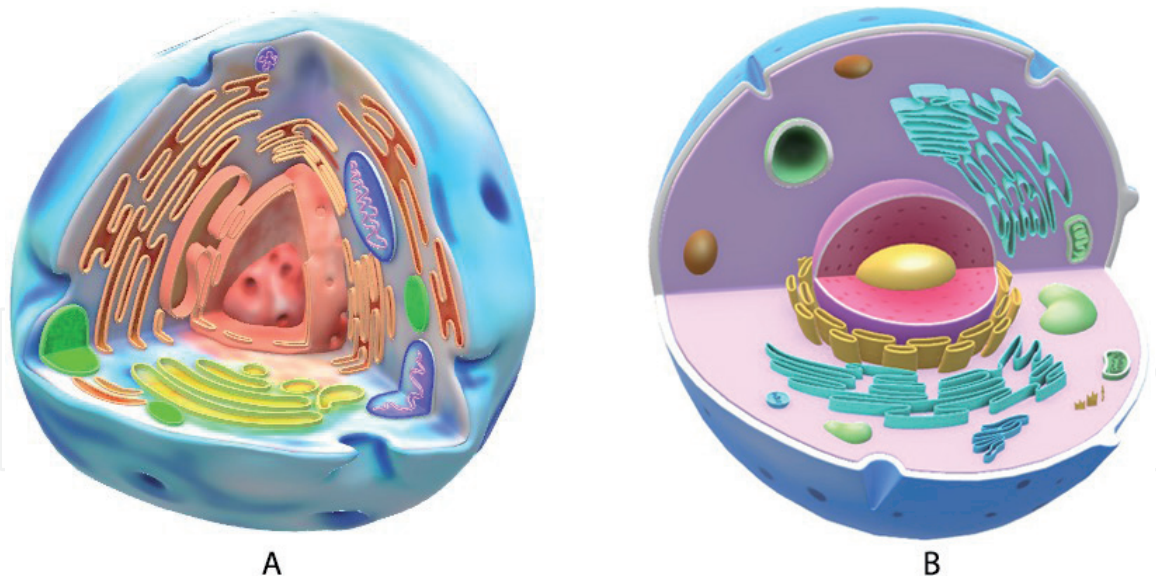


Figure 5.
Melanin is usually not represented in the eukaryotic cell models available in the different sources of information.

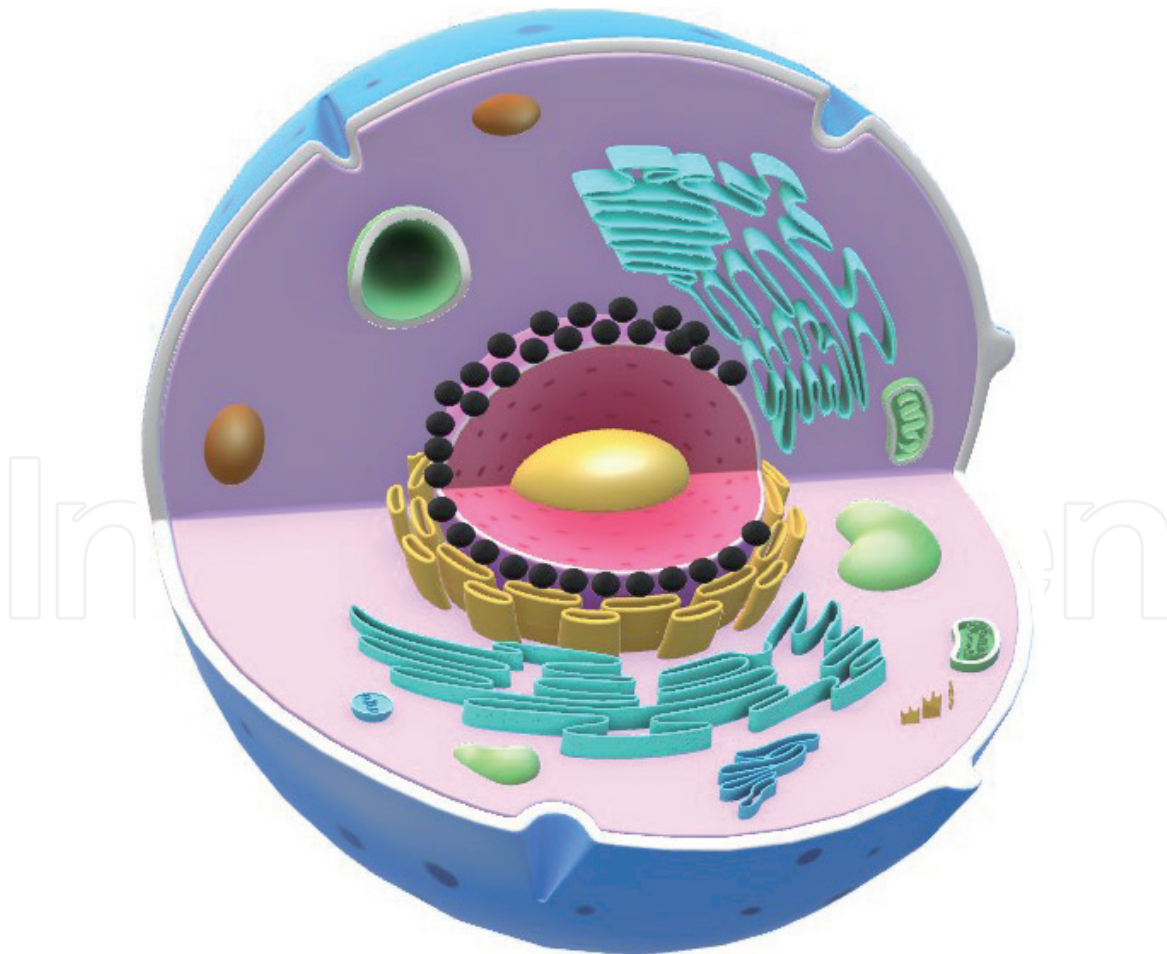


Figure 6.
Drawing of eukaryotic cell to which the melanosomes have been added in their most usual location, the perinuclear space, from releasing the energy symmetrically, in all directions, following the laws of simple diffusion. The melanosomes surround the cell nucleus, enveloping it in its entirety, thus constituting a constant source of energy for the largest intracellular organelle, since it contains neither mitochondria nor ATP.

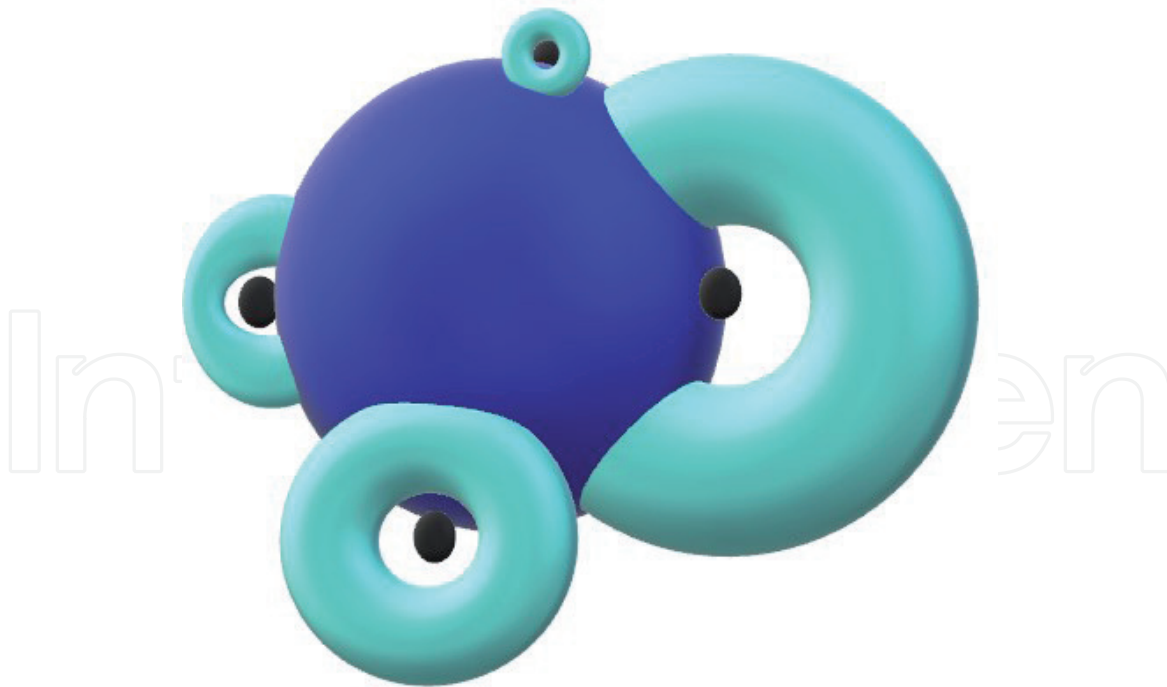


Figure 7. Schematic representation of the cell nucleus (deep blue) and some melanosomes (black dots) of which emanate the growing spheres (light blue) composed of molecular hydrogen (H_2), which transports the energy that is released by dissociating the molecule of water. Molecular hydrogen easily crosses any membrane or barrier inside the cell, so the growing spheres provide energy to both the inside of the cell nucleus and the rest of the organelles located outer of the nucleus by inside cell membrane. That molecular hydrogen does not combine with water is a crucial physic-chemical of hydrogen characteristic that explains the normal displacement of molecular hydrogen (H_2) along cytoplasm.

The amount of chemical energy in the form of H_2 and high-energy electrons that eukaryotic cells need at any moment is surprisingly accurate, and when water or melanin physic-chemical properties are altered by pollution of the surroundings (pesticides, herbicides, fertilizers, metals, plastics, solvents, industrial waste, anesthetic agents, drugs, alcohol, variations in climate, cold, heat; etc.), the cell seems as it goes into imbalance, experiencing a turning-point in evolution.

1.4 The DNA code

It is a sequence of chemicals that form information that control how humans are made and how they work. It is a digital-like code, but it is not binary, but quaternary with four distinct items: adenosine (A), cytosine (C), guanine (G), and thymine (T).

These four substances are the fundamental “bits” of information in the genetic code and are called “base pairs” because there are actually two substances per “bit.” Everything else is built on top of this basis of four DNA digits.

However, life origin cannot be explained arising from DNA. The sequence in melanin about dissociation and reformation of water, this is, liquid \rightarrow gas \rightarrow liquid \rightarrow gas \rightarrow liquid \rightarrow gas, and so on, can be reduced to 0 (liquid) and 1 (gas), a kind of binary code and a binary code that gives origin and therefore also regulates a quaternary code has room to explain the origin and evolution of life.

The genetic code is not an autonomous system, as any other chemical process, nevertheless complicated, requires energy to be created, to replicate, to carry out their functions, and even to preserve the shape, because the water of the cytoplasm tend to separate the molecules.

The human genome is about 3 billion bases in total, and every human being has 2 copies of this code; one copy from each parent, thereby a human's cell DNA contains around 6 billion bases.

These 6 billion base pairs are split among 46 chromosomes. Each person gets 2 pairs of chromosomes, 23 from each parent, to total 46 chromosomes per human cell. A chromosome is the largest form of a DNA molecule, with a large sequence of DNA codes, of differing lengths, usually hundreds of millions of base pairs in each chromosome.

Chromosomes are independent molecules of DNA, with the typical double helix, a start and end, but no cycles. Each chromosome has subsequences of DNA bases that encode features, and these are called "genes." All genes have different lengths. The total number of distinct genes in the human genome is believed to be around 30,000 genes.

Most genes clearly encode the data sequence representing a specific protein that would be synthesized in the precise moment, right temporality, exact amount, and accurate location; therefore, a gene, besides constant energy supply, also requires detailed information to adequately carry out its highly complex functions. All the genes together are only a small part of DNA code. The 30,000 odd genes in human DNA might only make up 4% of human DNA.

The structure of DNA and RNA are very similar, but RNA uses uracil (U) instead of thymine (T). Proteins are a base-20 code using the 20 amino acids. DNA represents a protein that has an ordered sequence of base-4 triplets, using 64 possible values to 20 amino acids.

1.5 Genetic versus hereditary

The following phrase "Chronic Myeloid Leukemia (CLL) is a genetic disease, but not a hereditary disease" is confusing because in any disease some degree of altered gene expression can be expected. Therefore, most leukemia patients have no family history of the disease, and there is no evidence that it can be passed on to the children of someone living with the disease. Occasionally, there are families that may have other members living with leukemia, however, without taking in account the role of toxic compounds capable to perturb the generation and distribution of energy, never was and never will conclusive genetic evidence that family members are predisposed to develop leukemia.

There are diseases that are difficult to classify, i.e., the CLL that is a B-cell lymphoproliferative disorder and is one of the most common adult leukemias [20]. Although the cause remains unknown, a family history of the disease is one of the best characterized risk factors, but more for familial exposure to external toxic compounds than for theoretical minute punctual mutations or loci that cannot be found yet or even less to probe.

This is a long-lasting observation that is congruent with the fact that the genetic code is as perfect as everything else, instead what we see are groups of people (family members or factory workers) exposed to similar toxics.

The family groups share the same customs, the same food, the same house, the same trades or professions, the same environment, etc.

In fact, familial aggregation of the disease has been observed for decades, with multiple reports in the literature of families in whom the occurrence of CLL is greatly enriched with what appears to be almost Mendelian inheritance [21], and worst, there are environmental toxicants so persistent that can be transmitted from parents to child, for instance, through mother's milk.

"Along with its antibodies, enzymes and general goodness, breast milk also contains dozens of compounds that have been linked to negative health effects,"

bisphenol A (BPA, a plastic component), PBDEs (used in flame retardants), perchlorate (used in rocket fuel), perfluorinated chemicals (PFCs, used in floor cleaners and nonstick pans), phthalates (used in plastics), polyvinyl chloride (PVC, commonly known as vinyl), organochlorine pesticides, dioxin, benzene (a known human carcinogen [22]), and the heavy metals cadmium, lead, and mercury as leading offenders [23].

Risk of childhood leukemia is increased for benzene exposures of $> 10 \mu\text{g}/\text{m}^3$ associated with traffic [24] and auto repair garages and gasoline stations [25].

Human milk serves as a valuable biological matrix for the assessment of public and environmental health. The more lipophilic the chemical is, the more likely it is to be found in human milk. By the way, the bone marrow has a high content of lipids.

Family predisposition should be understood as epigenetic predisposition, as external factors such as contaminated air, contaminated water, polluted air, contaminated food, pesticides, herbicides, fertilizers, metals, plastics, solvents, industrial waste, shocks, addiction drugs, emotional strains, etc.

Such factors are common to the group of people we define as family; these are father, mother, siblings, and sometimes close relatives who live in the same house.

The exposure to exogenous factors in factory employees is called professional risk, as is the newly sounded case of leukemia in Samsung employees. And the difference between one and another example is only the name that we put, because both in the families and in the factories, the effect of the toxins is similar as they alter the delicate balance between mass and energy in the processes that make up the life, in this case in the complex functions of the bone marrow.

Familial CLL does not appear to differ from sporadic CLL in terms of prognostic markers and clinical outcome [26].

But such external factors only modify the genetic expression in one way or another, but they do not have an effect that we could call direct on the DNA chains or their components. In fact, what is importantly affected is the generation and distribution of energy that emanates from melanin, and hence, general failures, characteristic of disturbances in the generation, and distribution of energy begin to happen, as it happens in any system.

So, it is to date, the identification of genes that predisposes to chronic familial leukemia has been unsuccessful in real terms, which is attributed to various factors, such as the small number of affected individuals susceptible to being studied and technological limitations or maybe because there are many genes affected and each contributes a little [27].

Farming-related exposure and occupational chemicals increase risk of CLL. This is congruent with population-based studies and cohorts that have shown significant family aggregation in CLL and related conditions such as non-Hodgkin lymphoma and other lymphomas; and on the other hand, the absolute risk of a first-degree family member for the development of CLL or a similar disease is very low.

Thereby, linkage studies have been conducted in high-risk CLL families to screen the whole genome for loci that contribute to susceptibility, but no gene mutations have yet been identified by this method.

The accumulation of small, mature-appearing lymphocytes in the bone marrow, blood, and lymphoid tissues in CLL indicates that many germ cells are altered, as well as the daughter cells that are produced. The possibilities that a point mutation (loci) or the joint failure of several genes occurs in a significant portion of the germ cells and that such dysfunction is also expressed in the daughter cells is so unlikely that it has not been able to prove much least explain.

On the contrary, a failure in the generation and distribution of energy from melanin that is repeated in numerous cells both germs and daughters is so feasible that it can easily be demonstrated, as is the case of the experiment described in Section 2.4.

Incidence rates in men are nearly twice as high as in women that can be explained due to men are exposed to environmental toxics more often than women. Although advanced age, white ancestry (less melanin equal to less water dissociation) and family history of hematologic malignancies are risk factors; the etiology of CLL is still not understood more than unknown [28].

1.6 Energy failure means generalized dysfunction: arsenic poisoning

In any system, when the failure is widespread, energy is the usual or main cause. And in the case of the eukaryotic cell, alterations are diffuse, so they can be found at any level, including genes, histones, chromosomes, etc. The study of cellular structures separately from the flow of energy leads to biased conclusions, because the mass and the energy are inseparable in the real world.

Any structural alteration of the cell is preceded and accompanied by a disturbance in the flow of energy that comes from the dissociation of the water, which happens inside the melanin. The name of the affected structures or substances (protein, histone, amino acid, nucleotide, gene, chromosome, etc.), does not have more relevance, because the cell ignores it; there is simply an imbalance between mass and energy.

The cell uses the energy in many ways, and it does in a surprisingly exact way, leaving almost nothing at random; as it has done since the beginning of time. When the amount of chemical energy available in the form of molecular hydrogen (H_2) and high-energy electrons (e^-) is not enough to fill the energy needs of the cell, then the role of chance begins to be significant, so the clinical manifestations also depend on chance, but the basic problem is still the same: balance between mass and energy.

1.7 Leukemia, a generalized failure?

Leukemia is cancer that starts in the tissue that forms blood. Most blood cells develop from cells in the bone marrow called stem cells. In a person with leukemia, the bone marrow makes abnormal white blood cells. The abnormal cells are leukemia cells. Unlike normal blood cells, leukemia cells do not die when they should. These may crowd out abnormal white blood cells, red blood cells, and platelets. This makes it hard for normal blood cells to do their work. The four main types of leukemias are acute lymphoblastic leukemia (ALL), acute myelogenous leukemia (AML), chronic lymphocytic leukemia (CLL), and chronic myelogenous leukemia (CML).

The risk factors already described in leukemia are genetic disorders, radiation exposure, physical and chemical exposures, and chemotherapy.

The greater incidence of leukemia per 100,000 persons is in white races, with 17.5/10.7 (male/female), and in black race, the incidence per 100,000 persons is 12.9/8.0, suggesting that a greater amount of melanin in the skin or body is a protective factor.

Supposedly, a clone of invasive cells may arise at any stage of cell maturation and specialization in the lymphoid, myeloid, or pluripotential stage. The cause of this apparent clonal development is quite unknown in most cases; it appears to involve the rearrangement of sequence of bases on DNA molecules or chromosomal instability syndrome.

External and internal factors such as ionizing radiation and chemicals favor chromosomal anomalies. These random DNA changes will lead to an uncontrollable mitosis of cells.

These leukemic blasts show abnormal behavior infiltrating into the bone marrow, altering, by means of diverse mechanisms, the astonishing accuracies of the normal processes of hematopoiesis (formation of cellular components of blood).

The abnormal cells eventually infiltrate into other organs as such as the spleen, the eye, or the liver, also disrupting the astonishing accuracy of their regular processes.

The blood becomes unable to carry out its functions, and the individual affected will experience within a few days or weeks increased fatigue and infections and will bruise and bleed more easily than they usually would have.

The clinical findings of leukemia, such as thrombocytopenia, anemia, severe infections widespread, bone pain, arthralgias, and involvement of the liver, spleen, thymus, lymph nodes, skin, gums, eye, head (CNS), and neck; it is compatible with a generalized system failure, which is typical of problems in the generation and distribution of energy (from light/melanin/water).

The experiment that we describe below points in that direction (**Figures 8–28**).

1.8 Arsenic (As)

It is a metalloid with atomic number 33, atomic mass of 74.92, and oxidation number: $\pm 3, 5$. It alters multiple metabolic pathways by supposedly uncoupling oxidative phosphorylation. Its effect is not specific; it attacks several organs and is tasteless and odorless. The ingestion of arsenic induces a general failure of the organism, suggesting that arsenic acts by disturbing the amazingly accurate generation and distribution of energy.

Arsenic binds the cofactor sulfhydryl, dihydrolipoate, which inhibits the oxidative metabolic pathway of pyruvate and succinate. The body also replaces arsenic with phosphorus, which inhibits oxidative phosphorylation, but the most significant alteration seems to be the inhibition of sulfhydryl.

Arsenic pentavalent is well absorbed by the GI tract, and it is initially located in blood, coupled with globulin; thereafter, redistribution occurs within following 24 hours mainly to the liver, lungs, intestine, and spleen. Arsenic replaces the phosphorus of the bone, where it remains 30 years or more.

Arsenic, when decoupling the oxidative phosphorylation, induces a significant decrease in the availability of energy of the cell. However, arsenic affects the melanin itself, because they have great affinity with each other, so arsenic (As) not

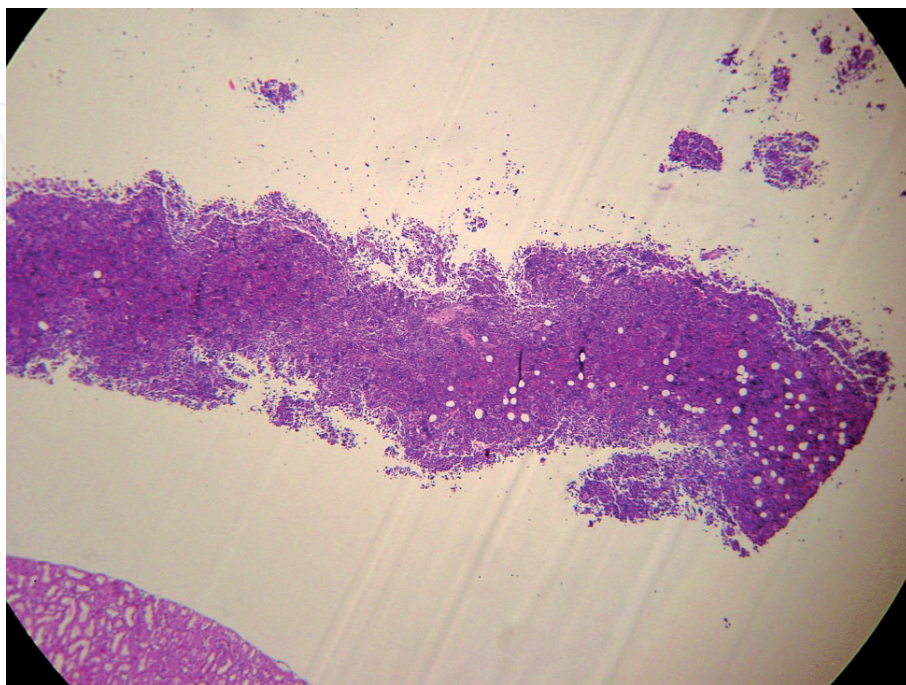


Figure 8.
Bone marrow, control group (A), H&E, 5X.

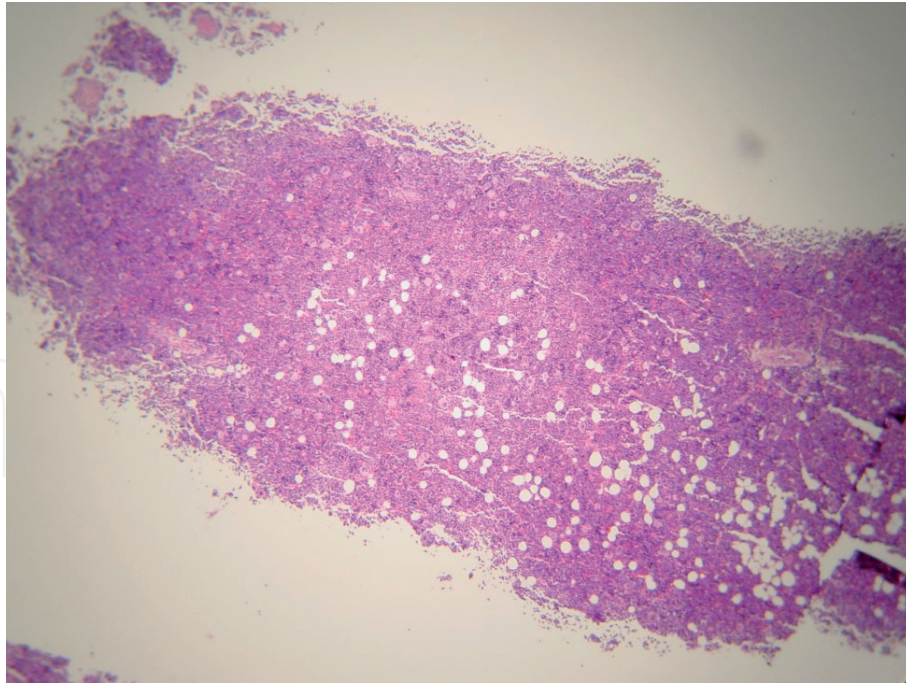


Figure 9.
Bone marrow, exposed group (B) to arsenic. H&E, 5X.

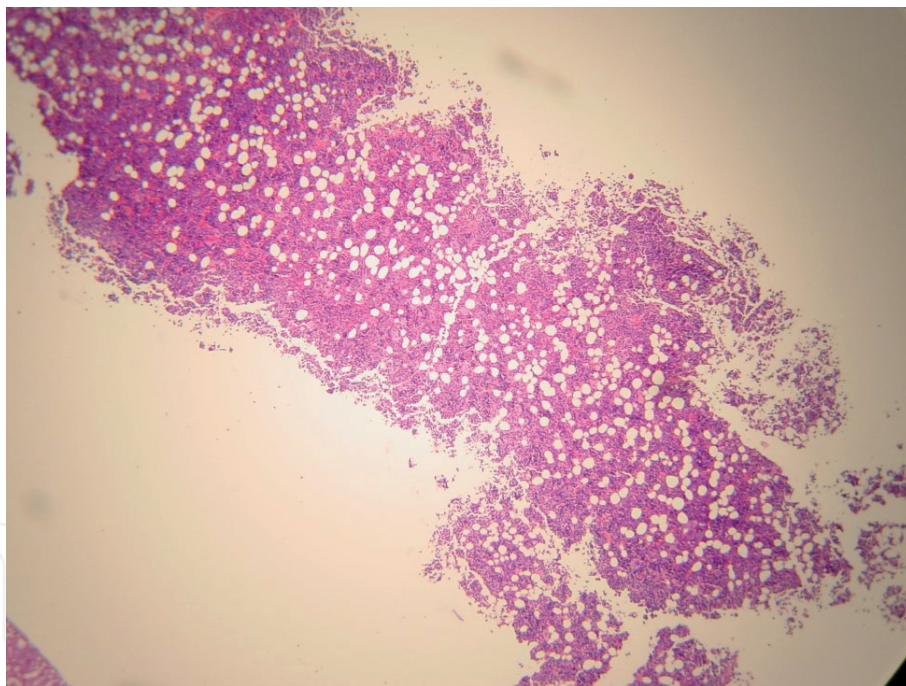


Figure 10.
Bone marrow. Group C exposed to arsenic and treated at the same time. H&E, 5X.

only damages the complex energy distribution system arising from the dissociation of the water molecule by melanin but damages the melanin itself, disturbing the generation of energy, so the damage is widespread.

Arsenic in small doses stimulates the generation and distribution of energy from melanin, so it is, in the seventeenth and eighteenth century, was used by the aristocracy in France to rejuvenate the skin of the face.

Furthermore, in the fifteenth century, William Withering, who discovered digitalis, was a strong proponent of arsenic-based therapies [29]. He argued, “Poisons in small doses are the best medicines; and the best medicines in too large doses are poisonous”.

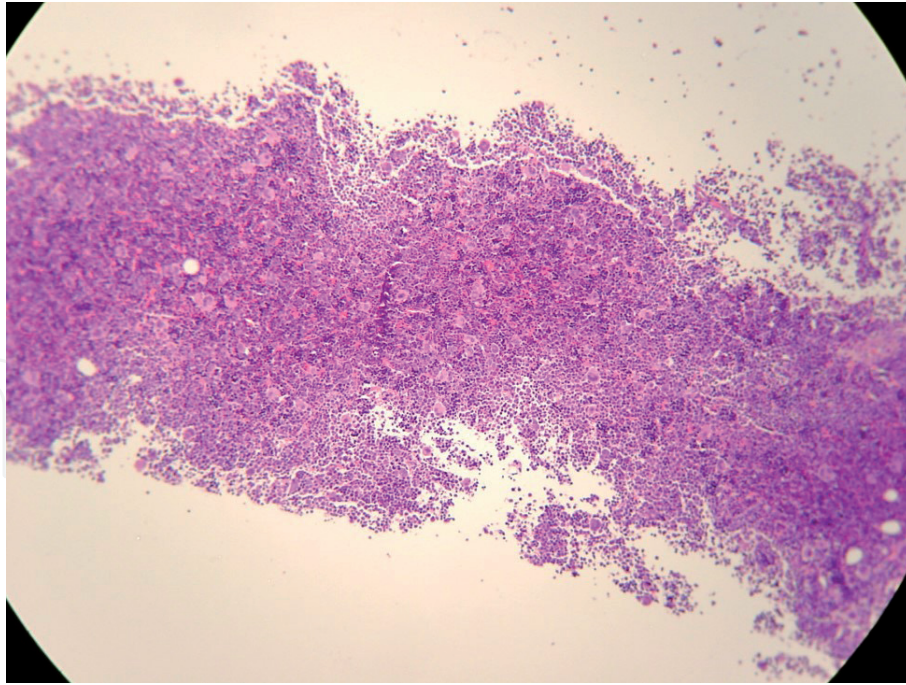


Figure 11.
Bone marrow, control group (A). H&E, 10X.

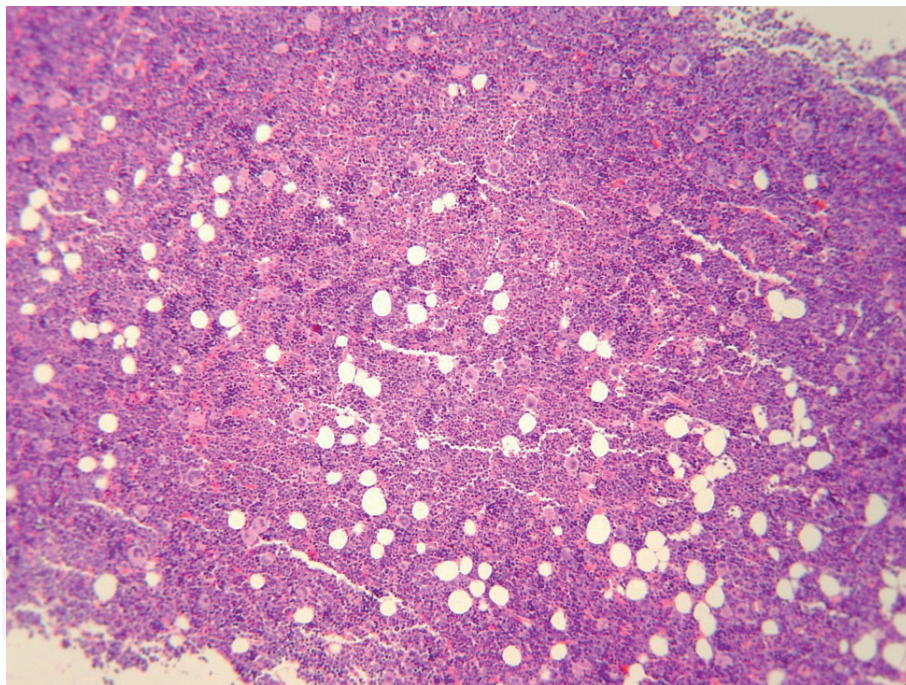


Figure 12.
Bone marrow. Exposed group (B) to arsenic in water. H&E, 10X.

Thomas Fowler compounded a potassium bicarbonate-based solution of arsenic trioxide (As_2O_3) and was used empirically to treat a variety of diseases during the eighteenth, nineteenth, and early twentieth centuries [30]. In 1910, Nobel Laureate and Paul Ehrlich developed Salvarsan, an organic arsenical for treating syphilis and trypanosomiasis.

But in higher doses, the opposite effect occurs; therefore, chronic exposure is a serious with arsenic public health problem in some parts of the world [31]. Intoxication by this heavy metal can result from breathing sawdust, workplace air, or arsenic-preserved wood or from ingesting contaminated water, food, or soil [32].

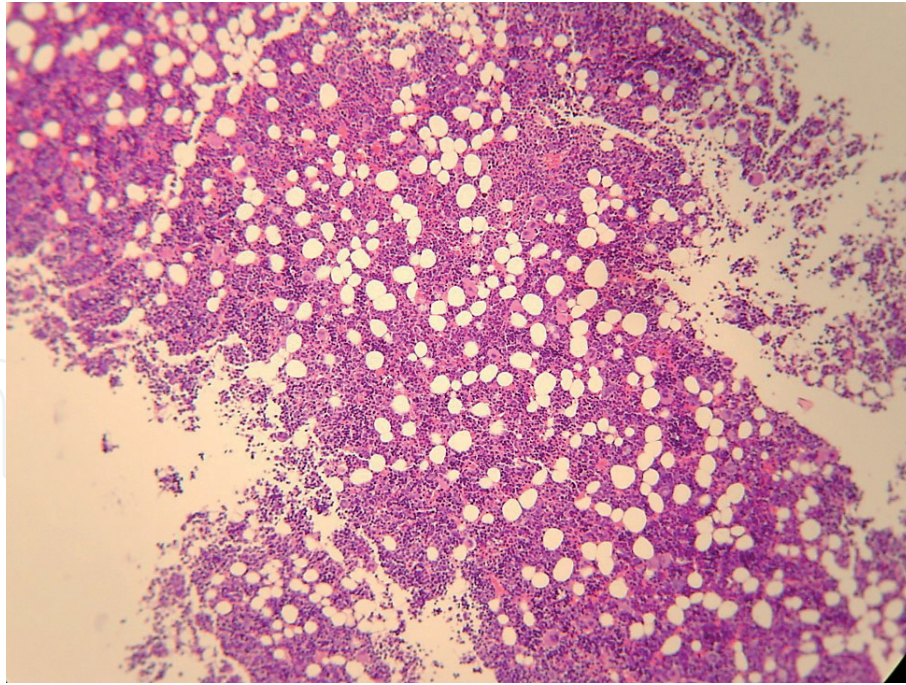


Figure 13.
Bone marrow. Group C exposed to arsenic in water and treated at the same time. H&E, 10X.

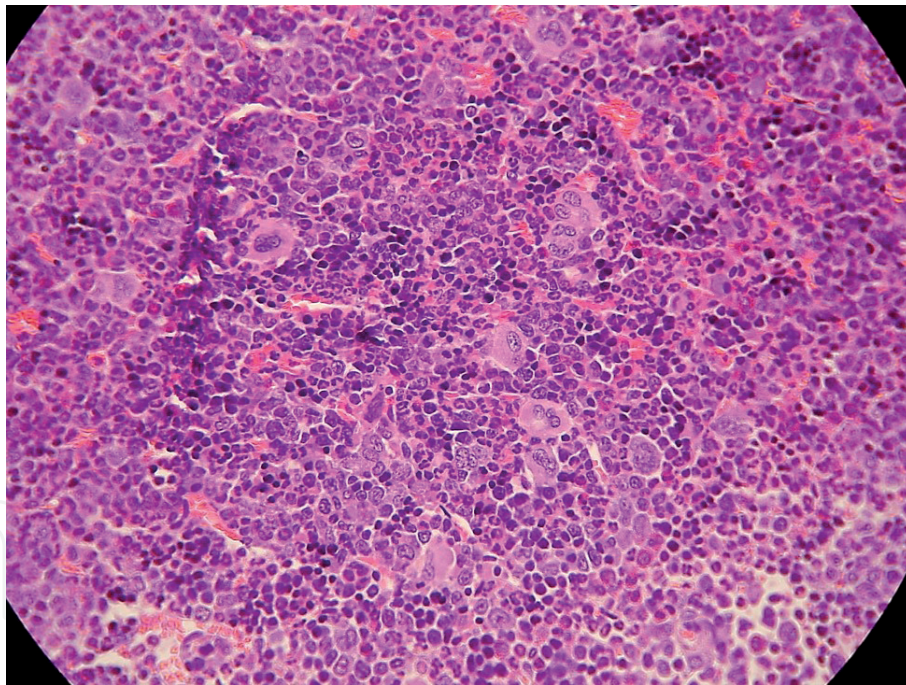


Figure 14.
Bone marrow, control group (A). H&E, 40X.

Contamination of groundwater happens by naturally occurring arsenic, also by widespread use of arsenic-containing herbicides and pesticides; its incorporation into feed as a substance to promote the growth of livestock and poultry and its industrial use has caused the environmental arsenic dispersion.

Biomagnification of arsenic is observed in many species of fish and shellfish. Sadly, the average daily human intake of arsenic is approximately 300 µg, mainly ingested with food and water. The World Health Organization (WHO) safe limit for arsenic in drinking water is 0.01 mg/L.

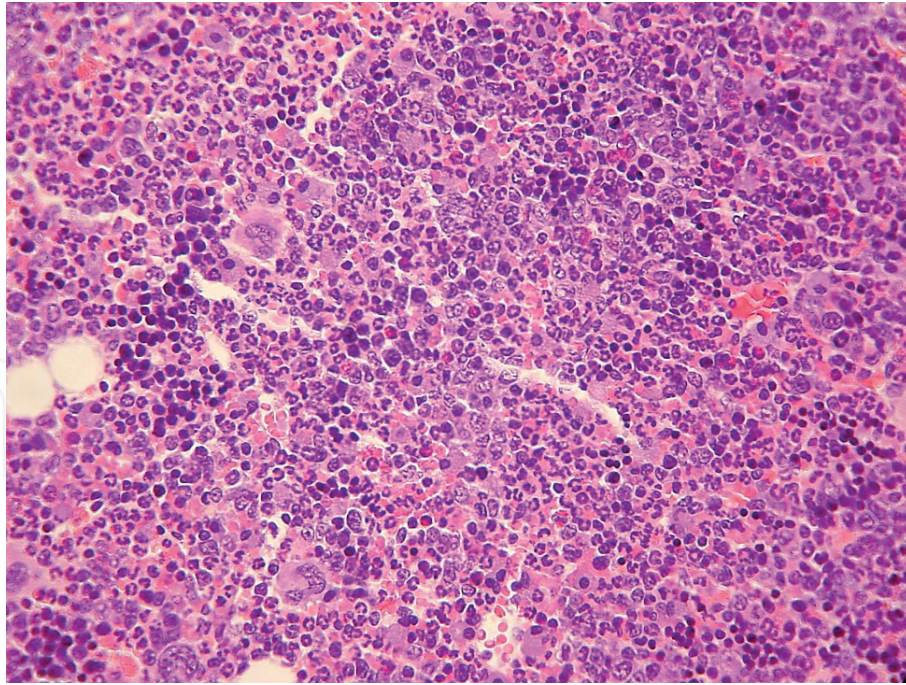


Figure 15.
Bone marrow. Exposed group (B) to arsenic in water. H&E, 40X.

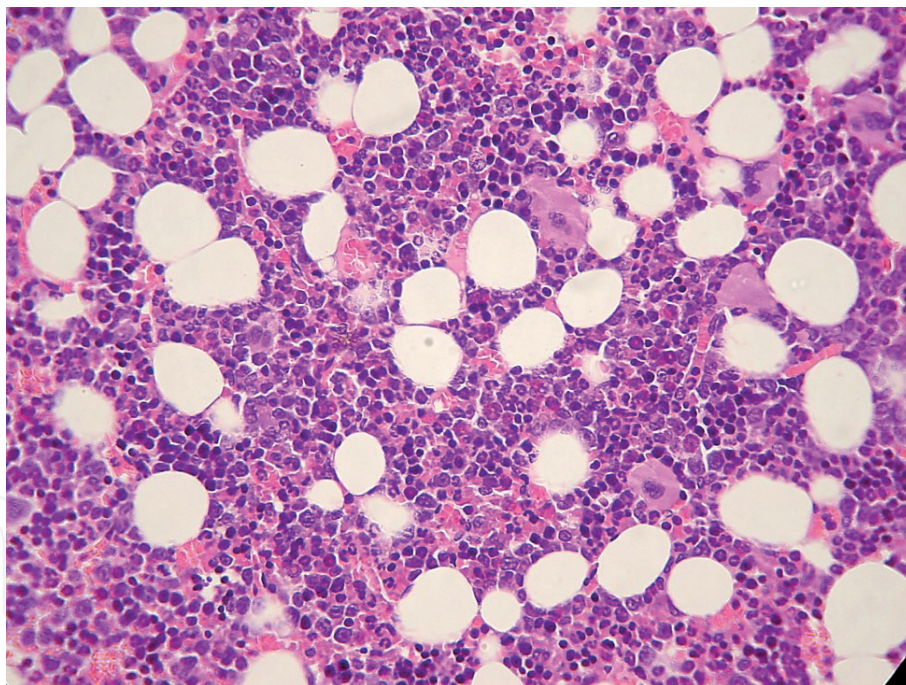


Figure 16.
Bone marrow. Group C exposed to arsenic in water and treated at the same time. H&E, 40X.

Acute and chronic poisoning of arsenic can be confused with hemorrhagic gastroenteritis, cardiac arrhythmias, and psychiatric disease. In 1878, Boston City Hospital described the effect of Fowler's solution on the reduction of white blood cells in two normal people and one patient with "leukocythemia" [33].

Subsequently, As_2O_3 was administered as a primary antileukemic agent until it was replaced by radiation therapy. In 1930, the hematologic use of arsenic experienced a resurgence in popularity, when its efficacy was reported in patients with chronic myelogenous leukemia [34].

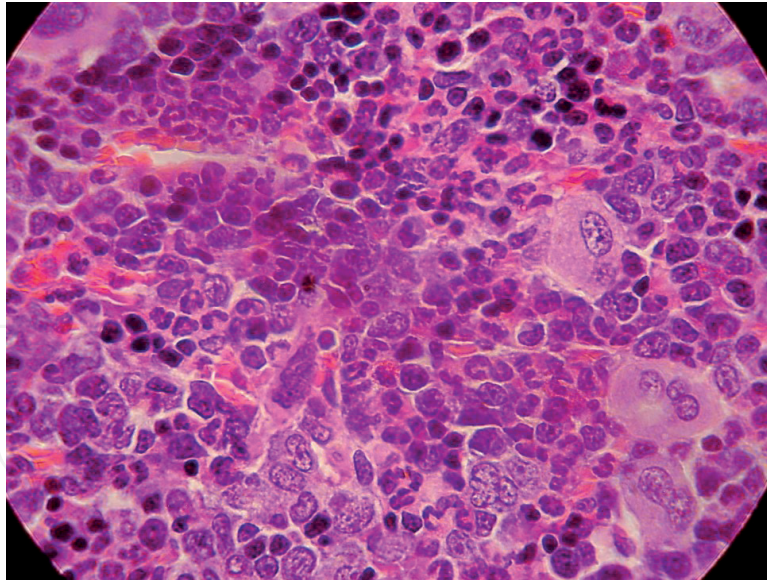


Figure 17.
Bone marrow. Control group A. H&E, 100 X.

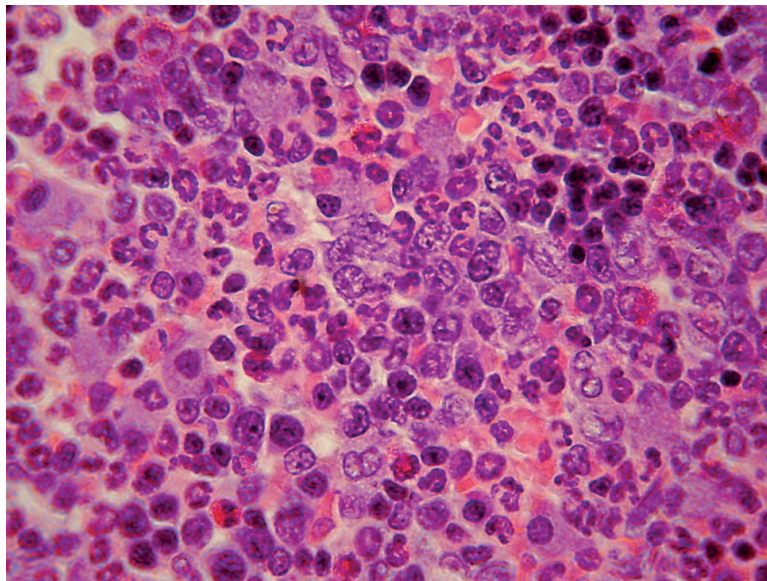


Figure 18.
Bone marrow. Group B exposed to arsenic in water. H&E, 100X.

Until supplanted by modern chemotherapy, arsenic trioxide after radiation was considered the most effective treatment for CML and other types of leukemia. Recently, reports from China have described the induction of clinical and hematological responses by arsenic trioxide in patients with de novo and relapsed acute promyelocytic leukemia (APL) [35]. This is an important observation, since around 20–30% of patients with this form of acute myelogenous leukemia relapse despite treatment with all-trans retinoic acid and combination chemotherapy.

Arsenic treatment was not associated with bone marrow suppression and produced only limited side effects. Thereby, arsenic trioxide (Trisenox®) was approved for the treatment of relapsed or refractory APL by the US Food and Drug Administration in September 2000.

It is interesting that the therapeutic application of arsenic in low dose is widely used. Due to generalized systemic effects, so far, a clear explanation about its therapeutic effects is not available. It is possible that other similar therapies, based in toxic compounds as all-trans retinoic acid and daunorubicin/doxorubicin/

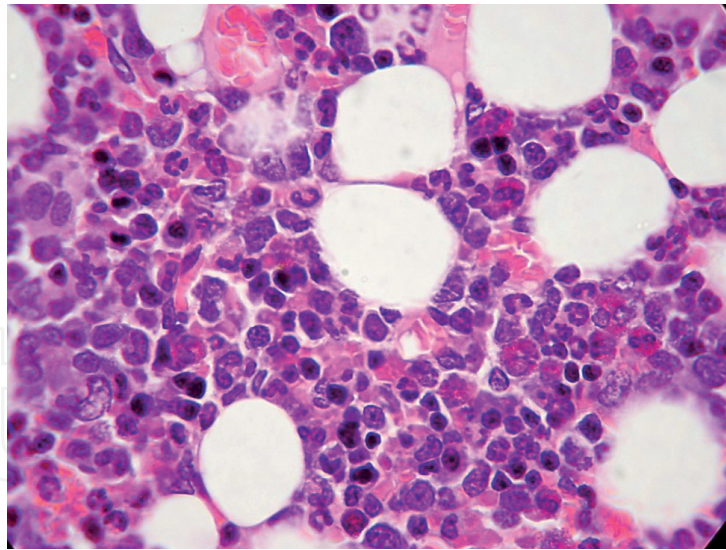


Figure 19.
Bone marrow. Group C exposed to arsenic in water and treated at the same time. H&E, 100X.

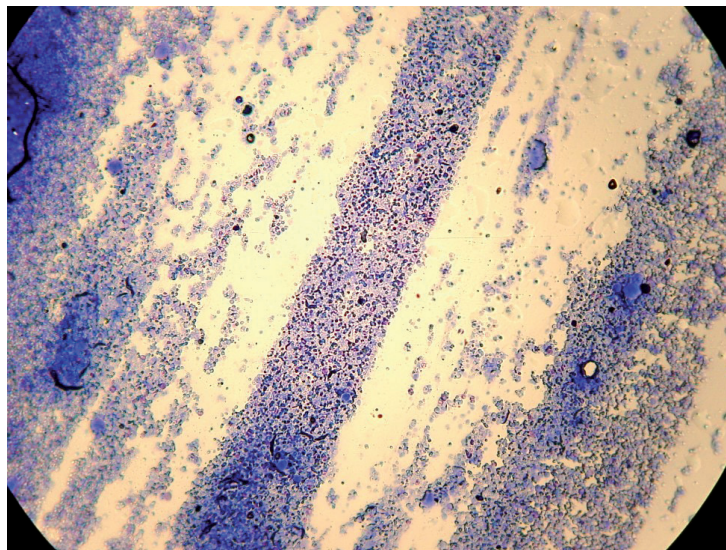


Figure 20.
Peripheral blood smear. Control group A. Giemsa stain. 10X.

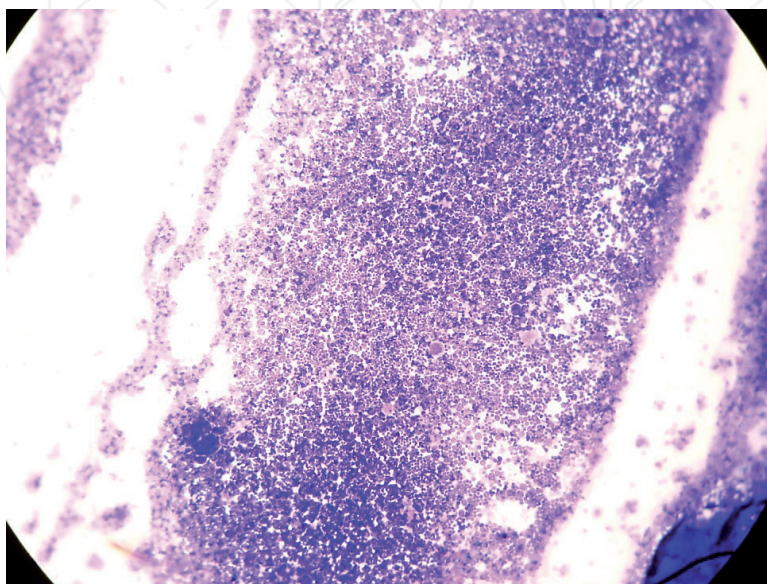


Figure 21.
Peripheral blood smear. Group B exposed to arsenic in water. Giemsa stain, 10X.

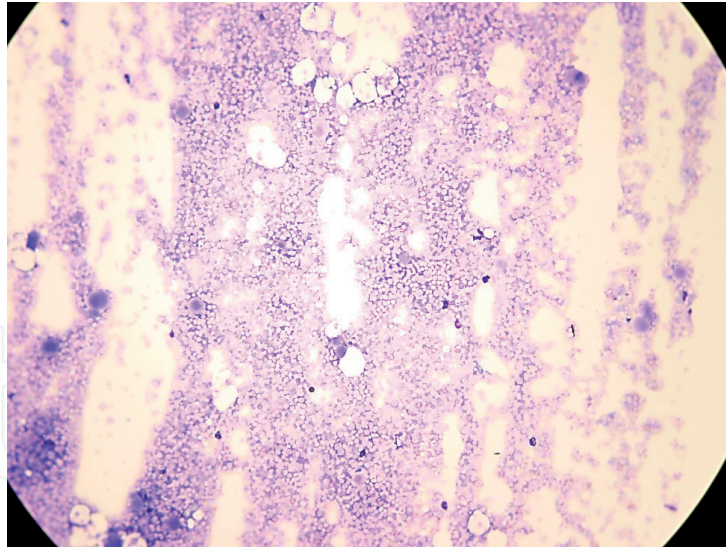


Figure 22.
Peripheral blood smear. Group C exposed to arsenic in water and treated at the same time. Giemsa stain, 10X.

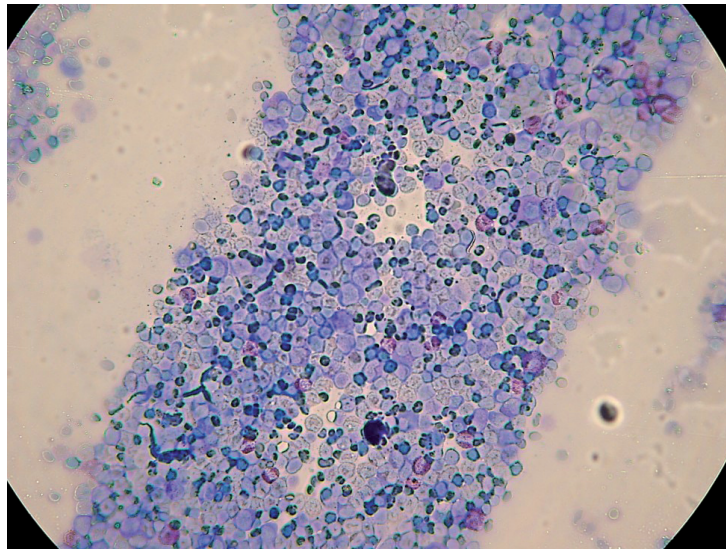


Figure 23.
Peripheral blood smear. Control group A. Giemsa stain, 40X.

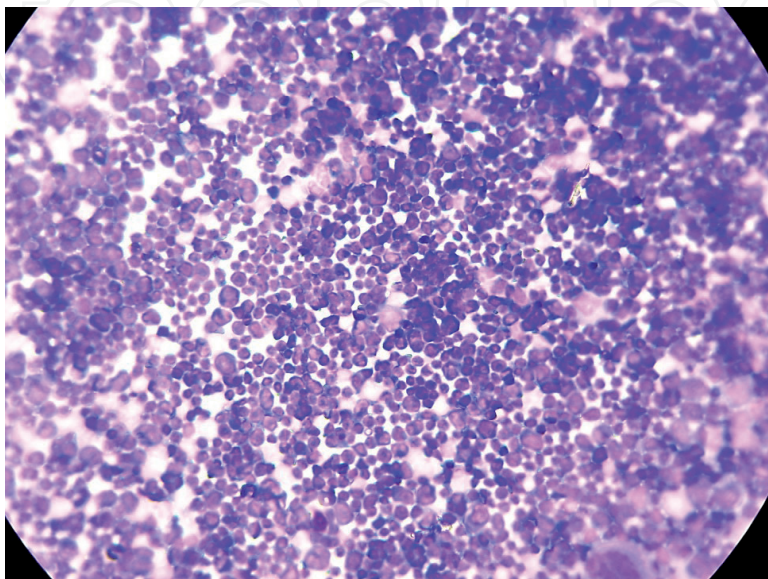


Figure 24.
Peripheral blood smear. Group B exposed to arsenic in water. Giemsa stain, 40X.

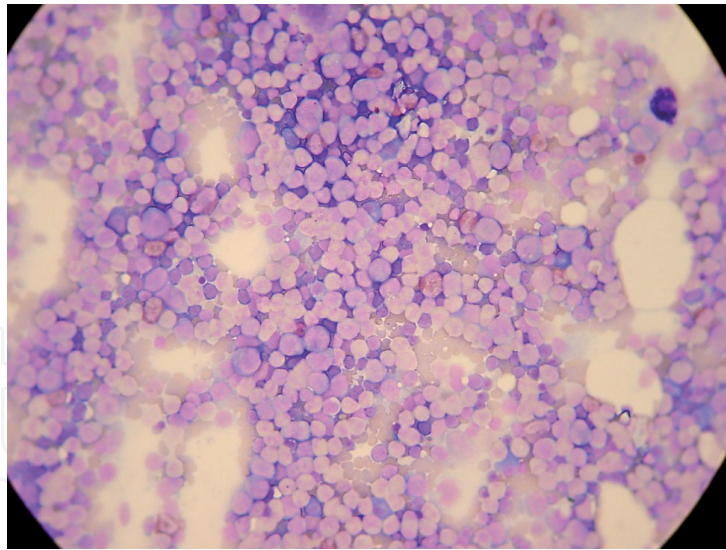


Figure 25.
Peripheral blood smear. Group C exposed to arsenic in water and treated at the same time. Giemsa stain, 40X.

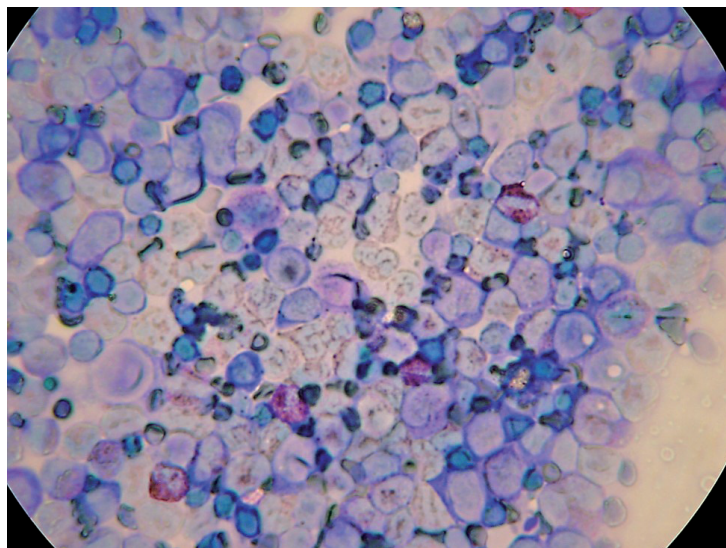


Figure 26.
Peripheral blood smear. Control group A. Giemsa stain, 100X.

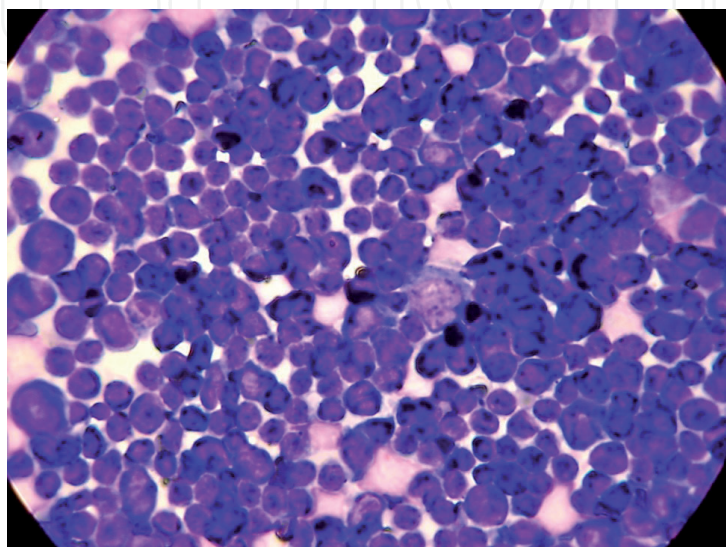


Figure 27.
Peripheral blood smear. Group B exposed to arsenic in water. Giemsa stain, 100X.

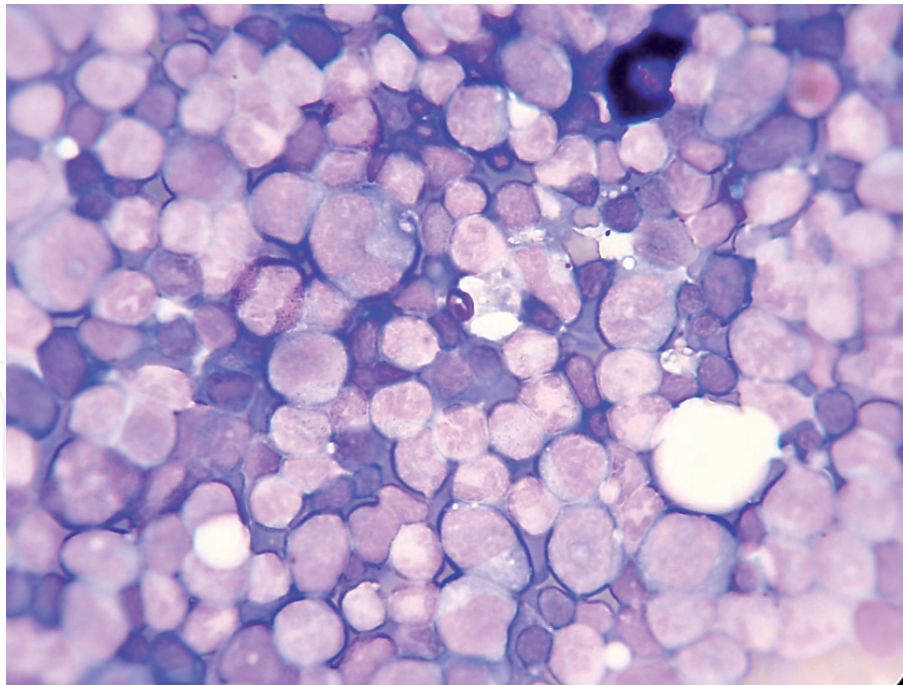


Figure 28.
Peripheral blood smear. Group C exposed to arsenic in water and treated at the same time. Giemsa stain, 100X.

epirubicin/idarubicin, an anthracycline-related compounds [36], are altering gene expression (genotoxic agents) through different pathways; thereby their effect is generalized, so it can be expected that it also affects the generation and flow of energy from melanin.

Arsenic, all trans-retinoic acid, and anthracycline-related compounds, when it is used at very high doses, then the amazingly accurate process of generation and distribution of energy, from the dissociation of the water molecule by melanin, stops almost completely, so death occurs in minutes.

Therefore, the administration of arsenic in laboratory animals is an easy way to induce general dysfunction or failure, as we are altering a fundamental process of life as is the generation and distribution of melanin energy.

Our working hypothesis was to induce widespread failure in rats and to study the effects on different tissues, such as the lung, kidney, liver, etc. [37]. The results in kidney and liver were published already. This is the first publication of results in the bone marrow.

2. Materials and methods

There were 3 groups of 10 Wistar rats each one, all males, adults. Group A was control. Group B was the exposed group to arsenic in water. The administration of pentavalent arsenic was 0.50 mg/L in the water and administered ad libitum. Group C was the group exposed to arsenic in the same way as group B and treated at the same time with a novel formula that restores the balance between mass and energy.

3. Results

The results of the experiment were according to what was expected. The administration of pentavalent arsenic was 0.50 mg/L in the water. Arsenic is a toxic and a carcinogen; among the noncarcinogenic harmful effects of this metalloid, the most common associated with its ingestion are those presented in the skin,

hyperpigmentation, agent hypopigmentation, and hyperkeratosis, damage to the cardiovascular system; renal and hepatic alterations, development of peripheral neuropathies and encephalopathies; and its capacity of endocrine disruptor related to the development of diabetes. The relationship between the presence of arsenic in water in several regions and the increase in the presence and mortality of the bladder, lung, kidney, and hepatic cancer has been recognized in the potentially exposed populations.

As described in literature and as we observed in the histological slides of the group of animals exposed to arsenic (group B), the damage is generalized. It would be necessary to elaborate multiple conjectures to try to explain the diffuse impairment to organs and systems that are produced from the ingestion of arsenic in the water. However, the significant disturbance caused by arsenic in the generation and distribution of energy derived from melanin, it could explain the different levels of microscopic alterations observed in the histological stains of the lung, kidney, liver, spleen, bone marrow, etc.

According to the adage that good experiments are those with few animals, many results are obtained; group B was constituted with only ten animals, and the size of the effect of arsenic was substantive. On the other hand, it fulfilled the observed fact that in any system, when the fault is widespread, we must think first of energy.

So, we can think that, in this experiment, we could induce and thereby demonstrated in a reasonable way that the widespread failure caused by arsenic ingestion is due to the perturbations of the generation and distribution of energy derived from melanin.

The findings of group C—exposed and treated at the same time—cast better than expected findings, because on the one hand, the generalized toxicity of arsenic manifested itself again, but significantly decreased by the simultaneous administration of the therapeutic drug. And on the other hand, we could demonstrate the usefulness of our therapy to prevent and treat the general failure of organs and systems that is induced with the ingestion of arsenic that also gives a real hope for the many patients in similar situation.

The improvement with the treatment was also manifested in the different tissues studied, which is consistent with the fact that, by reducing the alteration in the generation and distribution of energy, the improvement is detectable at the microscopic level and it is also a general improvement.

The induced changes during the experiment with the exposure and treatment mean widespread effects, positive and negatives. The size of the effect is noticeable in both cases, exposure and treatment. And the magnitude of the effect was similar in other tissues in which biopsy was taken.

The observable findings under the microscope are very interesting, as they involve numerous variables such as cell size, shape, color changes, etc. But there are so many changes that are hard to explain based only in analysis of observable structures.

The improvement in group C (treated and exposed) is notorious. Thereby, two hypotheses were tested with one experiment, few animals, and many results, a good experiment. The way melanin releases energy, symmetrically and in all directions, in the manner of growing spheres that follow the laws of simple diffusion, flooding of molecular hydrogen cytosol, allows the vast majority of chemical reactions to be driven by these hydrogen molecules, which are not combined with water, so they only move through it reaching until the last corner of the eukaryotic cells with its precious energy charge and its powerful antioxidant effect.

Therefore, when the generation and distribution of energy that comes from melanin is altered or at least disturbed by environmental factors, of a chemical or physical nature, many biochemical processes are randomly affected by the decrease in energy levels.

We must not forget that intracellular biochemical processes are surprisingly accurate in every one of their physical and chemical characteristics, as they have been since the beginning of time. But the exact chemical reactions require in turn to be driven by an exact amount of energy. And only a molecule as wonderful as melanin has the necessary bioenergetic capacity.

The multiple tissue changes observable in the histological images of the rat and arsenic experiment underpin the concept of the unsuspected bioenergetic role of melanin. The structural changes susceptible to being observed in the light microscope and stains Giemsa, in the case of the smears, and hematoxylin and eosin, in the case of histological cuts, allow to glimpse that the number of factors involved is vast.

And analyzing one by one from a structural point of view, without considering the incessant flow of energy, would lead us to the same errors that we currently observe in the literature. It is a fact that the cell uses energy in many ways, and in studying cell biology, we must be aware that even to study ultrastructure alone, our technological resources are relatively limited.

4. Discussion

The changes that we observed in the experiment are very interesting and highly significant, it would be very difficult to explain them based on genes, since genes are not autonomous, because they depend on the energy and surrounding cell scaffolding to replicate, express themselves and even to preserve the form, stability and function. They are also immersed in a highly complex biological system, with which they interact in a way that is not yet understood, but all the components of this highly complex system depend entirely on the energy that emanates from the melanin, so that by restoring the generation and Energy distribution, which it is so fundamental, then it is possible to explain the positive and negative changes that we could observe under the light microscope.

Characteristically, energy failures produce widespread alterations, we can say otherwise, when the problem of energy is improved or corrected, then many processes are in turn restored, which can be detected by microscopically examining the cellular structure, which is all what we can value, being an indirect indicator of the flow of energy.

Simplistically, if the ultrastructure is altered, the generation and distribution of energy is indeed disturbed, in a directly proportional form, and vice versa. That is why, despite many efforts, trying to explain diseases such as leukemia, based on purely observations of the structure, for example genes, histones or chromosomes, has given so far poor results, it is necessary to consider at the same time the highly dynamic generation and distribution of energy.

5. Conclusion

The current medicine is ensnared in the dogma that a single molecule, glucose, provides energy and mass at the same time; furthermore it also considers that only the chlorophyll of plants can transform the luminous energy into chemical energy by means of the dissociation of the water molecule. On the other hand, analyzing in a separate way the microstructure (mass) and the energy flow in the cells has led to important biases since the mass and energy are inseparable in the real world.

Trying to find the cause or explanation of diseases, based merely on the study of observable of micro or ultrastructural alterations has produced very limited results, because the cell is a highly dynamic living entity, in which the flow of energy and mass are incessant and inseparable. The optimal thing would be to study both phenomena (mass and energy) at the same time and in real time, which is not currently feasible.

During the study of biological phenomena, we must keep in mind that the size of the effect should be large [38]; otherwise, when the size of the effect is small, we end up studying in detail some prevalent bias. Bias is defined as the combination of various design, data, analysis, and presentation factors that tend to produce research findings when they should not be produced. There is an increasing concern that most current published research findings are false. The extremely large studies may be more likely to find a formally statistically significant difference for a trivial effect that is not meaningfully different from the null hypothesis [39].

It is likely that current unawareness of physicians about the human body's ability to take light energy and the impoverishment of it by environment toxicants is a significant factor of the poor performance of health systems. For instance, in the USA, 225000 annual deaths are estimated due to unnecessary surgeries, errors in patient medication, errors of different types in hospitals; nosocomial infections, and adverse effects of medications [40]. Most of the data are derived from studies in hospitalized patients, thereby are estimates of death only and do not include adverse effects associated with disability or discomfort.

Therefore between 4% and 18% experience adverse effects in outpatient settings, with 116 million extra physician visits, 8 million hospitalizations, 3 million long-term admissions, 199.000 additional deaths, and \$77 billion in extra costs [41].

The specific alterations of the genes cannot explain the diseases called genetic or hereditary, because the influence of genes is relatively limited and highly complex, i.e., the cystic fibrosis gene, codify to almost 600 proteins. Furthermore, disturbances in the generation and distribution of energy from melanin can manifest—structurally—as alterations in the genes, since the replication and the expression of chromosomes require an astonishing accurate source and level of available energy in the form of molecular hydrogen (H_2) and high-energy electrons (e^-).

And if we consider the effects of energy flow not only in the cell nucleus, histones, genes, and chromosomes but also in the scaffolding around them, things become even more incomprehensible to us; but to have understood that the energy of the cell comes from the light-melanin-water triad in order of abundance in the universe, and that it does not come from glucose, represents a critical advance in the knowledge, which can be translated in an expedited way to the clinic, for the benefit of the patient, especially if we take into account the role of environmental toxins and their detrimental and generalized effects on the amazingly accurate process of generation and distribution of energy by melanin.

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