

The “Theory of everything”

Editorial

Dr. Steven Hawking theorized the “Everything Theory” to explain the Universe we live in and the laws that govern its phenomena. Man has looked all along for the essence of his life on the Earth. First philosophy tried to give answers, later it was physics, biology, chemistry... These sciences discovered the basic laws that determine the behavior of our existence and contributed to the intellectual and technological progress of humanity. Physics also tried to explain not only what happens on the Earth, but also the mathematics that governs the whole Universe. Formulae and equations explain phenomena occurring everywhere, billions of light-years away from our planet and explain their dynamics. There are formulae that consider worlds that for now are only in the theories of physicists or mathematicians. A unitary view of the Universe could give us the notion that, in a way, we possess all the world, including our lives, in our hand: something that is far from the concept of infinite and its innumerable expressions. What we need or, at least, what we are after is a mathematical expression that contains and explains all that.

Similar efforts cannot be applied in the understanding of the body and its fundamental bricks: cells. Medicine is a discipline that can hardly be reduced to formulae or equations. Because of the complexity of the organism and the rules that are at the base of life, and also because of the unique characteristics proper to each individual, Medicine is far from being an exact science or something that can be simplified down to a handful of formulae, not to say a single one. It is not in all cases that a deviation from the healthy state or, even more complex, what each individual considers as wellbeing, is wholly understood. We suffer from a lot of diseases for which to date there is no explanation.

When, unfortunately less rarely than we like to believe, the pathogenic agent of a certain condition is not known and the mechanisms that are at the base of an illness are not understood, its pharmaceutical treatment represents an attempt whose efficacy is doubtful. Those treatments do not eradicate the pathology, and in some cases work only to mitigate or even hide some symptoms, since they are addressed not to the actual cause but only to collateral expressions of the disease.

Even if every man is different from any other, it must be recognized that the way organs, tissues and cells react to external stimuli cannot be too dissimilar. There must be a cascade of biologically logical reactions that are bound to follow universal rules. In general, diseases can be originated by the interaction of the bodies with biological and chemical entities like bacteria, parasites and viruses, but also physical entities like, for example, radiations and particulate matter.

As to particulate matter and just as an example, silicosis is a long-known pathology caused by the inhalation of silicon-based particles that, interacting with the lung cells, induce an inflammatory condition and scarring in the form of nodular lesions in the upper lobes of the lungs.

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Similarly, pneumoconiosis is the inflammatory response due to inhalation of micrometric particles, not only silicon-based ones. At that stage, the specialized cells macrophages are recruited to try and “eat up and digest” those foreign bodies. This mechanism is universal, namely, it exists in all humans and also in animals.

When macrophages do not succeed in eliminating/destroying those unwanted bodies from the organism, i.e. to “reduce” them to the original elements they are composed of or to simple molecules, there are cells that surround completely those particles and form a granuloma and/or a fibrotic capsule. This mechanism is universal as well.

But what happens when the particle is small enough to be internalized within a single cell? What happens at the cytoplasm level? What forms of defense can cells deploy? The internalization of the submicronic and nano-sized particles beyond the cell barrier is well-documented in literature. This internal interaction could be the keystone to understand some metabolic malfunctions and the ensuing diseases.

The discovery of a unitary vision in Medicine, a vision that can explain any disease, looks like an impossible mission. There are rare or the so-called orphan diseases or entirely mysterious pathologies, some of which do not even have a name, and that increase every year in number, now 6,500-10,000, according to different organizations.

At present the path that leads to clinical diagnosis starts from symptoms, goes through clinical tests and through the comparison of the data obtained with those already catalogued and described in the Pathology books. That way, the identification of a disease can be reached. In some cases, when uncertainty exists, other tests are performed to get closer and closer to the identification of the illness. When some symptoms described by the patient are not clearly understood or do not fit the disease, they are simply cancelled and not taken into account. When a new disease makes its appearance, often there is no way to fit it anywhere.

With the advent of nanotechnology and the artificial synthesis of nanoparticles, the possibility of interactions of nano-sized

particles with bodies started to grow more likely. Nano-bio-interactions are definitely intriguing and there is still a big debate about their actual degree of safety. If from one side Nanomedicine (controlled interactions) can offer novel pharmaceutical solutions, from the other side there are big concerns about uncontrolled bio-interactions, for instance with nano-sized by-products. The internalization of particles or their aggregation with proteins, enzymes, DNA can represent new stimuli that can trigger new pathologies and/or, in any case, a deviation from the healthy steady state in those who are exposed to their effects.

For this reason, it is necessary to change the approach to the study of a disease and its symptoms in order to understand the pathogenic mechanisms that are at the root of the illness. If we think of pathologies as the result of a sub-micro- and nano-bio-interactions of foreign bodies (bacteria, parasites, viruses in the biological field and dust in the physical one) with the organism and/or cells components, we will have more probabilities to understand many pathologies and to guess their evolution more accurately.

At present, the mission of doctors is to take care of their patients and cure them at the best of their possibilities with the drugs and the technological means available on the market, but, traditionally, there is no attempt to know more about the environment where the patient lives and his possible exposure.

It is obvious that, if the particulate matter, be it organic or inorganic, is nano-sized, the possibilities of nano-bio-interactions inside the cell and the ensuing diseases increase considerably. Inside the body, the interactions can occur in its "solid matter" (flesh) and in its fluids and, in the latter case, a little more in detail, particularly in the blood, specifically with proteins and blood components, and with the extra and intra-cellular matrix. Seen the nanoparticle ability to cross all physiological barriers, they can have free access virtually everywhere inside the organism. The ability of those "invisible bullets" to do that was already demonstrated. So, they have been seen internalized inside the cells and interact with the cell metabolism through direct interaction with organelles, compromising their functionality. The possibility of direct interactions is made easier when sizes are comparable with cytoplasm components like organelles and the nuclear DNA. Such phenomenon offers an interesting insight on many different dysfunctions. Those interactions are stochastic events influencing the probability a pathology has to start and, in some cases, its seriousness. The presence of nano-sized foreign bodies inside a cell does not necessarily cause its death, but can be the origin of a pathological behavior since, during the phase of mitosis, when the nuclear membrane disappears, there is a high probability that a close interaction occurs between those foreign bodies and the DNA, interaction that can damage the DNA.

This specific interaction can induce genetic or epigenetic DNA damages that can be inherited, and the entity of damage can condition the future offspring. Some damages can be

compatible with life, certainly not a healthy one, and cells can reproduce according to a quadratic function, arriving to develop a pathological mass that can interfere with other functions of the body.

Such a mass can be a cancerous one.

The demonstration of such an effect of stochastic interaction meets a few problems. In fact, if it is possible to see the presence of particles inside the cells by means of a transmission or a scanning electron microscope and, when the case arises, see them in contact with the DNA. If on one hand an interaction with the DNA can be morphologically demonstrated, on the other it is impossible to verify, simultaneously, the related biochemical stresses and their future implications.

That indetermination reminds us of the Heisenberg's uncertainty principle developed in physics. In fact, in quantum mechanics, there is a limit of accuracy in determining at the same time the position and the momentum of a particle. Also in biology, when the scale is at nano-level, something in a way similar may occur. Using an electron scanning- or a transmission microscope, a nano-bio-interaction can be seen, thus identifying the position of a particle and the DNA inside a cell. But that physical instrumentation does not allow to monitor the biochemical change of state. This aspect can be verified, for instance, with an instrumentation like a PCR (Polymerase Chain Reaction), but even if that technique amplifies the biological signal, it is unable to monitor a single DNA damage. These damages can be stochastic events, not homogeneously distributed among the cells and in relevant concentration.

That phenomenon can be called "the biological uncertainty principle", something that limits the monitoring and, in general, the possibility to be aware of the evolution of the nano-effect. So we can't be wise of how the phenomenon proceeds and what its pathological implications at macro-level are.

In Medicine, the identification of viruses, parasites or bacteria allows the doctors to issue their diagnosis about a specific disease. Similarly, starting from the observation of the presence of particulate matter in the pathological tissues, the doctor can identify the exposure the subject underwent and define the pathology as nanopathology. That pathology can be leukemia, numerous forms of cancer, one among a number of neuro-endocrine illnesses, cryoglobulinemia (a rare disease) and many others.

Such a unitary approach considering the size of the pathogenic agent, a sort of theory of everything, can explain how the body interacts with the environment, how it reacts to it and the diseases that ensue. That approach can help find solutions that are not only pharmaceutical but something that can show how to modify the environment so as to eliminate as much as possible its possibly harmful stimuli.