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Commentary

The Black Hole of Medicine

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In the field of Physics a "black hole" is defined as "a region of spacetime exhibiting gravitational acceleration so strong that nothing-no particles or even electromagnetic radiation such as light-can escape from it [1]. In a nutshell, an obscure area of space that has physical properties different from those of the surrounding space. If light arrives in its vicinity, it is captured never to re-emerge. There are many studies and theories about them, but none indubitably demonstrable, since no actually detectable, actually intelligible signals come from those mysterious holes.
In Medicine, at macroscopic level, there is something in a way similar: granuloma. A granuloma is a small area of inflammation, often found, incidentally, by X-ray investigations or other imaging tests. Typically, granulomas are noncancerous (benign) [2].

Seen by a physicist, granuloma can remind that scientist of the black hole, at least in some respects. Exogenous matter is trapped in a sort of capsule with no interaction with the surrounding tissue. But there is another "black hole" in Medicine: a three-dimensional gap of knowledge that few are investigating and that is conditioning not only Medicine but scientific knowledge altogether. In order to understand this "no-fly" zone, taking a look of the "state-of-the-art" of Medicine is necessary.

When they want to go deeper into the results of a purely clinical observation, biologists and medical doctors make a diagnosis of a pathology mostly looking at the morphological aspects of a tissue or of single cells through an optical microscope (OM). Of course, other macroscopic, complementary investigations, can be performed, and often are, (X-ray, PET, NMR, ultrasound, etc.) to identify in an unambiguous way the disease. Supplementary analyses of molecular biology can be implemented, but the results are actually only a list of numbers: the transformations into numbers of signals that are obtained by the "stimulation" with "ad hoc" reagents of blood, cells, fluids, etc. That means that biologists and medical doctors don't see anything and must be able to interpret the pathological meaning of those numbers in order to issue a diagnosis.

In few cases, medical doctors (microscopists, to be sure) obtain further cell images through a transmission electron microscope (TEM), but the scope of such observation is extremely limited and many samplings and observations are necessary to detect and show significant, pathological pieces of evidence. Histopathologists developed methods to fix and dehydrate biological samples. For the OM observations, a process of cell-staining is necessary, since the thin slices (4-10 micron) obtained by cutting the sampled pathological specimen look transparent under that instrument. Staining has the great advantage of showing various parts of the tissue in question in different colors. The most commonly used chemicals are hematoxylin and eosin, respectively basic and acidic stains, capable to reveal the structure of the cell membranes, the nucleus and other cytoplasm structures. More special dyes can show other biological entities like fungi, and bacteria. Then, there are methods of immunochemistry to reveal small entities that could not be seen with an optical microscope: attaching identifiable small gold or silver nanoparticles to these structures, we get the indirect proof of the presence of some molecular structures.

OM has an important limit: resolution (Resolution (r) = 0.61λ/NA where NA is a general term for the microscope numerical aperture, and λ is the imaging wavelength.) When magnification is pushed beyond the limit imposed by the wavelength of visible light, or, to be sure, the light used for that observation, nothing is actually visible anymore.

That means that between the histopathological observation through OM and the previously-discussed analyses of molecular biology a dimensional gap exists of at least 4-5 orders of magnitude. That is a "black hole" of knowledge, and in its span we can't see what is inside the tissue and the cells.

The "unorthodox" morphologies that we glimpse with OM can hide something else, something that may be responsible for their being "unorthodox" and for the formation of as "unorthodox" molecules. With an observation that makes use of light we can't see the nanometric and atomic structure of what we observe and 4-5 orders of magnitude are a yawning three-dimensional gulf that can contain organic and inorganic entities that can be important and that escape attention.

This challenge was (and keeps being) intriguing and we decided to explore this space that we knew not to be empty and devoid of information. A new "magnifying glass" was necessary: a glass adopting a smaller wavelength (smaller related to that of the light of OM). We knew that the electron wavelength is λ=hp where h is the Planck's constant and p is its momentum.

This formula to evaluate λ is called the de Broglie relation, and λ is called the de Broglie wavelength of the electron. There is a direct correlation between the velocity of the electron and the wavelength: "slowly moving electrons have a large wavelength, and fast moving electrons have a short wavelength."

With a suitable voltage, λ ≈ 10−10 m, where m is the electron mass, it can be done [3]. while visible light has a wavelength which is about 5,000 times as large. The use of a scanning

electron microscope applied to the biological sections of a sample used to make a histopathological diagnosis allows to identify both the biological structures at a much higher magnification and detect exogenous particulate matter, if there are any.

It is highly possible that no medical doctor takes that into consideration, since the interactions between the environment - and micro- and nanoparticles in particular - and the body are not part of any syllabus in any university or, when the subject is mentioned, it is done in a superficial way to say the least. They know that there are lung pathologies due to the exposure of the body to an environmental/occupational pollution like asbestosis, silicosis, talcosis, and berylliosis classified as pneumoconiosis. Those who have a more specific cultural background show some interest in the pathogenetic mechanism and know that those pathologies can result in cancer. But in most cases, that is all.

As a matter of fact, pathologies caused by the exposure to environmental pollution cause 7 million deaths/year [4,5]. Those deaths that are certainly caused by lung pathologies like development of respiratory diseases including acute respiratory infections and chronic obstructive pulmonary diseases (6% - lung cancer; and 3% - acute lower respiratory infections in children, 11% chronic obstructive pulmonary disease); but also by cardiovascular diseases (40% - ischemic heart disease; 40% -stroke). The interaction of this kind of pollution is not limited to the anatomic structures where particles stop, be it for a while or for good, but systemic.

The pathological mechanisms of those pollutants are largely ignored by medical science and do not seem to interest much medical doctors, since their mission is patient care through the appropriate pharmacological treatment. But drugs may be useless if the cause of the pathology is unknown, and useless drugs are harmful in any case, since there are no medicaments free from side effects. So, there are circumstances when, after having had to verify the failure of the attempted treatment, old medicaments used for entirely different pathologies are tried, hoping they work. That is the case with recent viral infections.

In other cases, some scientists invoke a genetic aetiology, a hypothesis supported by the identification of the alteration of a particular gene, but never or very seldom do they consider the possibility of an epigenetic effect due to a deep interaction of particulate pollutants with the DNA.

Our nanopathological studies performed via electron microscopy on more than 5,000 cases of different pathologies that in most circumstances left doctors at a loss show very often the presence of micro- and nanosized foreign bodies in the pathological tissue. In cases of primary cancer tissue, we see those pollutants at the border between the healthy and the ill tissue. This specific localization can have a meaning in the evolution of the disease.

In fact, our electron-microscopy morphological observation shows that tissues trap particles. Then, because of their tiny size, there is a non-negligible probability - and we showed it - that some of them are engulfed by cells and internalized in their cytoplasm, thus interacting with organelles and proteins. Our studies within the European Project DIPNA [6] verified that those non-biodegradable foreign bodies, once inside cells, do not kill them. During cell mitosis, when the nuclear membrane disappears, a close interaction of these foreign bodies with the chromatin and filaments of DNA is very likely. This nano-bio-interaction can induce epigenetic effects: effects that can be triggered by a physical-chemical interaction of the material with the DNA, an interaction we have photographed, that can induce a possible unfolding of the proteins having them lose their functionality [7].

The possibility to look inside this dimensional gap shows how intimately the particulate matter and the cell interact, but shows also how wide and deep the internalization of those pollutants inside the body is. We found foreign bodies inside pathological tissues of virtually any tissues, mainly, though certainly not only, tissues affected by cancer or by unknown (orphan) pathologies. Investigations on many different tissues including the blood, on many organs including the brain, on the seminal fluid, on the bone marrow, on the spinal fluid revealed the presence of very odd foreign bodies (regarding chemistry, size and morphology.) A recent study of ours about SIDS (Sudden Infant Death Syndrome) we are still being busy with showed the presence of nanoparticles in the brain of babies born a few days or, at most, a few months. These pieces of evidence make us think that this particulate pollution can pass, during the pregnancy, from the mother to the embryo through the fetal circulation. These findings give us a new possibility to understand the possible mechanisms of the evolution of that pathology.

The study of the chemical compositions of the particles we keep detecting reveals how polluted our world is and how the new technologies (nanotechnologies, in particular) are responsible for an environmental/occupational pollution Man had never experienced in the past. We found uranium in some patients, tungsten or zirconium in the pathological tissues of soldiers exposed to the new war pollution, nanoparticles of platinum and cerium in the diesel fumes, europium, dysprosium and other rare-earth elements in people working in the production of new microprocessors. Stainless steel (alloy of iron-chromium-nickel) is ubiquitous.

In many cases, the chemical identification of the internalized pollution allows to trace it back in the patient's life and environment. This allows to put in place forms of primary prevention and, in some circumstances, to eliminate that pollution from the patient's environment, food or drugs. Such knowledge can improve the patient's conditions, particularly when the point of no return has not already been reached. And we had also cases of complete recovery.

The "black hole" can be explored through the electron scanning microscope analyses offering a novel, powerful aid to reach a correct diagnosis of a non-negligible number of pathologies, thus helping doctors and, which is more important, patients.

[1]At present we use a Field Emission Gun Environmental Scanning Electron Microscope (FEGESEM) that accelerates the electrons approaching near-atomic resolution.

[2]Analyses obtained with an X ray microsensor of a Energy Dispersive System (EDS) that identify all the elements composing the particles.

But industries busy on health care can also get great advantage by the implementation of that technique and, with them, all technicians and decision makers who will have precious information available to prevent pollution or get rid of it when, unfortunately, pollution is already there. Finally, it would be extremely useful if a study of systems to free the organism from polluting particles already present in the tissues could be carried out. Yes: there is much to do.

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