MULTIPLE SCLEROSIS

Multiple sclerosis (MS), also called multiple sclerosis plaque, disseminated sclerosis or polysclerosis, is a chronic autoimmune demyelinating disease which affects the central nervous system causing a wide spectrum of signs and symptoms. The disease has a prevalence that varies between 2 and 150 cases per 100,000 individuals.

A north-south gradient in the northern hemisphere and a south-north gradient in the southern hemisphere has been verified. Populations living near the equator are less likely to be affected by multiple sclerosis. To explain this, at least in part, the lack of sunlight and reduced vitamin D assumption as a factor responsible for the disease, have been proposed . The ability of vitamin D to inhibit the formation of certain biofilms could credit the thesis of an infectious causality .

A genetic predisposition has also been attributed to MS.

Mutations in the HLA region of chromosome 6 increase the probability of multiple sclerosis, a series of genetic variations have demonstrated the capacity to increase the risk of developing the disease. The risk is higher in the relatives of a person affected than in the general population, particularly in the case of siblings, parents and children. This, however, can also lead one to think of infectious factors transmissible via transplacental.

Serious stress can be a risk factor and vaccinations too have been studied as causative factors of the disease, once again these observations can lead to an infective cause.. A hypothesis with which I agree proposes that the disease is due to a more common pathogen agent in regions with high prevalence of multiple sclerosis and it is assumed that this pathogen in most subjects causes a persistent asymptomatic infection and that, after many years and only in a few cases, involves axon demyelization. This hypothesis may be associated with a bad hygiene status. Individuals who have never been infected with the Epstein-Barr virus present a reduced risk of developing the disease, but this virus's infection is predisposed to other chronic infections .

Nerve cells transmit electrical signals, called action potentials, through long fibres called axons, which are covered by an insulating substance, the myelin sheath. In the disease, the patient's immune defences attack and damage this sheath. When this happens, the axons are no longer able to transmit the signals effectively.

Multiple sclerosis is thought to be an immune-mediated disease caused by a complex interaction between infectious agents, an individual's genetics and environmental factors .

Lesions

The name "multiple sclerosis" refers to scars (sclerosis - better known as plaques or lesions) that are formed in the nervous system. More often, the lesions affect the areas of white matter surrounding the cerebral ventricles or located at the cerebellum level, the brainstem, the base nuclei, the spinal cord and the optic nerve. The function of white matter cells is to propagate the signals between the

gray matter areas, where the processing takes place, and the rest of the body. The peripheral nervous system is rarely involved.

The myelin sheath acts as an insulator and allows a rapid conduction of electrical impulses along the nerve fibre. In particular, in multiple sclerosis there is the destruction of oligodendrocytes, the cells responsible for the creation and maintenance of a lipid layer known as myelin sheath, which allows neurons to transmit the action potential along the axon at high speed. The result of multiple sclerosis is a complete loss or thinning of the myelin sheath that occurs as the disease progresses . When myelin is lost, a neuron can no longer conduct electrical signals effectively. A repair process, called remyelination, occurs in the early stages of the disease, but the oligodendrocytes are not able to completely reconstruct the myelin sheath of the cells. Successively repeated attacks may result in less effective remyelination processes, until a plaque-like scar is formed around the damaged axons.

In a healthy individual the conduction speed of the neuronal electrical signals is 100 m/s, in a person affected by multiple sclerosis the speed gradually drops to 5 m/s. In the early stages of the disease, the slowing of conduction may simply be due to tissue edema, which may eventually decrease. In these initial phases neurological disorders can therefore regress in parallel following edema re-absorption. In the disease's progression, when the conduction slowdown is mainly due to the destruction of the myelin sheath, the neurological deficit remains constant and currently there is no possibility of recovery.

In addition to demyelination, the pathological hallmark of the disease is inflammation. According to a strictly immunological explanation of multiple sclerosis, the inflammatory process is caused by T cells, a type of lymphocyte, that play an important role in the body's defences. In multiple sclerosis, T cells enter the brain through breaks in the blood-brain barrier. Tests on guinea pigs demonstrate a role also for B cells in addition to that of T cells in the disease's development.

T cells recognize myelin as a stranger and bind to it as if it were a virus, triggering inflammatory processes and stimulating the release of other components of the immune system, such as cytokines and anti-bodies. Their presence in the blood-brain barrier provokes a number of other damaging effects such as swelling, macrophage activation and activation of further cytokines and cytotoxic proteins. In this way the blood-brain barrier is also broken.

Microglial cells perform the function of antigen-presenting cells and initiate the inflammatory reaction against myelin, this is supported by numerous cell types, such as activated autoreactive T lymphocytes (CD4 helper-inducer and CD8 cytotoxic-suppressor), arriving at the nervous tissue from the periphery through the blood-brain barrier and produce pro inflammatory cytokines such as TumourNecrosisFactor (TNF-α). Other cells responsible for inflammation are: monocytes, which reach the nervous tissue from the periphery through the blood-brain barrier and engulf the myelin fragments; resident B lymphocytes, which produce antibodies; polymorphonuclear cells, which release cytotoxic and cytolytic substances. Myelin disintegrates into fragments that are subsequently phagocytosed by macrophages and activated microglia cells .

Once the inflammatory phenomenon is reduced, there is an attempt to restore the axon's myelin sheath, with a partial or complete restoration of the neuronal function. However, as a result of

numerous repeated attacks, it is possible to incur permanent neuronal damage. Other frequently affected structures are the optic nerves, the optic chiasm and the spinal cord.

Clinical medicine

Multiple sclerosis can affect any area of the central nervous system, thus from a clinical point of view, be characterized by a great variety of signs and symptoms.

A sufferer can present almost any symptom or neurological sign, such as sensitivity loss, tingling, prickling, numbness (hypoaesthesia and paresthesia), hyposthenia (muscle weakness), clonus, muscle spasms, difficulty in movement or difficulty in co-ordination and balance (ataxia), language problems (dysarthria) and dyskinesias, through cerebellum involvement or in swallowing (dysphagia). There are frequent signs of cognitive impairment that can be manifested as cortical dementia, characterized by disregard for the disease and a state of euphoria, or pseudobulbar syndrome, with uncontrollable weeping and laughing. Also the appearance of depression is frequent, even serious, both as a response to the reduced life quality and as a manifestation of brain tissue deterioration. There may also be sexuality disorders, such as impotence and loss of sensitivity.

Eye problems such as nystagmus, internuclear ophthalmoplegia, diplopia and optic neuritis may also be common. The latter is one of the most frequent signs of onset of the disease and involves vision disorders, such as blurred image often accompanied by pain in the region around the eyes or bulbar movement. Examination of the visual field may result in the presence of central scotoma or, more rarely, hemianopia due to inflammation of the optic chiasm or of the optical pathways; rarely one has complete loss of vision.

The disease can also lead to difficulty in bladder control and intestinal problems with constipation, diarrhea or real fecal incontinence.

Two characteristic, but not specific, clinical signs of multiple sclerosis are the Uhthoff sign, an exacerbation of existing symptoms due to exposure to higher than usual environmental temperature and the Lhermitte sign, an electric shock sensation that runs through the vertebral column and lower limbs as a result of bending or, more rarely, in neck extension. The most widely used clinical scale to indicate the disability progression and symptom severity is the Expanded Disability Status Scale or EDSS, proposed in 1983 by the American neurologist John Kurtzke .

Symptoms usually appear in episodic periods of acute deterioration, in a gradual and progressive deterioration of neurologic function or a combination of both. Multiple sclerosis relapses are often unpredictable and occur without warning and without obvious provoking factors, with a frequency rate rarely greater than one and a half episodes per year. Relapses are more frequent during spring and summer. Viral infections and stress can trigger an attack, in fact breastfeeding, vaccination and physical trauma are hypothesized as being responsible for relapse.

Depending on the course, one can distinguish different types of multiple sclerosis. However, it is not possible to classify it in one form or another at the first manifestation or the first "recurrence" and it is difficult to understand how it will evolve over time. The clinical course of multiple sclerosis varies from patient to patient and may change over time. In some cases there is severe disability after the

first attack, in other cases, after the first "remission", decades can pass without any symptoms showing.

The benign form is characterized by one or two or more relapses with complete remission. Diagnosis can be made only 10-15 years after the first symptoms appear. The onset of this form is for the most part of a sensory type, it is not invalidating or if so only slightly, even if in some cases it can evolve into a progressive form. This form affects less than 10% of cases.

The relapse-remittent form's symptoms progress temporally in its different clinical variants and about 80% of cases subsequently evolve into a progressive form after a transitional phase.

In most patients signs and symptoms tend to appear and disappear during the first few years from onset. "Recurrence" often manifests itself with the appearance of new symptoms or with the aggravation of pre-existing ones.

The complete or incomplete disappearance of the symptoms is indicated instead by the term "remission". A recurrence is followed by a period of remission. The interval between two relapses is not a constant datum, since it can go from a few weeks to a few years. In the early days the relapses are followed by a complete recovery, however, with the passage of time, the regression that follows the relapse tends to become less and less complete. The relapsing-remitting form is characterized by the absence of progression between one relapse and the other. (this too would be a goal of therapy).

After 5-10 years on average from its onset and in 85% of cases, the relapsing-remitting form may evolve into a secondary progressive form .

After a few years the relapsing-remitting form can enter a transitional phase where the attacks are repeated frequently, almost never entering into the quiescence state. The interval between relapses is very short and usually attacks tend to have the same target. This stage represents the most difficult condition because it corresponds to a constant worsening of the patient's condition, who is at high risk of developing secondary progressive multiple sclerosis .

The secondary progressive form presents itself with or without phases of relative remission, the recoveries are incomplete and one assists in a progression of deficits even in the periods between one relapse and the other.

The initially progressive form starts right from the beginning with a progressive trend characterized by possible phases of relative improvement and stabilization. This form occurs in about 10-15% of cases.

Diagnosis

Images obtained by magnetic resonance of the same section of the brain at monthly intervals. Light spots indicate active lesions due to multiple sclerosis.

Multiple sclerosis can be difficult to diagnose because its signs and symptoms may be similar to other diseases.

McDonald's criteria focus on a demonstration performed by clinical, laboratory and radiological data on the spread of multiple sclerosis lesions, over time and in space, to arrive at a non-invasive

diagnosis. However, some studies have stated that the safe diagnosis of multiple sclerosis can only be done in post-mortem or occasionally by biopsy, through which the typical lesions of the disease can be detected through histopathological techniques.

Clinical data alone cannot be sufficient for a diagnosis. The most commonly used tools for diagnosis are biomedical imaging and cerebrospinal fluid analysis. Magnetic resonance imaging of the brain and spinal cord shows areas of demyelination (lesions or plaques) and gadolinium can be administered intravenously as a double dose contrast medium to highlight active plaques and, by elimination, demonstrate the existence of old lesions not associated with the symptoms present at the time of evaluation. The demyelinating lesions, on magnetic resonance, appear as "brilliant" focal areas, more often irregularly shaped, ovoid or roundish, with a hyperintense signal in the T2-weighted sequences and mainly distributed around the lateral ventricles, in the white matter of the encephalic trunk, in the cerebellum and spinal cord. However, the traditional magnetic resonance examination does not have sufficient sensitivity and specificity to reveal the true degree of pathological changes typical of multiple sclerosis. New techniques, such as measuring T1-weighted hypointense lesions, diffusion tensor imaging DTI, magnetic resonance spectroscopy, magnetic susceptibility imaging, are being tested. Positron emission tomography is able to detect inflammatory lesions of the spinal cord, thanks to the fluorodeoxyglucose used as a radioactive tracer.

Cerebrospinal fluid analysis, obtained by lumbar puncture, can provide evidence of chronic inflammation of the central nervous system. The cerebrospinal fluid is tested for oligoclonal IgG bands in electrophoresis and inflammatory markers are found in 75-85% of people with the disease.

The nervous system of a person with multiple sclerosis responds less actively to stimulation of the optic nerve and sensory nerves, due to the demyelination of the latter. The speed of such brain responses can be assessed using visual and sensory evoked potentials.

Treatment

There is no definitive cure for multiple sclerosis. It is difficult to determine the therapeutic effects of experimental treatments, since it is a disease characterized for the most part by spontaneous remissions. However, the drugs used today are able to positively influence the course of the disease and reduce its activity, but still do not represent a definitive solution to the problem. The primary goals of therapy are to prevent new attacks and prevent disability. As with any medical treatment, the drugs used for multiple sclerosis have several side effects. Some patients follow alternative treatments, despite the lack of reliable scientific studies to support them.

In the management of acute attacks, Methylprednisolone, a corticosteroid used for the treatment of symptoms, is used. In the past, the main treatment of multiple sclerosis was steroidal anti-inflammatory drugs such as adrenocorticotropin (known as ACTH), prednisone, methylprednisolone , prednisolone, betamethasone and dexamethasone. Studies have shown that intravenous administration of methylprednisolone is more effective than intravenous administration of adrenocorticotropin .

During symptomatic attacks, the administration of high doses of intravenous corticosteroids, such as methylprednisolone, is the routine therapy for acute recurrence of relapsing-remitting disease, as it has shown efficacy in reducing the severity and duration of the exacerbations. High doses of methylprednisolone have also been shown to be effective in improving spasticity in progressive multiple sclerosis. Although generally effective in alleviating symptoms in the short term, corticosteroid treatment does not appear to have a significant impact on long-term recovery. Oral and intravenous administration appear to have comparable efficacy.

Therapies modifying the disease's evolution

Graphical representation of a Fingolimod molecule, a drug approved by the FDA in 2010 for the treatment of multiple sclerosis. Fingolimod works by preventing the passage of lymphocytes through the blood-brain barrier so that they cannot attack the myelin, directing them to the lymph nodes and the periphery. In spring 2017, there were about a dozen disease-modifying drugs approved by the control agencies of different countries , including the European Medicines Agency and the USA Food and Drug Administration (FDA).

The seven approved drugs are interferon beta-1a, interferon beta-1b, glatiramer acetate, mitoxantrone (an immunosuppressant also used in chemotherapy), natalizumab (a humanized immunomodulatory monoclonal antibody that prevents T cell migration from circulatory flow to the central nervous system), fingolimod and teriflunomide, respectively the first and the second oral drug to be available. Most of these drugs are only approved for the relapse-remission form.

All the drugs listed above, even if with different mechanisms, are useful in reducing the number of attacks in relapse-remission multiple sclerosis even if with different pharmacological efficacy, moreover studies on their long term effects are still limited. Treatment of progressive multiple sclerosis is more difficult than relapse-remission multiple sclerosis.

Mitoxantrone has shown positive effects in patients with secondary-progressive and progressive-relapse forms. It has indeed been shown to be moderately effective in reducing the progression of the disease and the frequency of relapses in a short follow-up period. No treatment has proved capable of modifying the course of primary-progressive multiple sclerosis. Several studies have been carried out on the possible treatments specific for this form, including some studies with interferon and mitoxantrone, a phase III clinical trial with glatiramer acetate and another research that uses riluzole. Some patients with primary-progressive multiple sclerosis were included in studies using azathioprine, methotrexate, cladribine, immunoglobulin administered intravenously, cyclophosphamide, and hematopoietic stem cell transplantation tests. However, no proven treatment has shown the ability to change the disease's course.

As with many medical treatments, these drugs have several side effects.

There are numerous publications in the medical literature that describe the role of oxidation and lipid peroxidation in the evolution of multiple sclerosis. What has not yet been shown is whether an improvement in the antioxidant status of patients with multiple sclerosis could influence the progression of the disease. The antioxidants commonly used include selenium and vitamins A, C and

E. Other components belonging to the antioxidant category are lipoic acid, inosine, uric acid and coenzyme Q-10.

However, many antioxidant components activate immune cells such as T lymphocytes and macrophages in the first place. Such cells are already excessively active in the disease and their stimulation could potentially exacerbate it. According to International Medical and Scientific Board (IMSB), there is experimental and theoretical evidence that antioxidants may have therapeutic significance in multiple sclerosis. On the other hand, no well-defined clinical studies have been conducted to indicate whether antioxidants are actually safe and effective in the disease.

Symptomatic therapies

Disease-modifying treatments can reduce the rate of disease progression, but not stop it. With the progression of multiple sclerosis, its symptomatology tends to increase. The disease is associated with a variety of symptoms and functional deficits that result in a series of progressive impairments and disabilities. Management of these deficits is therefore very important. Both drug therapy and neuro-rehabilitation have been shown to relieve some symptoms, even if they do not influence the disease's progression. Some symptoms, such as urinary incontinence and spasticity, have a good response to drugs, while the management of many others is more complex. People affected by multiple sclerosis also require treatment for possible collateral diseases, from urinary tract infections to bedsores. Muscle relaxant drugs and physiokinesitherapy have proved to be very useful against limb spasticity. In the context of symptomatic therapies, it is possible to use, depending on the type of disorders and their entity, drugs for spasticity, fatigue, bladder dysfunctions, sensitivity disorders and so on.

Supervised physiotherapy can be useful to improve some consequences of the disease.

With regard to people with neurological deficits, it is believed that a multidisciplinary approach is the key to improving the quality of life. However, there are particular difficulties in specifying a "central team", as patients affected by the condition may need assistance from almost all health professions at some point.

Cannabinoids

There is numerous anecdotal evidence of patients suffering from multiple sclerosis who report a symptomatic benefit following the intake of cannabinoids, especially regarding spasticity and neuropathic pain. These substances exert their therapeutic effect through the stimulation of cannabinoid receptors (CB1 and CB2), whose activation has shown, in experimental models, to have an important role in counteracting demyelinating inflammatory processes.

In recent years, numerous controlled clinical trials have been conducted, the results of these studies are partly contradictory, but overall confirm the effectiveness of cannabinoids in reducing spasticity and associated symptoms, with a good safety and tolerability profile. The discordant results are explained by the fact that spasticity is a very difficult symptom to be reliably and objectively assessed.

The most frequent cannabinoid side effects seen in about 10% of patients are fatigue and dizziness, mental disorders and dry mouth. No significant side effects on cognitive function were observed, with a modest overall toxicity. Side effects are generally reduced after the first week of therapy.

At present, cannabinoid treatment is therefore recommended as a second-line therapy for the treatment of spasticity and neuropathic pain in patients who have experienced conventional treatments without success.

Vitamin D

Vitamin D, especially in its D3 form, cholecalciferol , could be used in the treatment of multiple sclerosis due to the immunomodulatory effects it has on chronically activated T cells.

While low levels of vitamin D are correlated with a higher risk of contracting multiple sclerosis and in a more severe form, elevated levels appear to be associated with fewer relapses, fewer new injuries and better clinical and movement conditions. A 2012 study found that for each increase of 10 ng/ml of vitamin D in the blood, the risk of new injuries decreases by 15% and the risk of relapse by 32%.

This could indirectly give credit to infection as causality.

The life expectancy of people with multiple sclerosis is 5 to 10 years lower than that of unaffected persons. Almost 40% of people with the disease reach the seventh decade of life. However, two-thirds of patients' deaths are directly related to the consequences of the disease. Suicide rates are higher than those for the healthy population, while infections and complications are particularly dangerous. Suicide can also be seen as an infectious component of the disease.

The name multiple sclerosis is derived from the scars (sclerosis, better known as plaques or lesions) that are formed in the white matter of the spinal cord and brain. Even if the mechanism by which the disease manifests itself is well understood, the exact etiology is still unknown. The different theories propose both genetic and infectious causes, and correlations with environmental risk factors have been highlighted. A more coherent assumption should find a way to draw in all these causalities. That is a certain genetic predisposition, in a given environment allows an infectious agent with specific characteristics to alter the privileged immune system of the central nervous system and the permeability of the blood-brain barrier, leading to an autoimmune pathological form, Multiple Sclerosis.

The infectious hypothesis has the same agents that create neurological pathologies in animals for which it can be considered a zoonosis and the treatment is related to that used in veterinary for these forms. In light of these aspects veterinarians can be indirectly involved in expressing considerations about MS.

The disease can occur with a very wide range of neurological symptoms and can progress to physical and cognitive disability. Multiple sclerosis can take many forms, including recurrent and progressive ones. To date, 2018,there is no known cure. Some pharmacological treatments are available to prevent new attacks and prevent disabilities, but the prognosis is difficult to predict and depends on

many factors, while life expectancy is about 5 to 10 years lower than that of the healthy population and often with severe handicap.

In progressive forms of multiple sclerosis we know that there is still a harmful inflammatory activity in both the brain and the bone marrow.

Stem cells and Multiple Sclerosis

Stem cells, in animal models of the disease, have been shown to be able to fight this type of inflammation. In addition, always in animals, we know that, once the stem cells have entered into the nervous tissue, they are also able to stimulate the production of neuro-protective substances, that can prevent and reduce myelin damage and, consequently, the axons too.

Therapeutic attempts that were made with **embryonic pluripotent stem cells** triggered an ethical question, but above all had caused side effects greater than the curative effects, so the direction was towards **adult stem cells** . The main objective of regenerative medicine research was the adult pluripotent stem cells, that is stem cells present in the by now conformed organism that can change themselves into every cell type. But the adult stem cells so far isolated and studied are **monopotent** that could only change themselves into a single cell type such as those of the dermis, the **hematopoietic** that can change themselves into every blood cell and the **mesenchymal** that have the characteristic of changing themselves into bone cells, cartilage, tendon, ligaments or muscle tissue. But it was important to have cells that interacted with other tissues such as hepatic, renal, cardiac, etc... and above all nervous tissue, both to treat nervous pathologies and to act on the autonomous nervous system that regulates all organic functions and therefore directs healing, for this it was important to find **adult pluripotent** stem cells.

Not being found in a suitable quantity in the conformed organism, another path was sought and some years ago the Nobel Prize was awarded to J. Gurdon and S. Yamanaka for having found the system of obtaining **induced adult pluripotent stem cells** by binding the pluripotency factors of embryonic stem cells to viruses and hybridizing some adult stem cell clones. But these cells had the same contraindications as the embryo ones . They created teratomas and triggered the characteristic reactions of allogeneic stem cells (belonging to another individual), the greater the allogeneic cell regenerative potential, the greater the side effects, besides there was the virus factor that brought them back to a gene therapy with all the contraindications of the case. Subsequently, it was possible to obtain induced pluripotent ones without using viruses, but the side effects were the same therefore one tried to eliminate these negative effects by eliminating one of their 4 pluripotency genes, c-MYC, which is a proto-oncogen. that is, it has the ability to transform a normal cell into a tumour and create the teratoma. Once the c-MYC gene was eliminated, the teratomas did not occur, but neither did the desired regenerative effects.

The research then used these induced pluripotent cells to produce various specific tissue cell types and directed itself above all to the cardiac ones and even more to the nervous ones that could help very serious pathologies. But these latter cells did not give the hoped for results, and it was thought that, amongst other things, these manipulations had rendered them less “efficient" and because the

results with cells obtained from induced pluripotent stem cells in neurological diseases were insufficient research passed onto the use of **neural stem cells obtained from abortive fetuses.**

What stem cell types have been and are mainly being used in multiple sclerosis research so far?

1-Neural stem cells, derived from the central nervous system (NSC) that foresees the use of cells extracted from brain tissue of fetal origin, therefore allogeneic.

2-Mesenchymal stem cells, extracted from the bone marrow and destined to give rise to muscles, bones, cartilage and connective tissue (MSC).

3-Hematopoietic stem cells, precursors of blood cells, also derived from bone marrow (HSC).

The neural stem cells of fetal origin are cells obtained using expensive processes and inoculated in diseases such as multiple sclerosis do not seem to give the desired results even if experimenting continues. But even in the case that the neural stem cells were obtained and re-inoculated in the same individual, therefore autologous, no progressive therapeutic results would occur. This is because exclusive relevance is given to the alteration of the nervous component without considering the value of the other tissue alterations implicated in multiple sclerosis (MS).

It is recognized that one of the most accredited causes of MS are triggering infectious factors, these produce an inflammatory reaction that induces encephalic barrier permeability allowing the introduction of new inflammatory factors predisposed to an autoimmune disease. However, even by excluding infectious causality, the privileged immune system of the Central Nervous System (CNS) and the vascular patency of the blood-brain barrier are altered in MS. If one does not also intervene on these vascular and immune alterations that inhibit the functionality of the neural stem cells already present, the new neural stem cells introduced would undergo the same involution making progressive improvement difficult .

Neural stem cells of fetal origin are allogeneic cells, that is, obtained from another individual, the greater the allogeneic stem cells energy is the greater the contraindications are. So it is better to inoculate allogeneic neural stem cells that have less energy than allogeneic pluripotent stem cells such as embryonic stem cells. I stress again that the costs of producing neural stem cells of fetal origin are considerable and in fact few cases are treated.

Another negative point is that the stem cells used so far in MS , autologous or allogeneic, are always purified and placed in terrain suitable for their growth or simply their nutrition. These terrain are foreign to the organism and create reactions, imagine putting these terrains containing the cells directly into the Central Nervous System.

Recently a drug used in veterinary medicine based on blood mesenchymal stem cells, allogenic, purified, placed in terrains extraneous to the body and frozen for intra-articular inoculation, has been approved Side effects are almost inevitable and could be exploited, as were the errors and limits of “Stamina " in Italy, to demonize regenerative medicine, to delay the blood stem cells therapy revolution that will lead to a change in the medical paradigm.

What are the possible risks to date for the use of stem cells in MS?

After transplant, the main risk factors are linked to the possibility of uncontrolled cell development with the consequent possibility of tumour growth (for example, teratomas manifested after inoculation of embryonic stem cells that are pluripotent or better totipotent and allogeneic) .

Another risk is the Graft Versus Host Disease, a particular immune rejection, resulting from the inoculation of allogeneic stem cells .

For hematopoietic stem cell transplant there is another possible risk element linked to the growth factors administered in vivo to obtain them. That is to stimulate the production and release of cells from the marrow to the blood.

So far stem cells are taken from the tissues that contain them and then stimulated in the laboratory (in vitro) to grow, proliferate and differentiate, when reaching an amount judged sufficient, they can be transplanted into the patient with an intravenous injection or through more complex interventions aimed at concentrating the cells in a particular organ.

Ultimately the major side effects are in the inoculation of allogeneic stem cells and are directly proportional to their potential, a totipotent embryonic stem cell has more contraindications than an allogenic stem cell that can transform itself into limited cell types, such as neural ones.

In the treatment of MS there are three possible injection routes used so far: intravenous, intrathecal, that is injection into the space surrounding the spinal cord; intraparenchymal, that is direct injection into the brain and spinal cord.

So far, what is the hypothesized action of stem cells in multiple sclerosis?

One theory speaks of neuro-protection, that is, one conceives using stem cells as a source of new myelin to slow down, or even block, the loss of axons and another theory thinks of immunosuppression, that is exploit their anti-inflammatory and immunomodulatory activity to protect nervous tissue. Only in the future will it be thought possible to achieve a re-myelination effect, leading to restoring the damage responsible for permanent disability.

Which of these limitations can be overcome with blood stem cells?

- Stem cells obtained by de-programming blood are autologous, that is, of the same individual to which they are re-inoculated, and are of three types: hematopoietic, mesenchymal and adult pluripotent that constitute a network that can act not only nerve cells, but also on the vascular system, the immune system and in general on the connective. Any kind of "accurate" therapy, meaning limited to a single agent and addressed to a single point, has logical limits: to act on a network and the body is a network, one can act only with a network.

- They are contained in autologous serum so there is no need to add culture mediums foreign to the organism. Any form of rejection is thus overcome and we could consider this therapy a self-transfusion with a cellular component of the increased blood: stem cells.

- You can get them easily so no need to conserve them through freezing.

- The factors that produce the de-programming are natural, in infinitesimal quantity and are no longer present at the time of inoculation.

- Sample taking is non-invasive, in fact it is not necessary to drill a bone, neither inoculate growth factors into the patient and there is no need to have fetal stem cells available.

- Preparation is much simpler, the cells do not need to be cultured to grow them, they do not need to be different and can be obtained without the need for a laboratory after the blood sample has been taken, in fact manipulation is minimal.

- As I have already said blood stem cells are not of a single type, they are haematopoietic and mesenchymal that can have influence on the connective, on vascularization and on the immune system with immunomodulatory effect, but the third component is the most interesting ... pluripotent stem cells, which can interact with the nervous system. This component is important because it not only acts on nervous tissue when it is pathological, but also regulates the autonomous nervous system that enters into every physiological process and therefore regulates the healing of each anatomical district. They are qualifiable cells because they only have staminal receptors therefore they can be used in experimenting and can be patented.

- The extraordinary effects obtained in diseases that are difficult to cure in veterinary medicine are explained by current physics: stem cells are not bricks so they do not have to go to the diseased tissue ... but must give information.

In the light of these characteristics it is clear that blood stem cells represent a breakthrough in regenerative medicine overcoming all the previous techniques' limitations.

So far we have seen that a single stem cell type has always been used as a therapeutic aid in MS. Neural stem cells of fetal origin, which are allogeneic, obtained using extremely complicated and expensive systems, have been used. But, regardless of these limiting reasons, one may ask.... even if these neural stem cells inoculated in situ reactivate demyelinated nerve cells, who will think about correcting everything that resulted in the demyelination, that is how will the complex pathological interaction surrounding the lesion and likely caused it, be replaced ?

If we consider the complex network linked to the interaction between the patient and pathology, between healthy tissue and diseased tissue, between the various elements of the same pathology, one is more likely to obtain a regenerative result not from a single element, but by a "therapeutic network" composed of different types of stem cells providing greater "therapeutic stem cell plasticity". It is precisely their plasticity that in recent years has changed the way we perceive the healing potential of stem cells once they have been transplanted.

So we arrive at another vision of regenerative medicine: stem cells are not bricks to restore a wall that crumbles, but orchestra directors who organize healing. Therefore, the less they are directed the better their action will be, according to this idea one understands the importance of **the information** brought by the stem cells. There is a change of paradigm that opposes the uniqueness of the chemical or biological drug.

The new information concept is not linked only to chemical messages and introduces us to the new realities of modern physics. To the network of autologous stem cells a biophysical effect from a distance is attributed, Entanglement. It is obvious that an allogeneic subsystem cannot manifest entanglement with the organism with which it is put into contact because there has been no previous interaction with it, so there is no sharing of informative energy that serves to complete a common design. Entanglement is a real scientific phenomenon and it allows us to not inoculate these cells in situ and obtain the same therapeutic effects even beyond the blood-brain and blood-ocular barriers. Therefore the number of cells administered becomes relative, it is important that they reach the quantity that will overcome the activation threshold.

In my experimenting I noticed that inoculating the blood stem cells in the parenchyma of the tendon vein gave much lower results than stem cells inoculated in the peri-tendinous tissue .

For systemic diseases, inoculation gives good results not only if done intravenously, but also simply intramuscularly.

I now show some of the publications where the materials and method obviously are incomplete .

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The therapeutic protocol was obtained after treatment over 10 years on 20,000 cases of dogs and horses with over 100,000 inoculations, intravenous, intramuscular, subcutaneous and peri-lesional.

We have had no side effects, no tumours or teratomas were manifested and we have not been cited in any lawsuits or even trivial disputes. Teratomas are tied to stem cells with a high energy charge like the embryonal totipotent, but to manifest themselves the stem cells must be allogeneic, that is there must be a conflict of information. The fact that this number of cases has been made and that the requests increase exponentially day after day only by word of mouth between one animal owner and another and now they are also requested for prevention, shows what tangible effects they have given .

Some horses and dogs that we have repeatedly inoculated with autologous blood stem cells more than 20 times over 10 years have shown no side effects and we have a horse that remained in competition until it was 21, now it is 24 years old. The treatment was done more than 40 times in the period between 14 to 24 years.

The only side effects that occurred where when stem cells obtained from allogenic blood, that is not autologous, were used, which in some subjects caused the graft versus host disease (some years ago allogeneic stem cells were legal in veterinary medicine, now they are not anymore). The subjects who were affected by this autoimmune disease and survived only due to immunosuppressive therapy, then returned to being complete normal after inoculation of the their own stem cells deprogrammed from their blood, therefore autologous, because of their immuno-modulating effect.

The animal models that we present carry immune-mediated diseases beyond the blood-ocular barrier and diverse effects on various neurological diseases.

Conclusions

Therapy with blood stem cells in MS will have a different effect depending on the disease's type of manifestation and in virtue of its stage, patient's age, etc.... what we propose as the first result is to counteract the disease's progression and see if in some cases it can be reversed. From similar clinical cases in veterinary I hope that positive result can be obtained in a percentage of patients affected by MS especially in the relapsing phase, but perhaps also in the progressive one if the anatomical damage is still reversible or if there is still a possibility of a functional compensation.

The videos I showed on the Web indicate that this is the future of medicine and the future cannot be stopped, the completion of the regenerative treatment is in considering these cells as orchestra directors and not as bricks to reconstruct a wall.

These results have been reached because the current medical paradigm has been completed and is based on the new knowledge of modern physics.

Physics is the science that tries to explain the phenomena that regulate Nature, so that even biology and medicine rest on this science. Medicine is based on Newton's mechanistic physics that was actual 120 years ago. This physics has not been erased by modern physicists' theories, but has undergone a gradual completion passing from Newton's physics to Einstein's relativity, Bohr's quantum physics, Bhom's quantum potential, attractor physics and fractal physics. In each passage there was not conflict but completion. Adapting medicine and biology to this transformation implies a leap that

destabilizes those who place their beliefs exclusively in mechanistic physics and in the single point treatment of a complex network.

To give you an example of the new reality on which this regenerative therapy is based I cite the non-local biophysical effect, the Entanglement of modern physics, which I already mentioned, is effective beyond the blood- brain or hemato-ocular barriers without inoculating stem cells in situ. This principle may seem counter-intuitive but, beyond any reasonable doubt, has been shown to be real.

To continue with this experiment we must define our common ends. The Institute that will carry out the experiment, the pharmaceutical company that has advanced it and the inventor will fulfil their objective and, above all, resolve in a non-invasive way one of the many pathologies, in this case we are contemplating MS, that cause suffering to humanity. Moreover we will put into practice the empathy and compassion towards the patient that so many biologists and doctors have forgotten.

If instead of finding common ends a conflict occurs, we will end up with nothing. In the sense that what I have put forward can be considered anecdotal or unscientific only because it does not fit in with the current medical paradigm, but also the doctor who embodies this new vision can consider current medicine a science outdated by 100 years by its not adapting to the new physics' discoveries.

If we consider together this new therapy as a complement of the current medicine paradigm, together we can assess the excellence in human medicine in this disease and we will work to get the best possible results, we will be able to make medicine take a huge leap forward therefore completing not opposing the old paradigm.

I end by simply explaining the meaning of this therapy by reintroducing an example by David Bhom .Imagine a ship made up of matter and driven by its engines' energy. In a critical situation of storm and thick fog.... with its solidity, full fuel tank and perfectly efficient engines it would never reach port if it did not have the radar's subtle energy.

The subtle energy of the radar is informative energy, the energy that belongs to the network of stem cells obtained from blood.

If we now consider Entropy, the gradual degeneration of a system towards the maximum balance and immobility, this value will be close to zero in the fetal state where there are pluripotent stem cells that produce informative energy. In a non-isolated physical system there are two competitive processes, one that increase entropy and the syntropic one that limits it.

$$\text{Informative energy} = \frac{\text{Syntropic energy}}{\text{Entropic energy}}$$

In a simpler way, in the fetus there is a very high vital energy while in the elderly it decreases. The fetus is rich in pluripotent stem cells which are therefore rich in this energy. In fact in the fetus there are no tumours, but only malformations or abortions. If we transform some of the stem cells from a blood sample, we produce a "moment" similar to the fetal environment....highly rich in vital energy and low in entropy .

This subsystem put into contact with the organism, for the second law of thermodynamics (natural processes tend to attenuate the irregularities present in the universe), influences the organism by increasing "informative" energy and decreasing entropy. It increases vital energy and contrasts aging and all that comes with it.