SCIENTIFIC RESEARCH INSTITUTE HANS SELYE

November 2th, 2023

To whom it may concern:

I, Dra. Susana Alcazar, MD., set forth within this document signed by me, that I am a business partner with Luminec Holdings and Luminec Pharmaceuticals and Mr. John Everding, Founder of both.

I am honored to hold board of director's positions in both companies. Further, our effort with this collaboration is to develop extraordinary pharmaceutical, nutraceutical, cosmeceuticals and holistic products for animals and humans fr om the base formulation already proven worldwide.

My sincere regards,

Dra. Susana Alcázar

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BTS & RESEARCH

Luminec Pharmaceuticals

COENZYMOTHERAPY AND ENZYMOTHERAPY

Background

Starting with Hans Selye's opinion on Medicine, he says that: "Current Medicine blinds itself against the disease (until it ends with it), forgetting about health. Medicine has to be able to ally itself with nature, helping it in its efforts, to safeguard health and fight against disease". Hippocrates already proposed with his famous aphorism: "first, no harm" (*primum non nocere*), which is a priority duty according to the medical ethical obligation of every physician.

Thus the coenzymatic and enzymatic therapy of Professor Heberto Alcázar-Montenegro, has given us the possibility, of achieving it, since its goodness has been confirmed, since the 1960s, as there is no risk of harming the patient with its application, neither in the short nor in the long term.

It can be used as the only therapeutic resource, or as an adjunct to other therapies, such as allopathy, homeopathy and those that are to come, that address the cause and prevent the disease.

—Dr. Susana Alcázar-Leyva

BTS RESEARCH

Luminec Pharmaceuticals

NUCLEASES, ENZYMES:
DEOXYRIBONUCLEASE (DNSM) AND RIBONUCLEASE (CRO-50),
Stable in Solutions

Nucleases activity (deoxyribonuclease and ribonuclease) within cellular homeostasis is the repair and metabolic regulation of nucleic acids: deoxyribonucleic acid (DNA) and ribonucleic acid (RNA); in its hydrolysis and synthesis, a significant increase in the metabolism of the nucleic acids is always accompanied by a corresponding increase in the appropriate nuclease.

The nucleases or restrictive enzymes recognize the specific sequence of DNA and RNA eliminating the segments of the damaged, transformed, aged and infected cells as well as neoplasic and carcinogenic cells. Therefore, they perform important functions such as: microbicide, anti-inflammatory and antitumoral.

It has been proven that in cancer there is a deficiency in deoxyribonuclease (DNase) or rbonuclease (RNase) activity. The decrease of these enzymes deter programmed cell death (apoptosis), it is inhibited in malignant cells avoiding their destruction. Therefore, its exogenous administration has proven effective in: cancer, viral and bacterial infections and inflammatory and autoimmune diseases.

Both enzymes only penetrate damaged cells (the damage is the signal), that is, a permeable membrane with a decreased membrane potential. Apoptosis is induced within abnormal growth cells; because of the capacity that the restrictive enzymes have to recognize and fragment the regions of DNA or RNA tumorals. Therefore, they have a selective effect, to recognize and eliminate the tumoral, aged, infected or damaged, cells, not the normal cells.

The application of deoxyribonuclease (DNSM) and ribonuclease (CRO-50) have made way for experimental trials that have obtained favorable clinical results, without side effects or interaction with other medication or therapy, in many patients.

For some time it has been known that both enzymes clinically liquefy exudates and purulent secretions, abscess and diminish the viscosity of mucus secretions, because of that we apply these enzymes locally or parenteral via (intramuscular and intravenous).
We have proven its autoimmune effect mainly in: Rheumatoid Arthritis, Systemic Lupus Erythematous, Multiple Sclerosis, Guillan Barré; due to its anti-mucolytic and anti-inflammatory effect, we have applied them in cases of: Pharyngotonsilitis, Bronchiolitis, Bronchitis, Pneumonia and Cystic Fibrosis, among others.

In cancer, leukemia's, lymphomas, melanomas and other benign or malignant tumor processes. In addition, the lytic effect of both enzymes has been demonstrated, *in vitro* in cancer cell lines: Hep-2, HeLa and L-929.

We have checked the antiviral activity of both enzymes. DNSM we apply in cases of DNA viruses, such as papilloma and herpes; CRO-50, in RNA viruses, such as influenza, respiratory syncytial, hepatitis, and HIV viruses.

Both DNSM and CRO-50 can be applied alone or together with X-2, both intramuscularly and intravenously.

—Dr. Susana Alcázar-Leyva

X-2

COCARBOXYLASE OR THIAMINE PHYROPHOSPHATE, STABLE IN SOLUTION

The cocarboxylase or thiamine pyrophosphate (TPP) is the biologically active form of thiamine (vitamin B1), essential coenzyme of energetic metabolism and cellular respiration. When the thiamine enters the organism, through feeding, is phosphorylated by ATP (adenosine triphosphate), in TPP or cocarboxylase. The TPP participates in the metabolism of the carbohydrates, by descarboxylating pyruvic acid (before it is transformed into lactic acid) in alpha ketoacids (alpha-ketoglutaric acid), promoting the production of ATP (high energy, phosphat doner) in the cycle of Krebs or tricarboxylic acid, in the mitochondria of all of cells of the organism. The TPP in the cytoplasm, participates in the formation and use of alpha ketoles, by means of transketolase (in the pentose's cycle), enzyme dependent of TPP, for the production of NADPH (nicotinamide adenine dinucleotide phosphate, reduced) and ribose-5-phosphate, pentose that forms a part of the nucleic acids: deoxyribonucleic acid (DNA) and ribonucleic acid (RNA). Thiamine and TPP are actively involved in the synthesis of neurotransmitters.

Thiamine and its esters (monophosphate, diphosphate or pyrophosphate and thiamine triphosphate), have a high degree of turnover in the body, since it is not stored in any organ or tissue for long periods (liver, muscles, among other tissues), so its continuous intake is necessary.

The main characteristic of X-2, whose formula is based on TPP, is its stability in solution, because the distance between its phosphate bonds is smaller, which allows greater potential for free energy. Therefore, it is indicated in conditions in which the immediate reactivation of the Krebs cycle is required, for the production of energy, in the form of ATP, whose hydrolysis is required for muscular contraction, transport of ions (active transport) and synthesis of proteins, mainly, to maintain homeostasis.

It is indicated and it has been applied for therapeutic purposes, mainly in: neonatal hypoxia, diabetes *mellitus*, coma, ketoacidosis, multiple trauma, encephalopathy's, liver disease, nephropathy, heart disease, pneumopathies, intoxications, intestinal malabsorption, neuropathies, neuritis, facial paralysis, preeclampsia and eclampsia, chronic alcoholism, before and after any type of surgery; and mainly before, during and after chemo and radiation therapy. Under conditions of stress, mental retardation, chronic fatigue, anxiety and depression.

In experiments, *in vitro*, *in vivo* and clinical, the stable TPP in solution, showed its energetic capacity by restoring the membrane potential (MP) in the lymphocytes of diabetic patients; in the liver, brain and cerebellum cells, on intoxicated rats with carbon tetrachloride (CCl4). In dogs myocardial heart attack was induced, proving that TPP improved cell viability in two ways: by reducing lactate levels, avoiding intracellular acidosis, and stimulating the production of ATP, achieving the remission of the ischemic process. In fibroblasts with oxygen radicals, its antioxidant action was proven by increasing the levels of GSH (glutathione) contributing to the body's antioxidant organism. In diabetic and non-diabetic patients, glycaemia and activity of glucose-6-phosphate dehydrogenase were measured, proving the incorporation of glucose into the cell, and the activation of the G6PDH and NADPH, necessary in the energy metabolism, depressed in these patients. Clinically they had a remarkable and long-term improvement, they avoided complications (retinopathy, neuropathy and nephropathy), which are produced by protein glycation and an inflammatory response due to advanced glycosylation products (AGE), which take place in diabetic patients.

The application of TPP is wide, because the common denominator of the pathologies can be:
- Loss of membrane potential (depolarization)
- Increase of Intracellular Na+
- Increase of permeability of the membrane
- Loss of negative charges
- Loss of the relation 3:1 (phosphorylations/oxidations)
- Increase of oxygen free radicals
- Blockade of Pasteur effect / Crabtree effect
- Blockade of neurotransmitter synthesis
- Ischemia / Inflammation

Other experimental tests consisted in the use of **X-2**:
- Induction of arteriosclerosis in dogs.
- Experimental heart attack in dogs.
- Active transport of Na+ through the bladder membrane of the *Buffus marinus* toad.
- Action from the cocarboxylase in perinatal respiratory problems, neonatal hypoxia.
- Cocarboxylase in pigeons that received a lethal dosage of cyanide.
- Consumption of glucose under the action of a non-degradable cocarboxylase using cyanide as a stimulant in cats.
- Effect of the non-degradable cocarboxylase on the incidence of arrhythmias in early stages of acute heart attacks in dogs. The effect of cocarboxylase on ventricular fibrillation in acute myocardial heart attack in dogs, double blind.
- Determination of glucose consumption variations of the electrophysilogical alterations of the aortic and carotid chemoreceptors, using cyanide on cats.

In Diabetes *mellitus*: Remission of diabetes in rats that where induced to diabetes, treated with cocarboxylase; as a regulator of carbohydrate incorporation into tissues; glucose activity dehydrogenase glucose-6-phosphate and transketolase in diabetic patients; Effect of the cocarbocylase on serum glucose in diabetic patients and healthy subjects; Evaluation and electrophysiological correlation of the effect cocarboxylase and the level of glycaemia in the diabetic patients lymphocytes; The relationship of MP and hyperglycemia in diabetic patient's lymphocytes; Decreased glycosylated hemoglobin in non-insulin dependent diabetic patients treated with cocarboxylase; X-2 as a treatment for diabetic patients with various pathologies: Metabolic and hormonal; Regulation of the MP in the neurons of diabetic, alcoholic or cirrhotic rats in presence of cocarboxylase; Effect of TPP (cocarboxylase) stable in solution on the growth and number of neurites of the embryonic neuroepithelium of Wistar rats, in vitro, and increase in the number of positive neurites for the neurotransmitters, mainly serotonin and gamma-aminobutyric acid (GABA); Effect of X-2 on nerve conduction velocity in lower limbs of diabetic patients with polyneuropathy; Preparation of the pancreatic beta cell implant project (islets of Langerhans) in *Wistar* rats induced to diabetes and also diabetic patients.

These studies were carried out in national and international institutions: UNAM, UAM, IPN, ECQUC, ESAANUQ, UAQ, INER, IN Cardiology, INN, CIW Maryland, HN Bayreuth and Germany, mainly. And the works and reports where published in Scientific Journals and Thesis.

—Dr. Susana Alcázar-Leyva

COMERCIAL NAME	MAIN ACTIVE INGREDIENT	PRESENTATION	THERAPEUTIC INDICATIONS	ADMINISTRATION	DOSAGE
N-N	Nicotinamide adenine dinucleotide (Coenzyme)	Vial with 50 ml of injectable solution (15 mg/ml) 750 mg each vial	Arthritis Anguish Depression	Intramuscular	3 a 5 ml (IM) per day
N-N* red	Nicotinamide adenine dinucleotide (Coenzyme)	Vial with 50 ml of injectable solution (30 mg/ml) 1500 mg each vial	Arthritis Anguish Depression	Intravenous	In 200 ml physiological solution (0.9% of sodium chloride), add 1 vial of NN* (50 ml), to apply over a minimum of 5 hours, once a week until improvement or daily for 10 days.
N-N* blue NAD	Nicotinamide adenine dinucleotide (Coenzyme) different raw material	Vial with 50 ml of injectable solution (30 mg/ml) 1500 mg each vial	ADICTIONS AGEING CELLULAR DETOXIFICATION (*)	Intravenous	In 500 ml physiological solution (0.9% of sodium chloride), add ½ or 1 vial of NN* (25 or 50 ml), apply over a minimum of 8 hours, daily for 10 days.

(*) Results are maximized when combined with X-2 (cocarboxylase or thiamine pyrophosphate), intramuscularly or intravenously.
Intramuscular: apply 3 or 5 ml every day for 2 weeks, continue every other day for 2 weeks, 3 times a week for one month, twice a week for the time the patient needs until complete recovery.
Intravenous: apply one vial (35 ml) of cocarboxylase in 200 ml of physiological solution, over a minimun of 3 hours, twice a week until improvment.

BRAND NAME	ACTIVE PRINCIPLES	PRESENTATION	THERAPHEUTIC INDICATION	ADMINISTRATION VIA	DOSAGE
NACRO	Niacinamide (Vitamina B3)	Bottle with 60 capsules of 250 mg	Vitamin B3 and PP factor Deficiency Dermatitis Nervousness Irritability and tension Anxiety and Depression Insomnia Coronary Diseases Cardiac Ischemia Prevention and treatment of Diabetes *mellitus*	Oral	1 or 2 capsules with each meal
AAL	Ascorbic acid (Vitamina C)	Bottle with 60 capsules of 250 mg	Antioxidant Antiscorbutic Increases resistance to bacterial and viral infections Asthma Allergy Furunculosis Cardiovascular Diseases Arteriosclerosis Osteoporosis Osteoarthrosis	Oral	1 or 2 capsules a day
EPH	Vitamine E (Alfa tokoferol)	Bottle with 60 capsules of 250 mg	Antioxidant Arterioesclerosis Degenerative Process Sexual impotence	Oral	1 or 2 capsules a day
MTX-2ALF	Thiamine mononitrate	Bottle with 20 g of powder	Pyrosis Heartburn Flatulence Meteorism Abdominal pain Constipation Intoxication Gastritis Colitis	Oral	¼ tablespoon of the powder dissolved in ¼ glass of water, before each meal 3 to 5 times a day. In case of food poisoning drink it every 30 mins until improvement. In case of vomit, repeat the dosage.
OFZIM	Deoxyribonuclease (0.00035 mg/ml) Ribonuclease (0.00070 mg/ml) Cocarboxylase (40 mg/ml)	Bottle with drops with 20 ml	Bacterial and viral Conjunctivitis, in any inflammatory process and in the prevention of maculopathy	Ophthalmic	2 drops in each eye 2 to 3 times a day

BRAND NAME	ACTIVE PRINCIPLES	PRESENTATION	THERAPHEUTIC INDICATION	ADMINISTRATION VIA	DOSAGE
X-2	Thiamine pyrophosphate or cocarboxylase stable in solution (Coenzyme)	Vial with 35 ml of injectable solution (40 mg/ml)	Krebs´s cycle alteration Deficiency in protein, carbohydrate and lipids metabolism STRESS Pregnancy and while breastfeeding Diabetes *mellitus* Liver Diseases Kidney Diseases Lung Diseases Heart Diseases Trauma and SHOCK To contribute in any emergency or in any acute or chronic illness	Intramuscular or Intravenous	According to age 1 to 5 ml intramuscular (IM) daily 2 weeks, every other day 2 weeks, 3 times a week one month, twice a week one month, depending on the case
DNSM	Deoxyribonuclease (Enzyme)	Vial with 35 ml of injectable solution (0.00035 mg/ml)	Antiinflammatory Antibacterial Antiviral Antitumoral	Intramuscular or intravenous	1 to 5 ml IM, together with X-2...
CRO-50	Ribonuclease (Enzyme)	Vial with 35 ml of injectable solution (0.00070 mg/ml)	Antiinflammatory Antibacterial Antiviral Antitumoral	Intramuscular or Intravenous	1 to 5 ml IM together with X-2...
N-N	Nicotinamide adenine dinucleotide (Coenzyme)	Vial with 50 ml of injectable solution (15 mg/ml)	Any kind of arthritis Anxiety Neurosis Depressive Neurosis Detoxification	Intramuscular	1 to 5 ml IM together with X-2...
RNA	Ribonucleic acid	Vial with 35 ml of injectable solution (15 mg/ml)	Mental deficiency Degenerative disorders Psychomotor deficiency Dementia	Oral	3 ml at first once a day

CRO-50/DNSM

RIBONUCLEASE/DEOXYRIBONUCLEASE

The nucleases: ribonuclease **CRO-50** and deoxyribonuclease **DNSM** are enzymes found in the organism, inside and outside the cells. These enzymes have important functions such as acting as microbicides or germicides, anti-inflammatories and antitumoral. They are known as restrictive enzymes due to the fact that they hydrolyze in specific zones of the nucleic acids of viruses, bacteria, aged, injured and dead cells. It has also been observed that they intervene in the regulation of cellular proliferation when they recognize that the DNA (deoxyribonucleic acid) of the cells presents a disorganized multiplication, like in the case of tumors. For a vast amount of time it has been known that they control the inflammatory processes because they eliminate the exudates, purulent discharges, abscesses and also decrease the viscosity of the mucous discharges. Their microbicidal action that causes the medicinal application of these nucleases to have a significant therapeutic impact is a result of the aforementioned mechanism. It has been proven clinically and experimentally how their activity controls, mainly, the following bacteria: *Staphylococcus aureus, Proteus vulgaris, Klebsiella pneumoniae, Pseudomona aeruginosa, Salmonella typhi, Escherichia coli and Proteus*. Likewise their lytic effect on *in vitro* cellular sequences from cancerous origins has been proven: HEp-2. HeLa, L-929 and on *in vivo* benign or malignant tumoral processes. This effect is related with the capacity these enzymes have to act in the DNA's degradation in the cancerous cell, of which the synthesis rate is 6 times bigger than in a normal cell. Regarding the aforementioned, the application of the nucleases is indicated to prevent the degenerative processes, of ageing and also tumoral cells, due to their hydrolysis function in the nucleic acids: ribonucleic acid (RNA) or deoxyribonucleic acid (DNA) giving the opportunity to the DNA-polymerases to reread the message or information from the intact DNA strand and to correct or repair the probable errors in the nucleic acids. The purpose of the nucleases is to break down the wrong information. The simultaneous use and of these nucleases with **X-2** (cocarboxylase or thiamine pyrophosphate) is indispensable, in order to assure the production of ATP (adenosine triphosphate) molecules and therefore maintaining an adequate energetic metabolism. **X-2** prevents, among other things, that the transportation of the hydrogens via the electrons (obtained from the molecules of the glycolysis and Krebs's cycle by the electronic transport chain to reduce the molecular oxygen and make water), is interrupted preventing the formation of oxygen free radicals, aside from being one of the main causes of ageing, favored in the development of tumors.

The blockage of the energetic metabolism consequentially increases the membrane's permeability therefore facilitating the passing of the cellular enzymes into the blood plasma, then the enzymes digest the injured cell or the different protein components of the organism, leading them to chaos and death. Resultantly, it is important to avoid extended hypoxemia or anoxemia. Our wide clinical experience and the success that has been obtained through the administration of these two nucleases (stabilized in solution), prove the advantages this medication has when used to treat pharyngoamygdalitis, acute laryngotracheobronchitis (croup), bronchiolitis, bronchitis, pneumonia, cystic fibrosis, infectious mononucleosis, hepatitis, lupus, scleroderma, multiple sclerosis, leukemia, lymphoma, malignant melanoma and generally malignant tumoral processes to avoid metastasis and in degenerative processes whilst always respecting and maintaining the organism's homeostasis. Before, during and after the removal of any tumor, the application of chemotherapy and/or radiotherapy the recommended treatment is based on the coenzyme **X-2** (cocarboxylase) with the enzymes: ribonuclease CRO-50 and/or deoxyribonuclease DNSM, with the purpose of increasing tolerance to these aggressive treatments. Likewise it is recommended prior and posterior to any type of surgical procedure, to achieve fast healing and an adequate physical recovery. This coenzymatic and enzymatic treatment is indicated for long term use to avoid metastasis and degenerative processes whilst always respecting and maintaining the organism's homeostasis.

Conclusion: An intensive treatment of both nucleases and cocarboxylase **X-2** is required in any medical emergency to prevent the patient's morbidity and mortality.

The successful therapeutic uses of these substances are a result of professor Heberto Alcázar-Montenegro's hard work and research. In 1960 he achieved the stabilization of cocarboxylase or thiamine pyrophosphate, ribonuclease and deoxyribonuclease in solution, amongst other molecules.
It is therefore thanks to him that we have this transformative medicine.

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CRO-50
RIBONUCLEASE

1. **Brand and generic name**: **CRO-50** (ribonuclease).
2. **Pharmaceutical form and formulation**: Every ml of the injectable solution contains: 0.00070 mg/dl of Ribonuclease and 1 ml of Vehicle E.D.P. (expiry date under proteins).
3. **Therapeutic indications**: **CRO-50**'s application is indicated in anti-inflammatorily, viral, bacterial and tumoral processes.
4. **Pharmacokinetics and pharmacodynamic**: The ribonuclease belongs to a family of enzymes or nucleases normally found in all tissue and cell compartments of all organisms. They are located in specific proportions depending on the type of tissue or liquid from which they're extract. They have diverse actions, the most widely known is the enzymes and their specific substrates in this case the ribonucleic acid and the ribonucleoproteins that are free, not only in the digestive tract, but also in the entire organism as a result of cellular death. Recently, it has been described that they have other functions alongside their digestive function, like their ability to recognize aged, injured, infected, transformed and tumoral cells. This recognition mechanism has not yet been explained, but it has been proposed that they penetrate the cells and exert their lytic effect because they are in plasma, special and interstitial fluids. It has also been proposed that the intracellular nucleases activate and cause the lysis of the altered cells. Moreover it has been demonstrated that they participate in the regulatory functions of the cell proliferation. Recent studies have demonstrated that ribonuclease inhibits the capacity of HIV replication without destroying it, avoiding the infection of other cells. It is probable that this same mechanism takes place with all viruses that are sensitive to the ribonuclease action. The nucleases in general have a short to medium life span. They are metabolized in the liver and its metabolites are then eliminated through the urine.
5. **Contraindications**: None.
6. **Precautions and restrictions during pregnancy and breastfeeding**: Do not administrate during the first three months of pregnancy.
7. **Adverse reactions and side effects**: Hypersensitivity to the formula's components.
8. **Medical interactions**: **CRO-50** does not alter the effect of any other medication nor cause reactions when administered with other medication. The effect of **CRO-50** is not modified by any other medicine or drug except alcohol; therefore it is recommended that during the administration of this medication, alcohol beverages be suspended.
9. **Laboratory altered tests**: None.
10. **Precautions and relationship with carcinogenesis, teratogenesis and fertility**: **CRO-50** does not produce any of the aforementioned effects, but it's administration is not recommended during the first three months of pregnancy.
11. **Dosage and administration**: Diverse doses of the **CRO-50** are applied: from 1 to 10 ml, every 24 hours, depending on age, level of suffering and each patient's clinical progress. **CRO-50** is administrated intramuscularly or intravenously.

12. **Overdoses or accidental ingest; manifestations and management (antidotes)**: Extended studies about acute toxicity and accumulation, indicate that there is a wide safe range between therapeutic and toxic doses. No secondary or adverse reaction has been found, neither in short or long term; even when applied in high doses.
13. **Presentation**: **CRO-50** comes in a bottle with 35 ml, of injectable solution that contains 0.00070 mg/ml of ribonuclease stable in solution.
14. **Recommendations for storage**: The product should be protected from the light and heat and therefore should be refrigerated.
15. **Protection label**: **CRO-50** requires a medical prescription for its sale. Keep out of reach of children.
16. **Laboratory name and address**: Hypatia. Philosophic and Scientific Researches S.A. (Anonymous Society) of V.C. (Variable capital). 215 Mariano Abasolo. Barrio de San Juan. P.C. 79610 Río Verde, San Luis Potosí, México.
17. **Register number**: No. 606M95 S.S.A.

DNSM
DEOXIRIBONUCLEASE

1. **Brand and generic name**: **DNSM** (deoxyribonuclease).
2. **Pharmaceutical form and formulation**: Every ml of the injectable solution contains: 0.00035 mg/dl of Deoxyribonuclease and 1ml of Vehicle E.D.P. (expiry date under proteins).
3. **Therapeutic indications**: **DNSM**'s application is indicated in anti-inflammatorily, viral, bacterial and tumoral processes.
4. **Pharmacokinetics and pharmacodynamic**: Deoxyribonuclease (DNase) is an enzyme that is normally present in all the tissues of the organism; it regulates the metabolism of the nucleic acids, in their hydrolysis and synthesis. During inflammatory, infectious, cancerous, and even ageing processes it has been demonstrated that it modifies the concentration and/or activity of the damaged cells. The DNase hydrolyses the deoxyribonucleic acid (DNA) that comes from dead or degenerated cells, as well as the bacterial and viral DNA that is found in the material from abscesses, hematomas and coagulates. It also regulates the cell proliferation because it has proven to act in the areas of maximum sensitivity of the DNA which are the areas where the transcription and replication takes place, probably because in these regions the chromatin is not condensed and resultantly, they are exposed. Due to the vulnerability of the regions and the high mitotic frequency cancerous cells have, this cell becomes susceptible to the lytic action of the nucleases. The nucleases generally have the same chemical composition in several organisms, they can be isolated from them and applied in humans. They're metabolized in a short period of time and eliminated through excretion.
5. **Contraindications**: None.
6. **Precautions and restrictions during pregnancy and breastfeeding**: Do not administrate during the first three months of pregnancy.
7. **Adverse reactions and side effects**: Hypersensitivity to the formula's components. In some cases, the administration of this product could cause a rash or urticaria.
8. **Medical interactions**: None.
9. **Laboratory altered tests**: None.
10. **Precautions and relationship with carcinogenesis, teratogenesis and fertility**: **DNSM** does not produce any of the aforementioned effects, but its administration is not recommended during the first three months of pregnancy.
11. **Dosage and administration**: Diverse doses of **DNSM** are applied: from 1 to 10 ml, every 24 hours, depending on age, level of suffering and each patient's clinical progress. **DNSM** is administrated intramuscularly or intravenously.
12. **Overdoses or accidental ingest; manifestations and management (antidotes)**: No secondary or adverse reaction has been found, neither in short or long term; even when applied in high doses.
13. **Presentation**: **DNSM** comes in a bottle with 35 ml of injectable solution that contains 0.00035 mg/ml of deoxyribonuclease stable in solution.
14. **Recommendations for storage**: The product should be protected from the light and heat and therefore should be refrigerated.
15. **Protection label**: **DNSM** requires a medical prescription for its sale. Keep out of reach of children.
16. **Laboratory name and address**: Hypatia. Philosophic and Scientific Researches S.A. (Anonymous Society) of V.C. (Variable capital). 215 Mariano Abasolo. Barrio de San Juan. P.C. 79610 Río Verde, San Luis Potosí, México.
17. **Register number**: No. 613M95 S.S.A.

nutritional imbalance, vomiting, diarrhea, dysentery, ulcerative colitis, achlorhydria, biliary disorders, alterations induced by chronic alcoholism, malnutrition, myalgia, delirium tremens, migraine, myocarditis, cardiospasm, acute and chronic pneumonia, cancer, infection diseases, diphtheria, tuberculosis, intoxications by soporific agents or gases, vomits or pre-eclampsia, eclampsia, paresthesia and spasms in the puerperium, subacute necrotisans encephalopathy, acetonemic vomiting, pre-toxic nutritive disorder, toxicosis in unweaned babies, acidosis during and after surgical procedures, X ray radiation, chemotherapy, Alzheimer syndrome, **Wernicke's encephalopathy**, severe deficiencies in the first months of life, Wolfram syndrome (diabetes *mellitus*, optic atrophy, insipid diabetes and deafness), dilatation of the urinary tract and other minor anomalies.

5. **Contraindications**: None.
6. **Precautions and restrictions during pregnancy and breastfeeding**: The application of **X-2** is recommended during pregnancy and breastfeeding to increase the daily contribution of this coenzyme due to increased metabolism and the physical requirements caused by this condition.
7. **Adverse reactions and side effects**: In humans negative effects have not been found except from light gastric alterations in elevated oral doses. However, the parenteral doses are tolerable, even with doses superior to 500 mg. No toxic effect has been reported with thousands of subcutaneous, intramuscular, and intravenous applications using doses superior to 100 or 200 mg which is more than the recommended daily dosage. **X-2** has no side effects or adverse reactions as it is a indispensable coenzyme in the energetic metabolism. Its deficiency causes serious biochemical alterations: production of free radicals, it blocks the Pasteur's effect and metabolic acidosis. It is eliminated through urine removing any possibility of risk.
8. **Medical interactions**: **X-2** does not alter the effect of any other medication nor cause reactions when administered with other medication. The effect of **X-2** is not modified by any other medicine or drug except alcohol, therefore it is recommended that during the administration of this medication, alcoholic beverages be suspended.
9. **Laboratory altered tests**: None.
10. **Precautions and relationship with carcinogenesis, teratogenesis and fertility**: **X-2** does not produce any of the aforementioned effects and is recommend throughout all stages of pregnancy, especially in the first three months of pregnancy and whilst breastfeeding. The administration of this product is also indicated to treat cancer.
11. **Dosage and administration**: Diverse doses of **X-2** are prescribed: from 40 mg to 1600 mg, every 24 hours, according to age, level of suffering and each patient's clinical progress. **X-2** is administrated intramuscularly or intravenously. Intravenously it is administrated in 200 ml of any kind of solution, preferable a physiologic solution, over the space of 2 to 3 hours.
12. **Overdoses or accidental ingest; manifestations and management (antidotes)**: Extended studies about acute toxicity and accumulation, indicate that there is a wide safe range between therapeutic and toxic doses. No secondary or adverse reaction has been found, neither in short or long term; even when applied in high doses.
13. **Presentation**: **X-2** comes in a bottle with 5 ml, of injectable solution that contains 40 mg/ml of cocarboxylase (thiamine pyrophosphate chlorhydrate) stable in solution.
14. **Recommendations for storage**: The product should be protected from the light and heat and therefore should be refrigerated.
15. **Protection label**: **X-2** requires a medical prescription for its sale. Keep out of reach of children.
16. **Laboratory name and address**: Hypatia. Philosophic and Scientific Researches S.A. (Anonymous Society) of V.C. (Variable capital). 215 Mariano Abasolo. Barrio de San Juan. P.C. 79610 Río Verde, San Luis Potosí, México.
17. **Register number**: No. 187M89 S.S.A.

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X-2

COCARBOXYLASE OR THAIMINE PYROPHOSPHATE

1. **Brand and generic name**: **X-2** (cocarboxylase or thiamine pyrophosphate).
2. **Pharmaceutical form and formulation**: Every ml of the injectable solution contains: 40 mg of cocarboxylase (thiamine pyrophosphate chlorhydrate) and 1 ml of Vehicle E.D.P. (expiry date under proteins).
   X-2, cocarboxylase or thiamine pyrophosphate (TPP) is the active form of thiamine or vitamin B_1. It is an organic molecule that contains a pyrimidine group and a thiazole ring joined by a methylene bridge. The condensed form of **X-2** is C14H20O6N4P2S and it is conserved in a watery environment in acid hydrogen potential.
3. **Pharmacokinetics and pharmacodynamics**: The thiamine participates in the metabolism of the carbohydrates because it is the precursor of thiamine pyrophosphate, the coenzyme that participates in pyruvate's decarboxylation, of α-ketoacids and in the formation or use of α-ketols by the transketolase and also in the metabolism of the ramify chain amino acids. Its participation in the conduction of the nervous impulse is proven, without modifying the normal processes, even though the neural membranes are repolarized in a short amount of time as it happens with natural neurotransmitters *in vitro*. It has been proven that it participates in the synthesis and liberation of the neurotransmitters and hormones, and so in the activation of the immune cell system. Thiamine and its esters have a re-change rate in the organism, even though it is not stored in any organ for extended times, therefore continuous ingestion is indispensable. In relatively short of inadequate incorporation, biochemical alterations are present and those lead to the clinical symptomatology characteristics of the deficiency. Thiamine and its products get into the organism orally or parenterally and they are deposited quickly into the liver, muscle, and other tissues to be converted into its three types of esters in specific concentrations, and when the level passes a certain limit, the excess is eliminated in the urine. The thiamine excess is stored, deposited and converted into any of its esterify forms or into its simple form when at a specific concentration. Passed certain limits, it is eliminated in the urine. To this date 6 catabolites have been identified: 2-methyl-4-amino-5-pyrimidine, carboxylic acid, 4-methyl-thiazol-5acetic acid, 2-methyl-4amino-5-hydroxymethyl pyrimidine, 5-(2-hydroxyethyl)-4-methyl-thiazol, 3(2-methyl-4-amino-5-pyrimidyl-metylo-4-methyl-thiazol-5acetic acid. And 2-methyl-4-amino-5-formylamino ethyl-pyrimidine.
4. **Indications**: The use of **X-2** is indicated in diseases that require the immediate reactivation of the tricarboxylic acids cycle for the production of energy such as: hypoxia, diabetes *mellitus*, diabetic coma, pre-coma, insulin shock, megaloblastic anemia, deafness, in patients with severe heart failure associated to alterations in the intestinal absorption of thiamine, multiple trauma, shock, myasthenia gravis, maple syrup urinary disease or ketoacidosis, cirrhosis, liver diseases, acute gastritis, pancreatitis, peripheral neuritis, neuralgia, trigeminal neuralgia, facial paralysis, nervous deafness, cardiomyopathy neuritis with strain and severe edema, confusion, lumbago, sciatic, neurasthenia, diffused pain of diverse origins,

X-2

COCARBOXYLASE OR THIAMINE PYROPHOSPHATE STABLE IN SOLUTION

X-2, cocarboxylase or thiamine pyrophosphate (TPP) is the active form of thiamine or vitamin B1, an essential coenzyme for our organism. Humans have limited synthesis, which is directly dependent on the ingestion of thiamine. When thiamine enters the organism, it is phosphorylated by ATP (adenosine triphosphate, donor molecule of phosphates) in cocarboxylase or thiamine pyrophosphate. The importance of this coenzyme is confirmed in the metabolism of carbohydrates, because of its intervention in the decarboxylation of the α-ketoacids. Aside from this, it is essential in the metabolism of the amino acids of the ramify chain and in the stimulation of the synthesis, liberation and refill of the neurotransmitters in the central nervous system. Therefore it is fundamental for the adequate functioning of the nervous system, because its deficiency produces serious encephalopathies or alterations like nervousness, irritability, anxiety and depression. The majority of pathologies of the nervous system are due to the accumulation of lactate, this is even observed in diverse metabolic malfunctions and this is directly related with the severity of the disease. The importance of the application of TPP is for it to decarboxylate the pyruvate before it is transformed into lactic acid and blocks the production of energy. The TPP decarboxylates the pyruvate in the glycolysis, and this glycolysis takes place in the cytoplasm of all cells, it also decarboxylates the α-ketoglutarate in the mitochondria's Krebs's cycle favoring the energy production in the form of ATP and maintaining an adequate cell metabolism. Therefore the cocarboxylase intervenes regulating the processes of ATP production in all the cells of the organism. X-2 is applied with therapeutic purposes in cases of severe mental illnesses, it is also used as preventive therapy to avoid senile dementia, both due to the increase of the entropy (disorder) or loss of the biological characteristic order of ageing. Consequentially specific changes are made to the structure and cellular function which is derived mainly from the incapacity to produce enough energy for the synthesis of crucial enzymes in cellular function and for the control of waste cell material. As a result of this, the common denominator of diverse diseases is deficient metabolic activity, because of this the applications of the X-2 are indicated in situations of stress, exercise, pregnancy, breastfeeding, fever, infections, shock, thyroid alterations or in surgical procedures. It is also used in situations where lack of absorption of thiamine is apparent, as in diarrhea, alcoholism and in cases where the coenzyme cannot be synthesized, like in hepatic malfunctions. It has been proven to be beneficial when administrated in: diabetes *mellitus*, hypoglycemia, arthritis; heart, lung and nervous diseases, low or high blood pressure, immune system deficiencies, cancer, multiple trauma, shock and in any medical emergency. In these cases the metabolism is regulated by the application of this coenzyme, and the cells recover the capacity to use oxygen to generate energy again and to avoid the production of oxygen free radicals. The essential characteristic of this cocarboxylase or thiamine pyrophosphate X-2 is its stability in solution, pharmacologically corroborated, and this characteristic blocks its degradation or oxidation when it gets into the organism. Because of this its intracellular action becomes effective in all the aforementioned medical conditions.

Conclusion: In any medical emergency the intensive application of X-2 is required, to avoid the morbidity and mortality of the patient.

Thermodynamic's second law establishes that in all the biochemical processes, the entropy of the system and its environment (Universe's entropy) experiences a constant increase until it reaches a maximum value of disorder. The performance of this law always leads from order to chaos. If we were to try to follow the opposite direction, the application of energy would be necessary. The same occurs in biological systems.
The information that the cells contain throughout time go towards the disorder, and when the energy is lost, the order can no longer be sustained. Energy and order are terms related to ATP and nucleic acids. The regulation of energy is fundamental in the conservation of order (homeostasis, health).

HISTOLOGICAL CHARACTERISATION OF THE CHRONIC ADMINISTRATION OF THIAMINE PYROPHOSPHATE IN SENILE WISTER RATS

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INTRODUCTION

Celular ageing is the result of the progressive declination of the proliferative capacity or celular division; the duration of cell life depends on the effects of continuous exposure to exogenic influences that give place to the progressive accumulation of celular and molecular damage. Within the mechanisms involved in ageing, the formation of free radicals (FR) and reactive oxygen species (ROS), play an important role in the physiopathology of this process. The main source of the aforesaid are the mitochondria and when these surpass a certain threshold, celular deterioration through mitochondrial damage begins. The main ROS' are: superoxide, nitric oxide and hydrogen peroxide. Loss of balance between their production and elimination provokes damage on different celular levels, presenting atrophy and accelerated ageing. Thiamine pyrophosphate (TPP), is a coenzyme that takes part in the energetic metabolism for the production of ATP (Adenosine Triphosphate). It has been found that when administrated parenterally TPP decreases the metabolic and mitochondrial changes that cause old age in an organism.

METHODOLOGY

TPP (X-2 Stable Thiamin Pyrophosphate solution), was administrated to senior male Wistar rats for a 14 month period with one dose of 4mg subcutaneously twice a week. The senior control rats were given saline solution. Upon finishing the investigation the rats were sacrificed and their organs were processed to obtain tissue and histological samples which were stained with haematoxylin and eosin. The results were compared with young 4 month old rats to evaluate the grade of recovery of the corresponding tissue in senile rats.

RESULTS

In the results analysis it was found that the majority of the studied organs treated with X-2 showed less atrophy and few changes related to ageing with an almost normal histology, whereas in the control group of senile animals a higher level of atrophy and diverse alterations related to ageing, including the appearance of tumours, were observed.

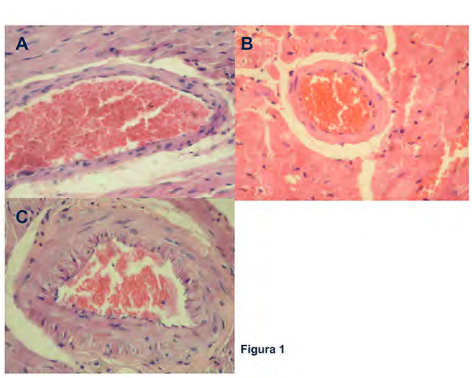

Figura 1

In the **cardiac tissue** of the senile animals in the control group (Fig. 1C), a thickening of the coronary vessel walls was observed; **the arteries of the young rat (Fig. 1A) and the X-2 treated rat (Fig. 1B) were similar.**

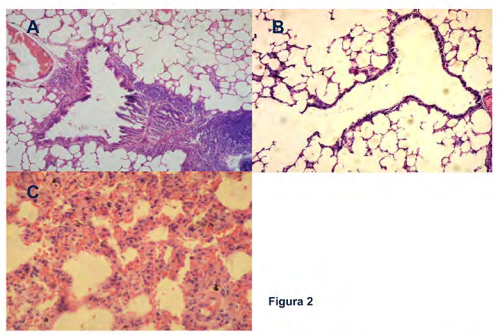

Figura 2

The **lungs** of the senile animals in the control group (Fig. 2C) showed acute and chronic bronchial and Intra–alveolar inflammatory processes; **in the group treated with X-2, they were normal (Fig. 2B).**

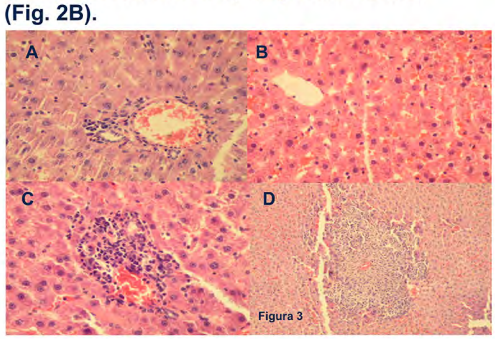

Figura 3

The **kidneys** of the senile control animals showed an increase in lymphocyte population on a sinusoidal level (Fig. 3C) and in the triadal portals compatible with reactive hepatitis; one of the controlled animals presented metastasis from the tumours in the interstitial testicle cells (Fig. 3D); **in the treated animals changes related to the intoxication resulting from the chronic administration of X-2 were not observed (Fig.3B), in fact they stayed almost the same as the control young rats (Fig. 3A).**

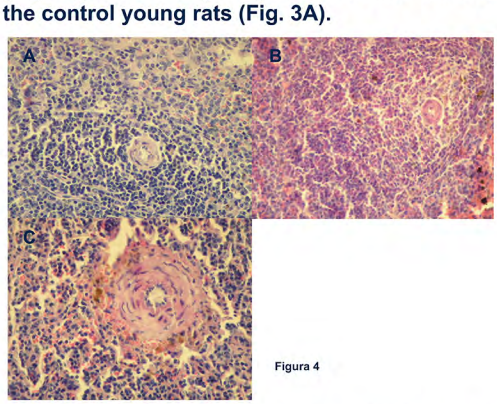

Figura 4

In the **spleen** of the senile control animals, more hyaline arterioesclerosis changes were identified (Fig. 4C).
The experimental treated with X-2 (Fig. 4B) was similar to the young control rat (Fig. 4A).

In the **testicle** the most drastic changes in the control animals were documented (Fig. 5C). Neoplasia in interstitial Leydig cells was found in more than half of the group (Fig. 5D); a decrease in the number of germinal layers; a decrease in the index of spermatogenesis; and interstitial fibrosis. **The experimental animals treated with X-2 (Fig. 5B), didn't demonstrate Sertoli cell or Leydig cell alteration, nor notable changes in the germinal layers, being similar to the tissue in young rats of 6 months of age (Fig. 5A).**

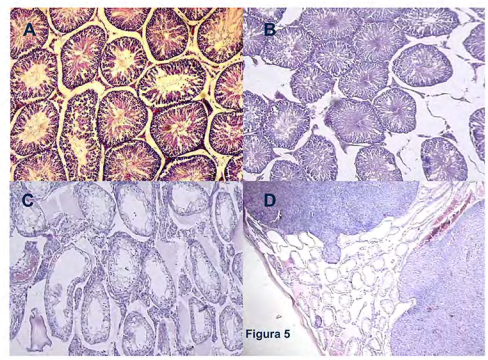

Figura 5

The studies carried out in the small intestine did not show any differences in the three groups.

DISCUSSION

The results show that the senile control animal's tissues continued an expected course according to age, while **the experimental animals treated with X-2 during the 14 months didn't show evident degenerative changes, since there was no significant celular deterioration in comparison to the young control rats,** according to the histological studies carried out and their comparison with the young control rats of 4 months of age.

The formation of free radicals throughout the life of an organism is inevitable, when these levels become pathological, great damage is caused at diverse celular levels, like in the mitochondria, where they cause mutations in the DNA of this organelle, affecting the production of ATP and originating other disorders. Mutation of the mtDNA can become significant, it can perpetuate and expand every time the cells multiply. Throughout ageing, the protective mechanisms that eliminate or deactivate the FR, such as certain antioxidant enzymes, proteins and coenzymes, are often deficient. An antioxidant therapy that can be administered chronically in senile organisms could help with a lasting homeostasis the permits the maintenance of health, to attain a physical ageing instead of pathological.

The results are notable, most of all in the organs that have an accelerated metabolism and constant celular degeneration; and because no toxic effects or secondary lesions were found with the frequent administration of X-2.

The current studies are routed in characterising the endochronic changes, sexual conduct and the celular oxidation that the animals present during ageing.

These results verify once more, that the frequent administration of Thiamine Pyrophosphate or Cocarboxylase, X-2 stable solution, decrease the pathological levels of free radicals and Reactive Oxygen Species, maintains an adequate energetic metabolism and homeostasis, and permits the organism treated with this coenzyme to adapt and maintain a good quality of life.

CONCLUSION

The frequent administration of X-2 decreases or avoids the generation of atrophic changes associated with ageing, and avoids the long and short term formation of tumours.