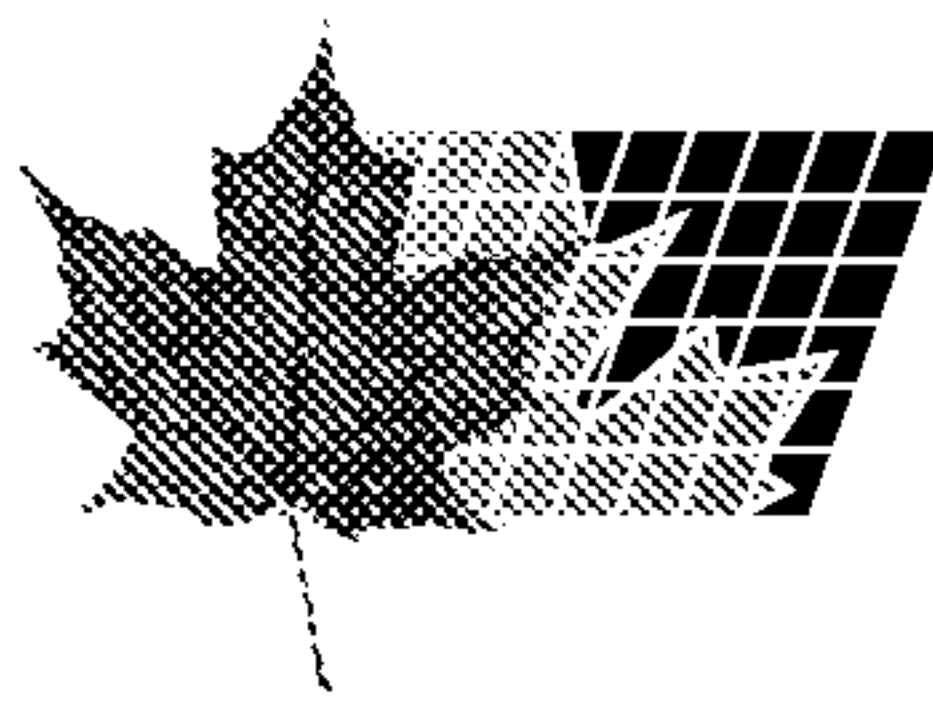




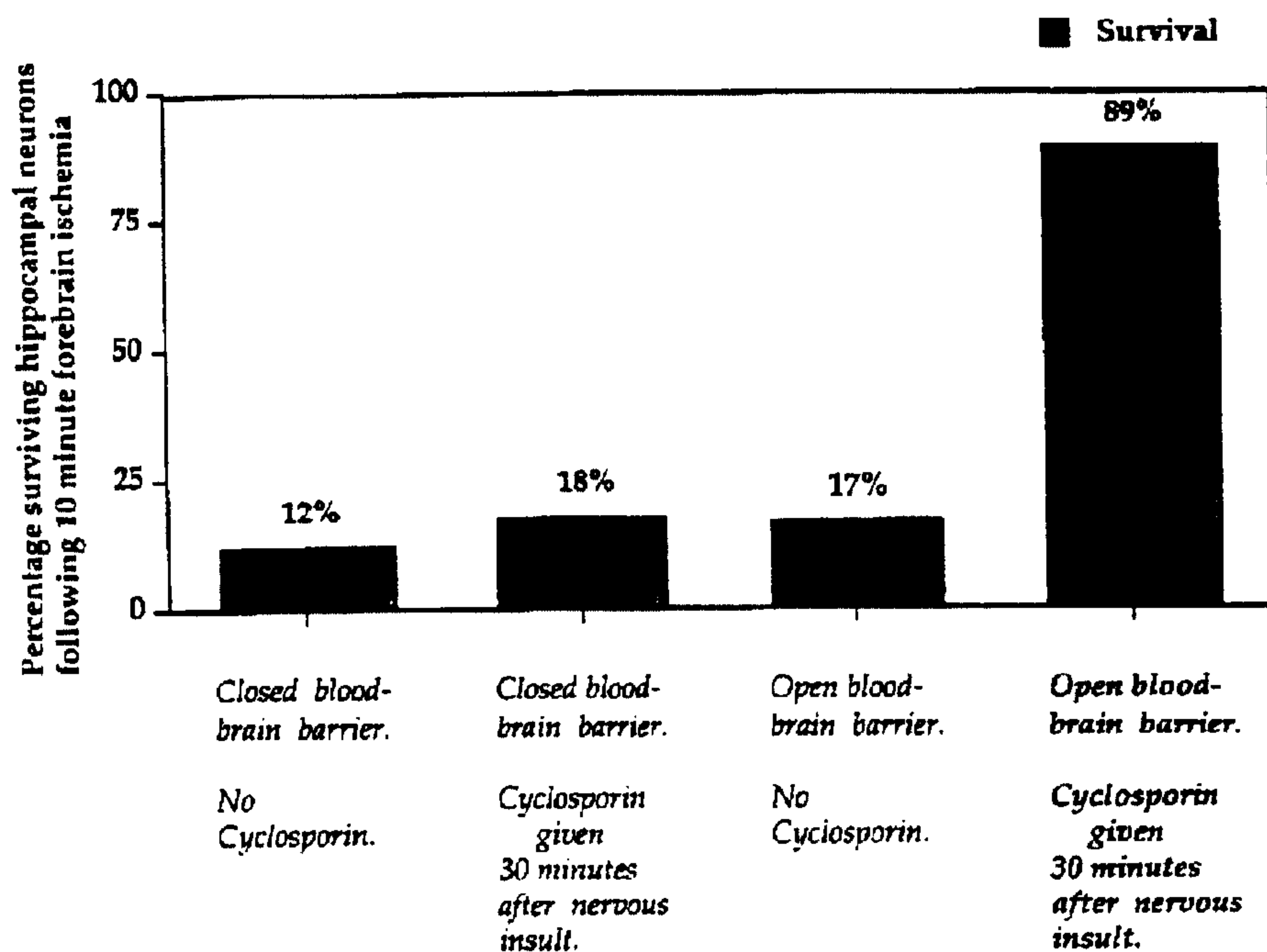
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(72) KEEP, Marcus, US
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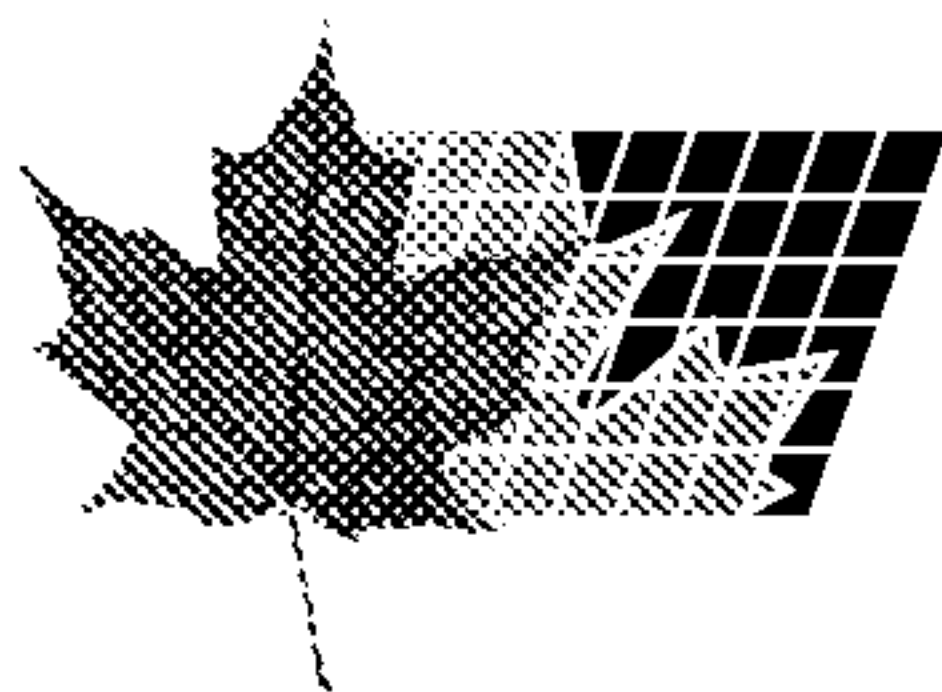
(54) **COMPOSITION PHARMACEUTIQUE RENFERMANT DE LA
CYCLOSPORINE POUR TRAITER UNE PERSONNE AYANT
SUBI UNE AGRESSION NERVEUSE**

(54) **PHARMACEUTICAL COMPOSITION CONTAINING
CYCLOSPORIN FOR TREATING A HUMAN WITH NERVOUS
INSULT**



(57) A novel article of manufacture and the use thereof is provided herein. The article of manufacture includes packaging material and pharmaceutical agent contained within the packaging material. The pharmaceutical agent is therapeutically-effective for reducing or preventing nervous damage caused by traumatic metabolic, ischemic or hypoxic neural insult. The pharmaceutical agent is able to cross the blood-brain-barrier to contact the nervous tissue





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in a therapeutically-effective quantity. The pharmaceutical agent includes cyclosporin A or a compound of the class of cyclosporins, or functional derivatives, metabolites, variants or salts thereof, or combination of such compounds, either alone or in admixture with diluents, or additives. The packaging material comprises a label which indicates that the pharmaceutical agent can be used for reducing or preventing nervous damage caused by traumatic, metabolic, ischemic or hypoxic neural insult.

ABSTRACT

A novel article of manufacture and the use thereof is provided herein. The article of manufacture includes packaging material and pharmaceutical agent contained within the packaging material. The pharmaceutical agent is therapeutically-effective for reducing or preventing nervous damage caused by traumatic metabolic, ischemic or hypoxic neural insult. The pharmaceutical agent is able to cross the blood-brain-barrier to contact the nervous tissue in a therapeutically-effective quantity. The pharmaceutical agent includes cyclosporin A or a compound of the class of cyclosporins, or functional derivatives, metabolites, variants or salts thereof, or combination of such compounds, either alone or in admixture with diluents, or additives. The packaging material comprises a label which indicates that the pharmaceutical agent can be used for reducing or preventing nervous damage caused by traumatic, metabolic, ischemic or hypoxic neural insult.

(a) TITLE OF THE INVENTION

PHARMACEUTICAL COMPOSITION CONTAINING CYCLOSPORIN FOR
TREATING A HUMAN WITH NERVOUS INSULT

(b) TECHNICAL FIELD TO WHICH THE INVENTION BELONGS

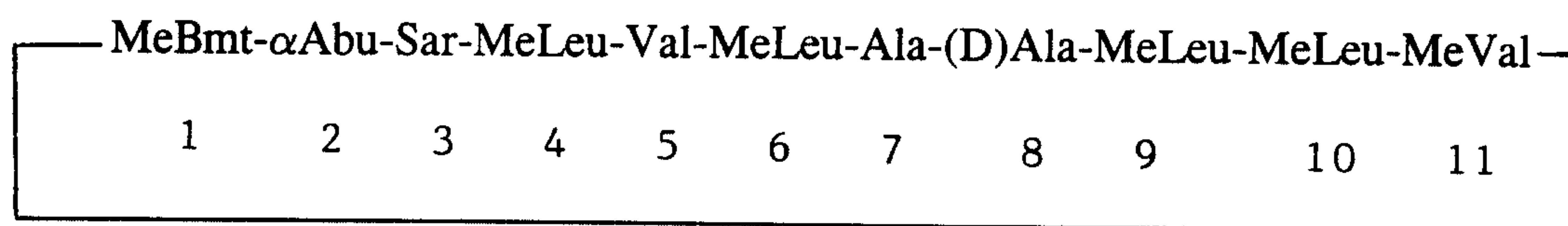
5 This invention relates to pharmaceutical compositions for treating a human having nervous insult.

(c) BACKGROUND ART

10 Central nervous tissue and to a lesser extent, peripheral nervous tissue, has poor reparative abilities. Thus damage to nervous tissue causes significant permanent disability and is a frequent cause of death. Damage to nervous tissue occurs in many ways, including ischemia in cerebrovascular accidents, cerebral circulatory disturbances, episodes of absolute and relative hypoxia, from metabolic disturbances and from various forms of trauma. In areas of focal ischemia or damage, there is a core of more profound damage, surrounded by a perifocal penumbra of lesser damage. The neurons in the
15 penumbra can for a time maintain homeostasis and are potentially more salvageable by pharmacological agents.

20 Current treatment of nervous damage is limited. Supportive measures are taken in hospital during the period after nervous insult, e.g., stroke or trauma. Several medications have met with differing but incomplete success as agents to protect nervous function from insult. Nimodipine, a calcium channel blocker, is used clinically to treat vasospasm after subarachnoid haemorrhage. Methylprednisolone, a steroid, in very high doses is helpful in spinal cord compression. Tirilazad, a 21-aminosteroid linked to a free radical scavenger, is undergoing clinical trials to decrease the damage caused by stroke. The high rate of disability from nervous insult and current lack of a truly effective
25 neuroprotective agent demonstrates the need for such a discovery.

It is already known that cyclosporin A having the formula:



is an immunosuppressive drug. The above-mentioned treatment medication has already been described, in United States Patent No. 4,117,118 and numerous patents since, which relate to its production, formulation and immunosuppressive properties.

5 Cyclosporin A is a product of the fungus *Tolypocladium Inflatum Gams*. It is a cyclic poly-amino acid molecule, consisting of 11 amino acids. One of the amino acids is unique for cyclosporin A, a β -hydroxyamino acid called butenyl-methyl-threonin (MeBmt). The molecular weight is 1202.6 and the chemical composition is $C_{62}H_{111}N_{11}O_{12}$.

10 The molecule is highly lipophilic and virtually insoluble in water. The bioavailability after an oral dose varies between 8% and 60% depending in part on the bile flow. The drug is absorbed mainly in the small intestine. The drug is transported in the blood within red blood cells to 58% and the remaining 10%-20% in leukocytes and 33% bound to plasma proteins. In the plasma, cyclosporin A is bound to high-density lipoproteins and low-density lipoproteins and very-low density lipoproteins and a small
15 fraction to albumin. A very small fraction is free in the plasma.

The drug undergoes extensive metabolism, mainly in the liver by the cytochrome P450 system. There are at least 30 known metabolites of cyclosporin A, with various chemical modifications, e.g., hydroxylation, demethylation, oxidation and epoxide
20 formations. There are a number of variants of cyclosporin A, differing, for example, in one amino acid, which have similar pharmacological properties.

There is an enterohepatic circulation and gut bacteria can metabolize the drug, with a further uptake of the metabolites in patients. 95% of a single dose given orally can be found in the feces within 95 hrs. The remaining fraction is excreted via the kidneys. Under normal conditions cyclosporin A and its metabolites do not pass the
25 blood-brain barrier.

The nervous system comprises many structures, which includes the following components, namely neurons, neural support cells, glia, Schwann cells, vasculature contained within and supplying these structures, the central nervous system, the brain, the brain stem, the spinal cord, the junction of the central nervous system with the

peripheral nervous system, the peripheral nervous system and allied structures, all of which are defined herein as "nervous tissue".

5 The function of the nervous system and its parts, are manifest in sensing the environment, awareness of it, homeostasis to it and interaction with it. The function of the nervous system is manifest, by example, in the ability to perform activities of daily living, work, cogitation and speech. These functions of the nervous tissue are defined herein as "nervous function".

10 Damage to nervous tissue can occur in many ways and come from many sources, with many different sequelae, which includes the following: damage to nervous tissue and death of nervous tissue, brain damage and brain destruction, in whole or part and resultant morbidity, disability, neurologic deficit and death are defined herein as nervous insult.

15 Nervous insult can be from various origins including ischemia hypoxia, cerebrovascular accident, metabolic, toxic, neurotoxic, trauma, surgery, iatrogenic, pressure, mass effect, haemorrhage, thermal, chemical, radiation, vasospasm, neurodegenerative disease, neurodegenerative process, infection, epilepsy and their secondary effects.

(d) DESCRIPTION OF THE INVENTION

20 It has now been discovered that the treatment medication known as cyclosporin A is a useful and effective neuroprotective agent.

25 Thus, by a first aspect of this invention, an article of manufacture is provided comprising packaging material and a pharmaceutical agent contained within the packaging material; the pharmaceutical agent is therapeutically-effective for reducing or preventing nervous damage caused by traumatic metabolic, ischemic or hypoxic neural insult when the pharmaceutical agent is able to cross the blood-brain-barrier to contact the nervous tissue in a therapeutically-effective quantity, the pharmaceutical agent comprising cyclosporin A or a compound of the class of cyclosporins, or functional derivatives, metabolites, variants or salts thereof, or combination thereof, either alone or in admixture with diluents, or additives; and the packaging material comprises a label which indicates

that the pharmaceutical agent can be used for reducing or preventing nervous damage which is caused by traumatic, metabolic, ischemic or hypoxic neural insult.

5 By a second aspect of this invention, an article of manufacture is provided comprising packaging material and two pharmaceutical agents contained within the packaging material; a first pharmaceutical agent is therapeutically-effective for reducing
10 or preventing nervous damage caused by traumatic, metabolic, ischemic or hypoxic neural insult when the first pharmaceutical agent is able to cross the blood-brain-barrier to contact the nervous tissue in a therapeutically effective quantity, wherein the first pharmaceutical agent comprises cyclosporin A or a compound of the class of cyclosporins, or functional derivatives, metabolites, variants or salts thereof, or
15 combination thereof, either alone or in admixture with diluents, or additives; the second pharmaceutical agent increases the permeability of the blood-brain-barrier to the first pharmaceutical agent, and wherein the second pharmaceutical agent comprises one or several compounds that open the blood-brain-barrier through one or several mechanisms including hyperosmotic mannitol solution, protamine sulphate electrostatic charge blocker
20 and inhibitors of the P-glycoprotein multidrug transporter system whether alone or in admixture with diluents, or additives; and the packaging material comprises a label which indicates that the two pharmaceutical agents can be used together for reducing or preventing nervous damage caused by traumatic, metabolic, ischemic or hypoxic neural insult.

By one variant of these two aspects of the present invention, the medication containing cyclosporin A or cyclosporins is in a form for being administered orally.

25 By a second variant of these two aspects of the present invention, and/or the above variant thereof, the medication containing cyclosporin A or cyclosporins containing cyclosporin A or cyclosporins is in a form for being administered intra-arterially.

By a third variant of these two aspects of the present invention, and/or the above variants thereof, the medication containing cyclosporin A or cyclosporins is in a form for being intravenously as a sterile, injectable formulary drug.

By a fourth variant of these two aspects of the present invention, and/or the above variants thereof, the medication containing cyclosporin A or cyclosporins is in a form for being administered parenterally as a sterile injectable formulary drug.

5 By a fifth variant of these two aspects of the present invention, and/or the above variants thereof, the medication containing cyclosporin A or cyclosporins is in a form for being administered into or adjacent to the brain, cerebrospinal fluids or spinal cord as a sterile injectable formulary drug.

10 By a sixth variant of these two aspects of the present invention, and/or the above variants thereof, the medication containing cyclosporin A or cyclosporins is in a form for being administered by a combination of the routes as described above.

15 By a third aspect of this invention, the use is provided of an effective nervous-insult-treatment-amount of cyclosporin A for the manufacture of a medicament as described above, for the treatment of a human with nervous insult and in whom the blood-brain barrier has been opened or where cyclosporin A is able to cross the blood-brain barrier.

20 By a fourth aspect of this invention, the use is provided of an effective nervous-insult-treatment-amount of cyclosporins, or functional derivatives, metabolites, variants or salts thereof, for the manufacture of a medicament as described above, for the treatment of a human with nervous insult and in whom the blood-brain barrier has been opened or where cyclosporins are able to cross the blood-brain barrier.

25 By a fifth aspect of this invention, the use is provided of an effective nervous-insult-treatment-amount of cyclosporin A as the medicament as described above, for the treatment of a human with nervous insult and in whom the blood-brain barrier has been opened or where cyclosporin A is able to cross the blood-brain barrier.

By a sixth aspect of this invention, the use is provided of an effective nervous-insult-treatment-amount of cyclosporins, or functional derivatives, metabolites, variants or salts thereof, as the medicament as described above, for the treatment of a human with nervous insult and in whom the blood-brain barrier has been opened or where cyclosporins are able to cross the blood-brain barrier.

By one variant of these third to sixth aspects of this invention, the use is provided for treating a human with nervous insult, with the exclusion of nervous ischemic insult.

By a second variant of these third to sixth aspects of this invention, the use is provided for the treatment of cerebral insult and cerebral disorders.

5 By a third variant of these third to sixth aspects of this invention, the use is provided for the treatment of penetrating injury, closed head injury, intracranial mass and raised intracranial pressure, surgery and iatrogenic damage, electrolyte physiologic abnormalities, glucose physiologic abnormalities, vitamin physiologic abnormalities, metabolic physiologic abnormalities and homeostatic physiologic abnormalities, metabolic
10 poisons, toxins, neurotoxins, radiation and vasospasm, secondary and delayed effects to the visual and optic system, secondary and delayed effects to the vestibular system, secondary and delayed effects to the olfactory system, nervous tissues of the brain stem, spinal, cord, e.g., myelitis and myelopathy and the peripheral nervous system, diseases and processes of neurodegeneration, e.g., Alzheimer's disease, Parkinson's disease,
15 Huntington's disease, epilepsy, e.g., herpes infection, AIDS-related neurological sequelae, AIDS myelopathy and ageing.

By a fourth variant of these third to sixth aspects of this invention, the use is provided for the neuroprotective treatment of nervous insult to embryonic and fetal nervous tissue for cell culture, production and clinical transplantation therapies in
20 humans.

By a fifth variant of these third to sixth aspects of this invention, the use is provided for neuroprotective treatment of neural cell cultures, glial cell cultures, neural and glial cell cultures, both neural and glial origin tumour cell cultures, transfected, genetically engineered cell cultures, including those of peripheral origin, sympathetic ganglia, dorsal root ganglia, pheochromocytomas and Schwann cells.
25

By a sixth variant of these third to sixth aspects of the invention, the use is provided for the treatment of the following conditions, situations and diseases in which nervous insult occur: from cerebrovascular accidents, stroke and ischemic damage and intracranial sources, pressure related ischemia, extracranial sources, embolic sources,

vasculopathy and coagulopathy and respiratory comprise and full body hypoxia, anemia, red blood cell and haemoglobin malfunction and hypotension.

"Neuroprotective" is defined herein as an effect which reduces, arrests, or ameliorates nervous insult and is protective, resuscitative or revivative for nervous tissue that has suffered nervous insult.

A "neuroprotective agent" is herein defined as a treatment medication, or formulary drug containing a nervous-insult-treatment dose of treatment medication which is effective in reducing, arresting, or ameliorating nervous insult and provides protection, resuscitation or revival to nervous tissue that has suffered nervous insult.

The entire family of cyclosporins, all derivatives, variants, amino acid variants, metabolites including variations of mono-, di- and trihydroxylates, N-demethylates, aldehydes, carboxylates, conjugates, sulphates, glucuronides, intramolecular cyclizations and those without a cyclic structure as well as shorter peptides and amino acids and their derivatives and salts will hereinafter be referred to as "cyclosporins". Pharmacologically-acceptable forms of cyclosporins will hereinafter be referred to as "treatment medication or treatment medications."

As described above, the present invention, in various aspects thereof, teaches medications of the family of cyclosporins and all known salts, variants, amino acid variants, derivatives, metabolites and their salts and derivatives, for use in treatments of the conditions listed below. This includes cyclosporin A, cyclosporin C, cyclosporin D, cyclosporin G. this includes all products of the fungus *Tolypocladium Inflatum Gams*. Some known metabolites of cyclosporin A include the following: (according to Hawk's Cay nomenclature) AM1, AM9, AM1c AM4N, AM19, AM1c9, AM1c4N9, AM1A, AM1A4N, AM1Ac, AM1AL, AM11d, AM69, AM4N9, AM14N, AM14N9, AM4N69, AM99N, dihydro-CsA M17, AM1c-GLC, sulphate conjugate of cyclosporin, unfdl, BH11a, BH15a, B, G, E, (and with some overlap with the Hawk's above, according to Maurer's nomenclature) M1, M2, M3, M4, M5, M6, M7, M8, M9, M10, M11, M12, M13, M14, M15, M16, M17, M18, M19, M20, M21, M22, M23, M24, M25, M26, MUNDF1 and MeBMT. Some metabolites of cyclosporin G include GM1, GM9, GM4N, GM1c, GM1c9 and GM19.

Cyclosporins are believed to be neuroprotective by the mechanism of protecting the intracellular biochemistry, form, function and organelles from irreversible damage during the period of loss of cellular homeostasis. The pathway from cell damage to cell death is blocked by this neuroprotective agent, so that once the physiologic disruption passes, the cell is able to re-establish equilibrium and repair the damage, instead of dying. No treatment medication blocks the nervous tissue cell death as well as cyclosporins. Cyclosporins block either the final common pathway to cell death, or block several crucial sequential steps, or parallel biochemical and organelle failure pathways leading to cell death. This powerful cerebral neuroprotective action has not hitherto been disclosed from any of the known cerebral therapeutic medications from the state of the art.

As described above, the present invention in other aspects also provide novel and completely new applications for the cyclosporins. Cyclosporins, as cyclic peptides, are a completely new class of substances other than those which have been found to be useful before as neuroprotective. Cyclosporins are neuroprotective agents for treating cerebral disturbances and insufficiencies of various origins, and are neuroprotective agents at acceptable physiologic and pharmacologic doses. Cyclosporins are particularly- suited for treating nervous insults from cerebral vascular diseases and insufficiencies, hypoxias and traumatic brain damage. The invention, in its various aspects, embraces the general neuroprotective effect of cyclosporins, in all conditions comprising the cellular viability of nervous tissue.

As described above, the invention in other aspects provides the use of cyclosporins for obtaining a treatment medicine and formulary drug intended for the therapeutic neuroprotective use of treating the following conditions, situations and diseases in which nervous insult occur: trauma (e.g., penetrating injury, closed head injury, intracranial mass and raised intracranial pressure, surgery and iatrogenic damage), physiologic abnormalities (e.g., electrolyte, glucose, vitamin, metabolic, homeostatic), poisons (e.g., metabolic, toxins, neurotoxins), radiation (including acute and delayed effects) and vasospasm and for each of the above, their secondary and delayed effects: to special systems including visual and optic, auditory, vestibular and olfactory: to

regions of special interest in addition to the brain including nervous tissues of the brainstem, spinal cord (e.g., myelitis and myelopathy) and the peripheral nervous system: from the diseases and processes of neuro degeneration (e.g., Alzheimer's, Parkinson's, Huntington's etc.), epilepsy (including status epilepticus), infection (e.g., herpes infection, AIDS-related neurological sequelae, AIDS myelopathy, etc.) and ageing.

Cyclosporins are suited for the neuroprotective treatment of nervous insult to embryonic and fetal nervous tissue for cell culture, production and clinical transplantation therapies in humans.

Cyclosporins are suited for the neuroprotective treatment of neural cell cultures, glial cell cultures, neural and glial cell cultures, both neural and glial origin tumour cell cultures, transfected, genetically engineered cell cultures, including those of peripheral origin, e.g., sympathetic ganglia, dorsal root ganglia, pheochromocytomas and Schwann cells.

As described above, the invention in yet another aspect provides the use of cyclosporins for obtaining a treatment medication and formulary drug intended for the therapeutic neuroprotective use of treating the following conditions, situations and diseases in which nervous insult occur, from cerebrovascular accidents, stroke and ischemic damage, causes and sources of cerebrovascular accident include intracranial sources, pressure related ischemia, extracranial sources, embolic sources, vasculopathy and coagulopathy, causes and sources of hypoxia include respiratory comprise and full body hypoxia, anexmia, red blood cell and haemoglobin malfunction and hypotension.

As described above, this invention in its broad aspects embraces the administration of cyclosporins both before, or during and after a nervous insult has occurred as neuroprotection for nervous tissue and nervous function. This is a new treatment of nervous insult.

The neuroprotective properties of cyclosporins were previously-unknown because cyclosporins do not normally cross the blood-brain barrier. As described above, this invention in its broad aspects is based on the discovery that cyclosporins are neuro-protective in conditions, situations and methods wherein the blood-brain barrier has been

opened, disrupted, bypassed, transgressed, obviated or crossed so that cyclosporins can come into contact with nervous tissue.

The blood-brain barrier is present in the endothelial cells lining the capillaries of the brain. Between these special endothelial cells are close knit connections called zonulae occludentes which prevent the diffusion of larger molecules from the vascular space into the brain. There is an electrostatic charge on the vascular surface of the capillaries, which repels charged molecules and blocks their entry. There is a mechanism of active transport of certain molecules into the brain and others out. Highly lipid-soluble drugs usually cross the blood-brain barrier easily. Methods for breaching this barrier are well-known in the art and include administration of hypertonic solutions intra-arterially and intravenously, administration of charged chemicals, mechanical disruption, trauma, packaging the treatment medication within microsomes, altering the treatment medication to make it more lipophilic or conjugating it to another substance which crosses easily.

The same principles apply to other methods of delivery. Specifically in the case of intra-arterial injection, with catheter injection or infusion into cerebral artery leading to the brain, the agent to open the blood-brain barrier and treatment medications might be administered one after the other, or together. Cyclosporins could be administered via the venous route, while the drug to open the blood-brain barrier could be administered by the arterial route.

(e) DESCRIPTION OF THE FIGURE

In the accompanying drawing:

FIG. 1 is a bar graph showing the results of neuroprotection treatment.

(f) GENERALIZED DESCRIPTION OF THE INVENTION

Normally, cyclosporins are unable to cross the blood-brain barrier. While they are lipophilic substances, they are thought to be blocked by the endothelial cell tight junctions. Interestingly, once the blood-brain barrier is disrupted, e.g., in culture, cyclosporins are specifically-taken-up and accumulated in neurons, achieving a high neuron to solution ratio of 20 after 25 minutes. This suggests, that, if the blood-brain

barrier were opened for even a short period of time, significant quantities could be actively-taken into the brain neurons. Once the blood-brain barrier reclosed, the cyclosporins would remain trapped in the brain. The endothelial cells of the brain capillaries also have an ATP-dependent active efflux mechanism for cyclosporins on their luminal surface mediated by the "multidrug transporter" P-glycoprotein. If cyclosporins were able to enter the endothelial cells, then their lipophilic nature would probably allow them ready access to the adjoining glia and neurons. Short term blocking or "poisoning" of this P-glycoprotein with medications or antibodies might provide an elegant and simple entry of cyclosporins across the blood-brain barrier during the crucial early hours after ischemia.

Cyclosporins can cross the blood-brain barrier in a number of ways: After cerebrovascular accident, the ischemia itself disrupts the blood-brain barrier within hours and molecules, e.g., cyclosporins are able to enter the brain. Osmotic agents, e.g., hypertonic radiocontrast agents, mannitol, urea, arabinose and saccharose solutions are able temporarily to disrupt the blood-brain barrier which can allow therapeutic drug delivery to the brain. These are typically given as a hypertonic solution infused for 30 seconds through a major cerebral artery. The increased permeability can begin immediately and lasts between 20 minutes to 2 hours, with blockage of large molecules before small ones. This method of opening the blood-brain barrier for delivery of otherwise excluded chemotherapeutic drugs is used successfully to treat brain tumours in humans. The blood-brain barrier could be opened by the less-invasive and more-convenient intravenous route (through standard intravenous line in the antebrachial vein of the arm) with a mannitol solution P. Chemicals, e.g., positively-charged protamine, disrupt the negative-repulsing-charge on the brain vascular endothelium, temporarily opening the blood-brain barrier. These are typically given by intracarotid injection. Cyclosporins could be chemically-altered in their composition in order better to cross the blood-brain barrier by making them more lipid soluble, by (de)glycosylating, by cationizing, by liposome entrapping or by coupling or conjugating with a substance or carrier that facilitates transfer across the blood-brain barrier.

Administration of the treatment medication may be by any suitable route including oral, sublingual, buccal, nasal, inhalation, parenteral (including intraperitoneal, intraorgan, subcutaneous, intradermal, intramuscular, intraarticular, venous (central, hepatic or peripheral), lymphatic, cardiac, arterial, including selective or superselective cerebral arterial approach, retrograde perfusion through cerebral venous system, via catheter into the brain parenchyma or ventricles), direct-exposure or under-pressure onto or through the brain or spinal tissue, or any of the cerebrospinal fluid ventricles, injections into the subarachnoid, brain cisternal, subdural or epidural spaces, via brain cisterns or lumbar puncture, intra and peri-ocular instillation including application by injection around the eye, within the eyeball, its structures and layers, the ear, including the Eustachian tube, mastoid air cells, external and internal auditory canals, tympanic membrane, middle ear, inner ear including the cochlear spiral ganglion and labyrinthine organs, as well as via enteral, bowel, rectal, vaginal, urethral or bladder cisternal. For *in utero* and perinatal indications, then injections into the maternal vasculature, or through or into maternal organs including the uterus, cervix and vagina and into embryo fetus, neonate and allied tissues and spaces, e.g., the amniotic sac, the umbilical cord, the umbilical artery or veins and the placenta, with parenteral being the preferred route. The preferred route may vary depending on the condition of the patient.

Included in aspects of the invention is the teaching of administration of the treatment medication via any means with purposeful disruption of brain or spinal parenchyma, or disrupting the blood-brain barrier via mechanical, thermal, cryogenic, chemical, toxic, receptor inhibitor or augmentor, osmotic, charge altering, radiation, photon, electrical or other energy or process.

As disclosed above, this invention in other aspects includes a disclosure of all methods of administering treatment medications along with all methods of opening, bypassing or disrupting the blood-brain barrier in combination, simultaneously or in sequence to get the treatment medication in contact with nervous tissues.

As disclosed above, this invention in yet other aspects includes a teaching of the possibility of the timing and sequence of delivery of treatment medications to include pretreatment. For the treatment medications to have the best opportunity to protect

nervous tissue from nervous insult, it needs to be available as soon as possible within the affected cells. This would include administration before the nervous ischemic insult in situations of increased likelihood of ischemia or stroke. Known or anticipatory situations include surgery (carotid endarterectomy, cardiac, vascular, aortic, orthopedic) endovascular procedures, e.g., any type of arterial catheterization (carotid, vertebral, aortic, cardiac, renal, spinal, Adamkiewicz and others) for diagnostic or therapeutic purposes including evaluation and treatment of vascular stenosis, aneurysm or arteriovenous malformation and/or injection of embolic agents, coils or balloons for haemostasis, interruption of vascularity or treatment of brain lesions, predisposing medical conditions, including crescendo transient ischemic attacks, anticipated emboli or sequential strokes. Post-treatment, for stroke, or ischemia that has occurred prior to the administration of cyclosporins, it is important to get the drug to the affected cells as quickly as possible during or after the event. The time between stroke, diagnosis and treatment should be reduced to its minimum to save the ischemic cells from damage and death. The ideal temporal relation would be the simultaneous-opening of the blood-brain barrier and availability of cyclosporins to enter the brain ischemic tissue as soon after the stroke as possible.

While it is possible for the treatment medication to be administered alone, it is preferred to present it as part of a pharmaceutical formulary drug. The formulary drug used in this aspect of this invention may comprise at least one administered treatment medication as defined above, together with one or several appropriate carriers thereof and possibly other pharmaceutical treatment medications. The carriers must be appropriate in that they can readily coexist with the other agents of the formulary drug and are not detrimental to the receiver thereof. This treatment medication combined, as described in this paragraph, with other appropriate agents common to the art, is defined herein as the formulary drug.

The formulary drug includes those suitable for administration by the routes including oral, sublingual, buccal, nasal, inhalation, parenteral (including intraperitoneal, intraorgan, subcutaneous, intradermal, intramuscular, intraarticular, venous (central, hepatic or peripheral), lymphatic, cardiac, arterial, including selective or superselective

cerebral arterial approach, retrograde perfusion through cerebral venous system, via catheter into the brain parenchyma or ventricles), direct exposure or under pressure onto or through the brain or spinal tissue, or any of the cerebrospinal fluid ventricles, injections into the subarachnoid, brain cisternal, subdural or epidural spaces, via brain cisterns or lumbar puncture, intra and peri-ocular instillation including application by injection around the eye, within the eyeball, its structures and layers, the ear, including the Eustachian tube, mastoid air cells, external and internal auditory canals, tympanic membrane, middle ear, inner ear including the cochlear spiral ganglion and labyrinthine organs, as well as via enteral, bowel, rectal, vaginal, urethral or bladder cisternal. For *in utero* and perinatal indications, then injections into the maternal vasculature, or through or into maternal organs including the uterus, cervix and vagina and into embryo fetus, neonate and allied tissues and spaces such, e.g., the amniotic sac, the umbilical cord, the umbilical artery or veins and the placenta, with parenteral being the preferred route.

The formulary drug may be distributed and made available in convenient unit dose form, e.g, capsules and ampoules, containing the treatment medication of aspects of the invention and may be manufactured and distributed by any of the methods known to the pharmaceutical arts. In addition to the treatment medication, the formulary drug can also contain other usual agents of the art relating to the type of formulary drug produced. The formulary drug may, by example, take the configuration of suspensions, solutions and emulsions of the treatment medication in lipid, non-aqueous or aqueous diluents, solvents, dissolving agents, emulsifiers, syrups, granulates or powders, or mixtures of these. The formulary drug can also contain colouring agents, preservatives, perfumes, flavouring additions and sweetening agents. In addition to the treatment medication, the formulary drug can also contain other pharmaceutically-active medications. The manufacture and distribution of the formulary drug is carried out by techniques known to the art, e.g., evenly and intimately bringing together the treatment medication with liquids or fine solids or both and then if needed, forming the formulary drug into a dose unit form. The discrete dose, portion and carrier vehicle constituting the formulary drug

will generally be adapted by virtue of shape or packaging for medical administration and distributed for this purpose.

5 The formulary drug which is acceptable for oral administration may be manufactured and distributed as individual dosage units e.g., capsules, pills, tablets, dragees, dissolvable powders, or cachets, each containing a known dose of the treatment medication, as powder or granules, as solution or suspension in syrups, elixirs as a lipid, aqueous liquid or a non-aqueous liquid, or as an oil-in-water emulsion or as a water-in-oil emulsion.

10 Tablets can be manufactured and distributed by compressing or moulding, from treatment medication possibly with one or more additional pharmaceutically-active compounds. Compressed tablets can be manufactured and distributed through compression in a machine typical to the art a known quantity of the treatment medication in a dispersible configuration, e.g., powder or granules, possibly mixed with other agents including binders, lubricants, inert diluents, preservatives and dispersing agents.

15 Moulded tablets can be manufactured and distributed by moulding, in a machine typical to the art, a mix of known quantity of treatment medication, additional pharmaceutically-active compounds and other additives, moistened with a liquid diluent. The tablets can possibly be coated, enveloped or covered, with substances including protective matrices, which can contain opacifiers or sweeteners and can be formulated to allow slow or

20 controlled release, or also release within a certain part of the digestive system of the contained treatment medications. Capsules can be manufactured and distributed by placement of a known quantity of treatment medication, additional pharmaceutically-active compounds and additives within a two part or sealed capsule of gelatine or other aqueous dissolvable substance. The treatment medication can also be manufactured and

25 distributed as formulary drug in microencapsulated, microsomal, micellar and microemulsion forms.

30 The formulary drug containing the treatment medication acceptable for oral topical administration can be manufactured and distributed as lozenges containing the treatment medications, other pharmaceutically-active compounds and additives in a flavoured basis, e.g., acacia and tragacanth, pastilles containing the active treatment medication with

other pharmaceutically-active compounds and additives in an inert base, e.g., gelatine and sucrose, mouthwashes or rinses containing the treatment medication with other pharmaceutically-active compounds and additives in an acceptable liquid.

5 The formulary drug containing the treatment medication which is acceptable for skin topical administration can be manufactured and distributed as ointments, oils, creams, lotions, gels, pastes and transdermal patches containing the treatment medication, other pharmaceutically-active compounds, and additives and an acceptable carrier medium.

10 The formulary drug containing the treatment medication which is acceptable for nasal administration can be manufactured and distributed with other pharmaceutically-active compounds and additives as a powder for inhalation, or as an oily, aqueous or non-aqueous liquid for nasal spray or drops.

15 The formulary drug containing the treatment medication which is acceptable for rectal administration can be manufactured and distributed as suppositories, creams, foams, douches or enemas with other pharmaceutically-active compounds, suitable bases of the usual water-soluble diluents, fats and additives known to practitioners of the art.

20 The formulary drug containing the treatment medication which is acceptable for vaginal administration can be manufactured and distributed as pessaries, suppositories, creams, gels, foams, douches or sprays with other pharmaceutically-active compounds, suitable bases and additives known to practitioners of the art.

25 The formulary drug containing the treatment medication which is acceptable for parenteral administration can be manufactured and distributed from aqueous and non-aqueous sterile injection solutions, other pharmaceutically-active compounds, additives including anti-oxidants, bacteriostats and solutes and sugars, e.g., mannitol to make the formulary drug isotonic, hypotonic or hypertonic with the blood of the recipient; and aqueous and non-aqueous sterile suspensions which can include suspenders and thickeners. The formulary drug can be manufactured and distributed in unit-dose or multi-dose containers, e.g., sealed-glass or plastic ampoules, vials, bottles and bags as a liquid and in a dry-state requiring only the addition of sterile liquid, for example, 30 water, saline or dextrose solutions, immediately prior to use. Extemporaneous solutions

and suspensions for injection can be prepared from powders and tablets of the kind described above.

5 The formulary drug containing the treatment medication which is acceptable for administration into the brain and related structures, spinal cord and related structures, ventricular system and cerebrospinal fluid spaces can be manufactured and distributed from aqueous and non-aqueous sterile injection solutions, other pharmaceutically-active compounds, additives including anti-oxidants, bacteriostats and solutes and sugars, e.g., mannitol, to make the formulary drug isotonic hypotonic or hypertonic with the cerebrospinal fluid and also aqueous and non-aqueous sterile suspensions which can include suspenders and thickeners. The formulary drug can be manufactured and distributed in unit-dose or multi-dose containers, e.g., sealed-glass or plastic ampoules, vials, bottles and bags as a liquid and in a dry-state requiring only the addition of sterile liquid, for example, water, saline or dextrose solutions, immediately prior to use. Extemporaneous solutions and suspensions for injection can be prepared from powders and tablets of the kind described above.

15 The desired unit doses of formulary drugs are those containing a daily dose or nervous-insult-treatment dose, or an appropriate fraction thereof, of the administered treatment medication. Unit dose forms of the compositions of aspects of invention may also include more complex systems, e.g., double-barrelled syringes, syringes with sequential compartments, one of which may contain the treatment medication and the other any necessary diluents or vehicles, or agents for opening the blood-brain barrier. The agents in the syringes would be released sequentially, or as a mixture or combination of the two, after the triggering of the syringe plunger. Such systems are known in the art.

25 The formulary drug generally contains from 0.1% to 90% of the treatment medication by weight of the total composition. Amounts of from 0.0001 mg to 50 mg/kg, or preferably 0.001 mg to 25 mg/kg, of body weight per day for parenteral administration and 0.001 mg to 100 mg/kg, preferably 0.01 mg to 60 mg/kg, of body weight per day for enteral administration, and be given to achieve neuroprotection. Nevertheless, it could be necessary to alter those dosage rates, depending on the

condition, weight and individual reaction of the subject to the treatment, the type of
formulary drug in which the treatment medication is administered and the mode in which
the administration is carried out and the stage of the disease process or interval of
administration. It may, thus, be sometimes adequate to use less than the before-stated
5 minimum dose, while in other instances the upper-limit must be surpassed to obtain
therapeutic results.

As described above, the invention in another aspect teaches the use of the
treatment medication in the conditions described throughout the application. The
invention in other aspects, thus, also includes all advertising, labelling, packaging,
10 informational materials, inserts, product descriptions, advertising materials, the written-
word, including letter, pamphlet, brochures, magazines and books, as well as other
medium of communication including the spoken-word, fax, phone, photos radio, video,
television, film, internet, e-mail or computer-based and proposal for clinical trials and
study protocols for clinical trials using the treatment medication for its neuroprotective
15 effect.

(g) EXPERIMENT

Experimental animals were subjected to hypotension by exsanguination and
forebrain ischemia by clamping the bilateral carotid arteries for 10 minutes. The neurons
of the CA1 area of the hippocampus are highly-sensitive to ischemic insult, with their
20 resultant cell death. Animals that received vehicle with or without opening the blood-
brain barrier had more than 80% cell death. Animals that received cyclosporin A but
without opening the blood-brain barrier had more than 80% cell death. Animals that
received cyclosporin A with the opening of the blood-brain barrier had only 11% cell
death. This dramatic neuroprotection is much greater than for any other known
25 neuroprotective agent. This neuroprotection from hypoxic and ischemic insult by a
combination of cyclosporin and opening the blood-brain barrier is a novel discovery.
Results of neuroprotection by the treatment medication wherein the blood-brain barrier
has been opened in the animal model of human nervous ischemic insult are presented in
the graph of FIG. 1.

(h) AT LEAST ONE MODE FOR CARRYING OUT THE INVENTION

The following Examples 1 through 10 illustrate various aspects of the invention.

Examples 1 through 6 illustrate conditions and situations wherein the treatment medication of aspects of the invention can be brought into contact with nervous tissue and which are means to getting it in contact with nervous tissue, that is, when the blood-brain barrier is disrupted or open.

Example 1

Under local anaesthesia, a catheter is inserted percutaneously in the femoral artery and then passed cephalad into one of the internal carotid arteries. A volume of 270 ml of hypertonic solution of 20% mannitol is infused at a rate of 9 ml per second for 30 seconds into the internal carotid artery to produce blood-brain barrier disruption and opening. The extent of blood-brain barrier opening can be seen with MRI or contrast CAT scan.

Example 2

Under local anaesthesia and sedation, incision is made through the scalp, exposing the bone of the skull. A drill is used to make a hole through the skull. The dura is opened. A catheter is placed through the brain parenchyma, disrupting and opening the blood-brain barrier. The catheter tip will rest within the ventricular system.

Example 3

A patient has had a cerebrovascular accident with breakdown and opening of the blood-brain barrier.

Example 4

A patient has had trauma to the head, with disruption of brain tissue and disruption and opening of the blood-brain barrier.

Example 5

A patient has had trauma to the spinal cord, with disruption of spinal cord tissue and disruption and opening of the blood-brain barrier in the spinal cord.

Example 6

A patient has had surgery of the brain, with disruption and opening of the blood-brain barrier.

Once the blood-brain barrier is disrupted or opened, the following examples 7 through 10 illustrate the administration of formulary drugs of the aspects of the invention.

Example 7

5 Sterile Injectable Concentrate Formulary Drug

Containing per ml:

Cyclosporin A	50 mg
<i>Spiritus fortis</i>	280 mg
Polyoxyethylated castor oil	650 mg

10 The formulary drug is sterilized by heat or radiation and then placed in a sealed container, e.g., a glass in doses of 1 ml or 5 ml.

A sterile injectable concentrate formulary drug is diluted 1 ml in 20 ml saline so that it may be administered by infusion or by injection into artery, vein, brain, spine or cerebrospinal fluid spaces.

15 Example 8

Capsule Formulary Drug

	Cyclosporin A	100 mg
	Iron oxide (E172)	1 mg
	Titanium dioxide	3 mg
20	Ethanol	100 mg
	Corn oil	415 mg
	Gelatine	280 mg
	LABRAFIL _{TM}	300 mg
	ANDRISORB _{TM}	105 mg
25	Glycerol (85%)	3 mg

A one or two part capsule is prepared by placing the formulary drug in a one or two part gelatine capsule.

21

Example 9

Capsule Enhanced Absorption Formulary Drug

	Cyclosporin A	100 mg
	Iron oxide (E172)	1 mg
5	Titanium dioxide	2 mg
	Propylene glycol	150 mg
	Tocopherol	1 mg
	Ethanol	100 mg
	Corn oil	345 mg
10	Gelatine	300 mg
	Glycerol 85 %	40 mg
	POLYOXYL 40 _{TM} (hydrogenated castor oil)	405 mg

A one or two part capsule is prepared by placing the formulary drug in a one or two part gelatine capsule.

15

Example 10

Liquid Oral Formulary Drug

	Containing per 1 ml:	
	Cyclosporin A	100 mg
	Ethanol	100 mg
20	Corn oil	430 mg
	LABRAFIL _{TM}	300 mg

CLAIMS

1. An article of manufacture comprising:

packaging material, said packaging material comprising a label which indicates that a pharmaceutical agent can be used for reducing or preventing nervous damage caused by traumatic, metabolic, ischemic or hypoxic neural insult; and

a medication comprising a pharmaceutical agent contained within said packaging material, said pharmaceutical agent being therapeutically-effective for reducing or preventing nervous damage caused by traumatic metabolic, ischemic or hypoxic neural insult when the pharmaceutical agent is able to cross the blood-brain-barrier to contact the nervous tissue in a therapeutically-effective quantity, said pharmaceutical agent comprising cyclosporin A or a compound of the class of cyclosporins, or functional derivatives, metabolites, variants or salts thereof, or combination thereof, either alone or in admixture with diluents, or additives.

2. An article of manufacture comprising:

packaging material, said packaging material comprising a label which indicates that two pharmaceutical agents can be used together for reducing or preventing nervous damage caused by traumatic, metabolic, ischemic or hypoxic neural insult; and

a medication comprising two pharmaceutical agents contained within said packaging material;

wherein a first of said two pharmaceutical agents is therapeutically-effective for reducing or preventing nervous damage caused by traumatic, metabolic, ischemic or hypoxic neural insult when said first pharmaceutical agent is able to cross the blood-brain-barrier to contact the nervous tissue in a therapeutically-effective quantity, said first pharmaceutical agent comprises cyclosporin A or a compound of the class of cyclosporins, or functional derivatives, metabolites, variants or salts thereof, or combination thereof, either alone or in admixture with diluents, or additives and

wherein a second of said two pharmaceutical agents increases the permeability of the blood-brain-barrier to the first pharmaceutical agent, said second pharmaceutical agent comprising one or several compounds that open the blood-brain-barrier through one or several mechanisms including hyperosmotic mannitol solution, protamine sulphate

electrostatic charge blocker and inhibitors of the P-glycoprotein multidrug transporter system whether alone or in admixture with diluents, or additives.

3. The article of manufacture as claimed in claim 1 or claim 2, wherein said medication containing cyclosporin A or cyclosporins is in a form for being administered orally.

4. The article of manufacture as claimed in claim 1 or claim 2, wherein said medication containing cyclosporin A or cyclosporins is in a form for being administered intra-arterially.

5. The article of manufacture as claimed in claim 1 or claim 2, wherein said medication containing cyclosporin A or cyclosporins is in a form for being administered intravenously as a sterile, injectable formulary drug.

6. The article of manufacture as claimed in claim 1 or claim 2, wherein said medication containing cyclosporin A or cyclosporins is in a form for being administered parenterally as a sterile injectable formulary drug.

7. The article of manufacture as claimed in claim 1 or claim 2, wherein said medication containing cyclosporin A or cyclosporins is in a form for being administered into or adjacent to the brain, cerebrospinal fluids or spinal cord as a sterile injectable formulary drug.

8. The article of manufacture as claimed in claim 1 or claim 2, wherein said medication containing cyclosporin A or cyclosporins is in a form for being administered by a combination of the routes as claimed in claims 4 to 7.

9. Use of an effective nervous insult-treatment-amount of cyclosporin A for the manufacture of a medication as claimed in claims 1 to 8, for the treatment of a human with nervous insult and in whom the blood-brain barrier has been opened or where cyclosporin A is able to cross the blood-brain barrier.

10. Use of an effective nervous-insult-treatment-amount of cyclosporins, or functional derivatives, metabolites, variants or salts thereof, for the manufacture of a medication as claimed in claims 1 to 8, for the treatment of a human with nervous insult and in whom the blood-brain barrier has been opened or where cyclosporins are able to cross the blood-brain barrier.

11. Use of an effective nervous-insult-treatment-amount of cyclosporin A as a medication as claimed in claims 1 to 8, for the treatment of a human with nervous insult and in whom the blood-brain barrier has been opened or where cyclosporin A is able to cross the blood-brain barrier.

12. Use of an effective nervous-insult-treatment-amount of cyclosporins, or functional derivatives, metabolites, variants or salts thereof, as for the medication claimed in claims 1 to 8, for the treatment of a human with nervous insult and in whom the blood-brain barrier has been opened or where cyclosporins are able to cross the blood-brain barrier.

13. The use as claimed in claim 11 or claim 12, for treating a human with nervous insult, with the exclusion of nervous ischemic insult.

14. The use as claimed in claim 11 or claim 12, for the treatment of cerebral insult and cerebral disorders.

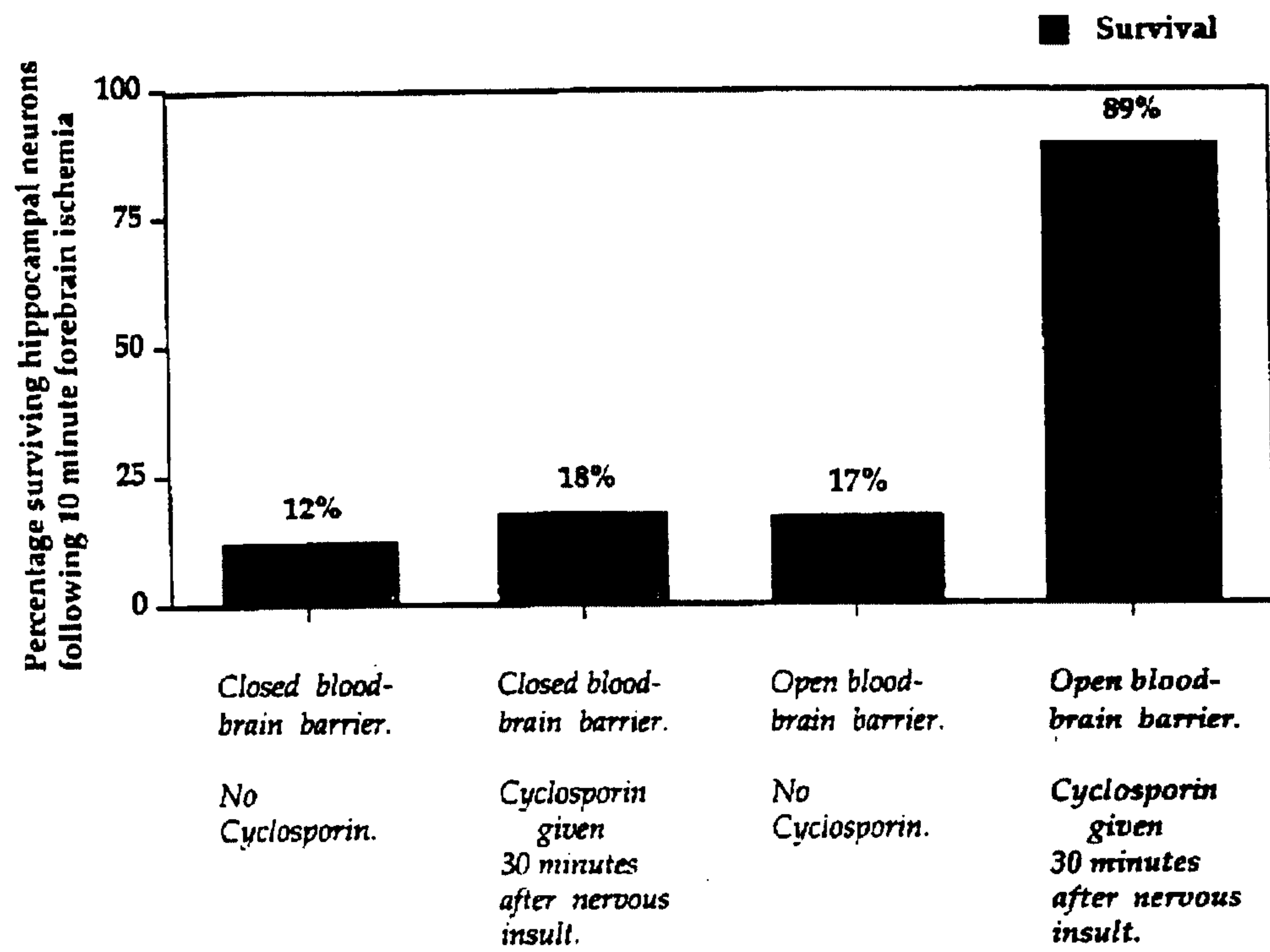
15. The use as claimed in claim 11 or claim 12, for the treatment of: penetrating injury, closed head injury, intracranial mass and raised intracranial pressure, surgery and iatrogenic damage, electrolyte physiologic abnormalities, glucose physiologic abnormalities, vitamin physiologic abnormalities, metabolic physiologic abnormalities and homeostatic physiologic abnormalities, metabolic poisons, toxins, neurotoxins, radiation and vasospasm, secondary and delayed effects to the visual and optic system, secondary and delayed effects to the vestibular system, secondary and delayed effects to the olfactory system, nervous tissues of the brain stem, spinal, cord, myelitis and myelopathy and the peripheral nervous system, diseases and processes of neurodegeneration, Alzheimer's disease, Parkinson's disease, Huntington's disease, epilepsy, herpes infection, AIDS-related neurological sequelae, AIDS myelopathy and ageing.

16. The use as claimed in claim 11 or claim 12, for the neuroprotective treatment of nervous insult to embryonic and fetal nervous tissue for cell culture, and production and clinical transplantation therapies in humans.

17. The use as claimed in claim 11 or claim 12, for neuroprotective treatment of neural cell cultures, glial cell cultures, neural and glial cell cultures, both neural and glial origin tumour cell cultures, transfected, genetically-engineered cell cultures,

including those of peripheral origin, sympathetic ganglia, dorsal root ganglia, pheochromocytomas and Schwann cells.

18. The use as claimed in claim 11 or claim 12, for the treatment of the following conditions, situations and diseases in which nervous insult occur: from cerebrovascular accidents, stroke and ischemic damage and intracranial sources, pressure related ischemia, extracranial sources, embolic sources, vasculopathy and coagulopathy and respiratory compromise and full body hypoxia, anemia, red blood cell and haemoglobin malfunction and hypotension.

**FIG. 1**