Spongiform encephalopathies- as a loss of parasympathetic function ?

Most cases of BSE in Great Britain have occurred in dairy cows between 3 and 6 years of age… There were variations in the frequency with which some signs were recorded in animals observed at different times during the epidemic (WILESMITH et al., 1992). These „different variations“ in older animals; it seems are in connection with the neurovegetative disorders…

Cows affected by BSE show a reduced time spent ruminating, although eating time is maintained at normal levels. This reduction can be marked and rumination can cease(AUSTIN and SIMMONSON, 1993).

More detailed research of the clinical neurology has indicated a reduced heart rate such that more than 50 percent of measurements from BSE cases were less than 50 beats per minute. In addition, the administration of 35 mg of atropine suplhate increased the heart rate of animals with BSE, but had no effect on healthy cows. These observations have led to the suggestion that the bradycardia is mediated by increased vagal tone and could result from the pathology in the medullary vasomotor centers (AUSTIN et al., 1996).

Concernig the association between the autonomic nervous system function and the BSE incidence; much evidence suggests that so-called prions are harmless, noninfectious products. The importance of the cholinergic system allows a new simplified interpretation of these conditions. According to AXELSSON (2001), a change in handedness (chirality) in some acids appears to be the basic physical change in degradation- resistant proteins (prions) found in conditions such as CJD, Alzheimer´s disease, BSE, and ovine scrapie. **The affected structures are primarily innervated by cholinergic nerves. The main steps are the acetylcholine- cholinesterase splitting of body water with release of free protons in solution, followed by electron dissipation, dioxygen activation and Ca- fluxes (AXELSSON, 2001)**

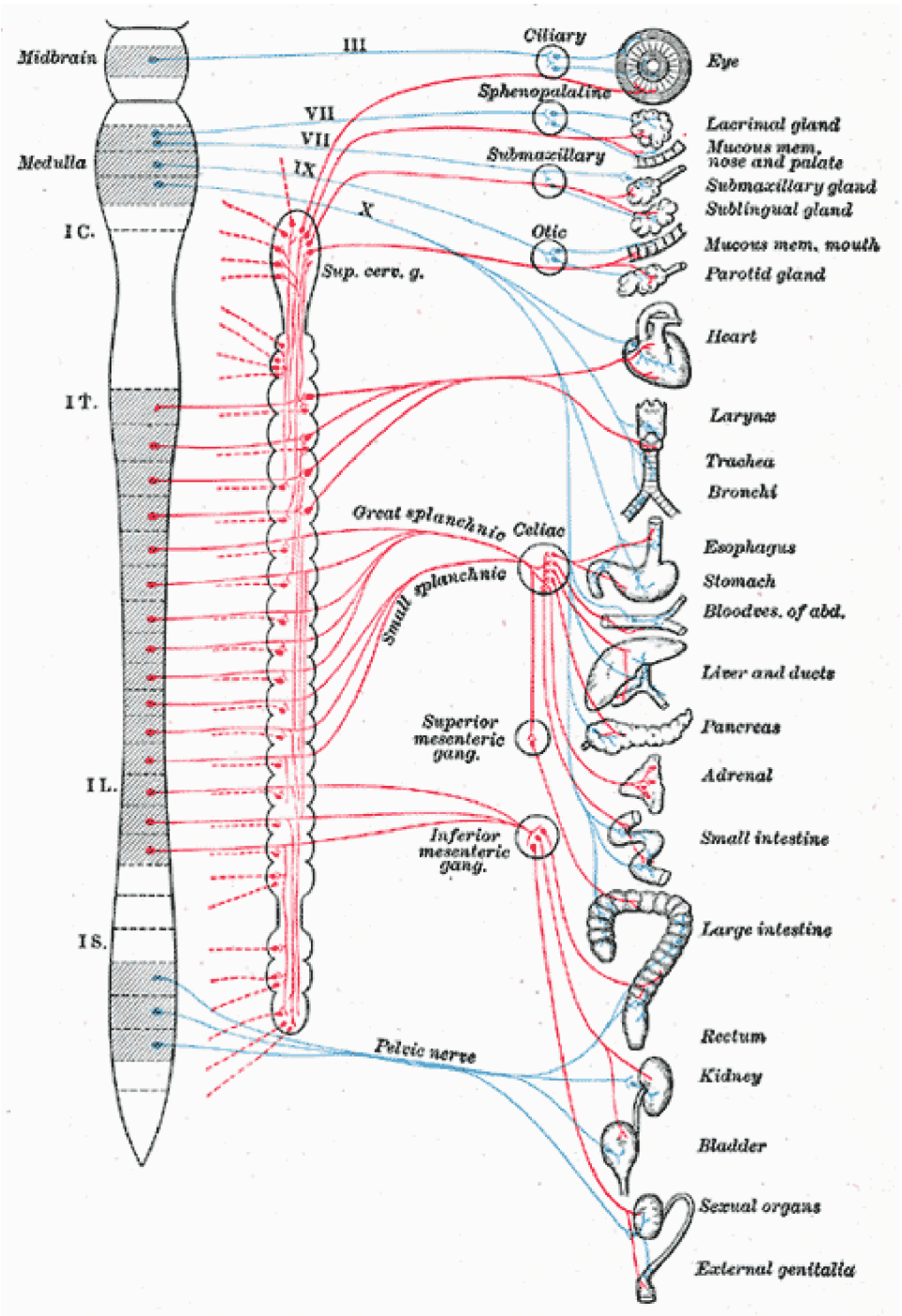
Abiotic physics conserves parity and symmetry by equal amounts of L- and D- forms of molecules. In contrast, the asymmetric pattern of life must be homochiral. Such biomolecules dissolve in water and are thus able to interact in cholinergic hydrodynamics. It is supposed that the instability of the composite interact in cholinergic hydrodynamics. It is supposed that the instability of the composite weak force by beta-decay causes changes in chirality. These extremely rare events are not frequent enough to explain disease pathology. Experimental, accidental, surgical and abusive inoculations will propagate chirons according to the physical law of self-replication, which also occurs in test tubes without added biological products. **Chirons will not to be degraded into amino acids in the alimentary canal and will, because they are indigestible, leave the body with the faeces.** Chirons are inert also to the immune system and will be engulfed without reaction by phagocytosing cells. They are then stored away in tissues, where they do no harm (if not detected and suspected to be deleterious, thereby causing pathogenic anxiety).

The cholinergic system reacts to all kinds of integrity threats and it is this reaction which AXELSSON (2001) proposes causes the so-called prion diseases. This pathology seems generally valid, and is here exemplified in AD, CJD, and Kuru disease. **It is a cholinergic reaction and not the agent per se that is pathogenic.** This is also true of viral infections where the interaction between viral infection and response may explain the enigmatic epidemiology of many neurovegetative diseases. Intensity and duration of challenges will determine pathophysiology. **The new variant of CJD (vCJD), is assumed from mutation of a slow virus agent into a more intense variant, which will give disease in younger patients.** The **pathology is primary protonic**, with overactivity in most sub-systems of

either enhancing or inhibiting character., but also functional failure or cell death by membrane damage and acidification, for instance in the CNS.

The practical results of this proposal will be alleviation of the current BSE crisis. So, the important main aspects are; **chirons are not infectious proteins but inert physical by-products;** they are indigestible and not immunogenic, so beef is safe; properly processed and handled meat and bone meal are not likely to transmit neurovegetative diseases**; chirons cannot even serve as markers in neurologic disease (AXELSSON, 2001).**

Fig 1 Autonomic nervous system
Sympathetic (red) and parasympathetic (blue) nervous system



The loss of parasympathetic function unmasks the baseline syphathetic bias inherent

in the end-organs, resulting in the familiar **signs of aging including tachycardia, constipation,** insomnia, erectile dysfunction, fluid retention, and systemic inflamantion**.** Thes consequences in turn may contribute to many of the common diseases associated with aging including type-2 diabetes, Alzheimer´s, atherosclerosis, and cancer. **Maintenance and resoration of the parasympathetic function** may enable upstream control over the deleterious aspects of inherent end-organ adrenergic bias (LEE et al., 2004).

Transmissible spongiform encephalopathies are commonly propagated by extracerebral inoculation of the infectious agent. Indirect evidence suggests that entry into the central nervous system occurs via the peripheral nervous system. GLATZEL et al. (2001) **concluded that sympathetic innervation of lymphoid organs is rate limiting for prion neuroinvasion and that splenic sympathetic nerves may act as extracerebral prion reservoirs.**

The autonomic nervous system (ANS) regulates bodily functions and the activity of specific organs. As example, the ANS plays a role in the diameter of the pupils. The mechanism of mydriasis usually involve either a disruption of the parasympathetic nerve which causes contraction of the pupil, or over- activity of the sympathetic nervous system (SNS). LEGGETT et al (1990) reported that a cat which developed a change of temperament, with muscle tremors, ataxia and **pupillary dilatation** was suspected and later confirmed histopathologically to have a spongiform encephalopathy. So, we can conclude that the SNS prevails in „**spongiform encephalopathy cat".**

These findings show that the autonomic (vegetative) nervous system is involved. It was summarized, that the tonicity of parasympathetic nervous system is maintained by Mg^{2+} and OH^{-}: the tonicity of the sympathetic system is maintained by Ca^{2+} and H^{+}. Overdosage of Ca^{2+} (and H^{+}) causes the inhibition of the sympathetic and the parasympathetic nervous system action prevails (excites). Overdosage of the Mg^{2+} (and OH^{-})causes the inhibition of the parasympathetic and the sympathetic nervous system prevails –excites (BEČKA; 1935). This sympatikotony is evident in cow´s paresis puerperalis (HLÁSNÝ, 2000).

The **autonomic nervous system** (ANS) is the part of the nervous system of the higher life forms that is not consciously controlled. It is commonly divided into two usually antagonistic subsystems: the sympathetic and parasympathetic nervous system, and involves the homeostasis of organs and physiological functions. In general, the parasympathetic nervous system (PNS) is involved with digestion and energy conservation, while the sympathetic (SNS) nervous system is involved with energy expenditure and the 'fight or flight' response.

Function

The autonomic nervous system regulates bodily functions and the activity of specific organs. As examples, the ANS plays a role in the diameter of blood vessels, heart rate, force of contraction of the heart, diameter of the pupils, salivation, perspiration, bronchiole diameter, peristaltic movements in the intestine, spinctor diameter, erection, ejaculation, and parturition.

The SNS and PNS often have opposing effects in the same organs or physiological systems, and the ANS is a major factor in homeostasis.

The sympathetic nervous system (SNS) is frequently referred to as the "fight or flight" system, as it has a stimulating effect on organs and physiological systems. For example, the SNS constricts blood vessels feeding blood to the GI tract and skin, while dilating skeletal muscle and lung blood vessels. Bronchioles also dilate allowing more oxygen to be

exchanged at the lungs. At the same time, the SNS increases heart rate and contractility of the heart. This vastly increases blood flow to the skeletal muscles and diverts blood away from organs such as the GI tract which are not important during the "fight or flight" response. Sympathetic nerves also dilate the pupils and relax the lenses, allowing more light to enter the eyes and enabling one to see further.

The parasympathetic nervous system has sometimes been called the "rest and digest" response. The PNS slows and relaxes many functions of organs and body systems. For example, the PNS will **dilate blood vessels to the GI tract, while slowing the heart beat and decreasing the force of the heart's contractions.** These effects help to lower the metabolic strain on the body, resulting in energy conservation. The PNS can divert blood back to the skin and the gastrointestinal tract. **Increased blood flow to the GI tract aids digestion**. The PNS also **constricts the bronchioles** when the need for oxygen has diminished. During accomodation, the PNS **causes the constriction of the pupils and lenses**. The PNS **stimulates salivary gland secretion, and accelerates peristalsis**, so although the PNS generally has a calming effect on the body, it does stimulate activity too.

The cell bodies of preganglionic autonomic nerve cells are situated in the central nervous system (CNS). Those of the sympathetic nervous system arise in the thoracic and lumbar segments of the spinal cord. The preganglionic parasympathetic cell bodies are situated in the brain stem (cranial parasympathetic) and in the sacral spinal cord (sacral parasympathetic).
In order to reach the target organs and glands, the axons of neurons in the SNS and PNS often must travel long distances in the body. In the SNS and PNS, neurons from the CNS synapse at ganglions; a site where a group of neurons of similar function (called presynaptic neurons) connect to another group of neurons (called postsynaptic neurons), by means of a synapse. Ganglions allow for the modulation of the presynaptic input before it is sent along the postsynaptic neurons to their effector sites.

The main neurotransmitter that is located at the ganglion is acetylcholine. Acetylcholine is released from the presynaptic neuron and acts on postsynaptic nicotinic receptors in both the SNS and PNS. Postsynaptic cells pass signals to the effector organs. At the effector organs, SNS postsynaptic neurons release noradrenaline (norepinephrine) to act on adrenoceptors, with the exception of the sweat glands and the adrenal medulla. At sweat glands, the neurotransmitter is acetylcholine, which acts on muscarinic receptors. At the adrenal cortex, there is no postsynapic neuron. Instead the presynaptic neuron releases acetylcholine to act on nicotinic receptors. Stimulation of the adrenal medulla releases adrenaline (epinephrine) into the bloodstream which will act on adrenoceptors, producing a widespread increase in sympathetic activity. In the PNS, all postsynaptic cells use acetylcholine as a neurotransmitter, to stimulate muscarinic receptors.

The sympathetic axons build a chain of 22 ganglia, the so-called paravertebral ganglia, on each side of the spinal column. From these the splanchnic nerves run to the prevertebral ganglia, which lie in front of the aorta, at the level where its unpaired visceral arteries branch off. The left and right trunks of the sympathetic nerve fuse to form an unpaired ganglion in the pelvic area. Organs innervated by sympathetic fibres include the heart, lungs, esophagus, stomach, small and large intestine, liver, gallbladder and genital organs.

These organs are also innervated by the part side of the parasympathetic nervous system. The digestive system distal to the lower part of the colon is regulated by the sacral parasympathetic fibres via the pelvic ganglia. The more proximal digestive tract is controlled by the vagus nerve, the largest element of the cranial parasympathetic system. Like those of the vagus, other cranial parasympathetic fibers arise in the brain stem before exiting the skull with various cranial nerves, en route to the cranial parasympathetic ganglia and the innervation of the eye muscles and salivary glands.

Controversy surrounds the efficasy of enteral Mg in growing pigs

We reviewed these more than 60 years known findings of BEČKA (1935), taking the **porcine stress syndrome** (PSS) as an example (parasympathetic tonicity is maintained by homeopatic Mg doses). As indicated by tachycardia, tachypnoea, hyperglycaemia, and increased blood catecholamine and cortizol concentrations the action of the **sympathetic nervous system prevails in this condition.**. This can be due to long term Mg-deficiency, because PSS is a hypermetabolic syndrome that produces a sustained increase of intracellular Ca2+ levels, and, as the PSS progresses, the **combination of Mg-deficiency with acidosis**, triggers circulus viciosus which continues until serum K+ reaches cardiotoxic levels. It is generally known that without any systemic regulatory response, Mg deficiency would be associated with hyperkalaemia and intracellular deficiency of Mg2+ is thought to be responsible for a rise of Ca2+ in and loss of K+ from the cells.

A/ *Improved meat quality- the effect of Mg-supplementation on the PSS („organic forms")*

This mechanism when the parasympathetic tonicity is maintained by homeopatic Mg doses (BEČKA, 1935) was confirmed by Germany researchers. EHRENBERG and HELBIG (1992) investigated pigs fed 5 mg of Mg as **magnesium aspartate** hydrochloride (MAH) per kg b.w. throughout the fattening period (ca 0.016% of Mg supplemented in the diet) . The „**long term**" prolonged administration of low-dosed MAH was found to reduce the metabolic disorders that are typical features of the PSS (pH, water-binding power and meat conductivity), and **improved meat quality**. Similarly, OTTEN et al (1992; 1993) reported that **chronic low-dosed magnesium fumarate supplementation** during the growing and finishing period; (a) reduced plasma norepinephrine but not epinephrine (b)improved meat quality (muscle pH, conductivity values) and less pale meat (PSE) than when pigs were fed a standard diet.

However, SCHAEFER et al. (1993) reported that meat from pigs supplemented with **MgAsp short- term (40 g, 5 d before slaughter**), also exhibited reduced muscle temperature at 45 min after slaughter and a reduced percentage drip loss. It is clear that a high dose of MgAsp was used. The similar results were found (D´SOUZA et al.1998), when pigs (mean live weight 77 kg) in the MgAsp diet treatment were supplemented with 40 g of **MgAsp per pig per day for 5 days before transportation to the abattoir**. Pigs fed the MgAsp supplemented diet had: higher plasma Mg levels, lower plasma norepinphrine levels, lower lactic acid in the longissimus thoracis (LT), higher the muscle pH in the LT muscle at 40 min and 24 h after slaughter, lower percentage of drip loss, and had no PSE carcasses compared to pigs fed the control diet. However, pigs fed the MgAsp- supplemented and the control diet had similar glycogen concentrations in the LT and biceps femoris (BF). Data from this experiment suggest that plasma catecholamines, in particular norepinephrine, do not increase to an extent in MgAsp supplemented pigs (D´SOUZA et al., 1998). Dietary magnesium asparate (MgAsp) supplementation to pigs can be used to reduce the effects of preslaughter "stress", possibly through reducing catecholamine secretion at slaughter, and can reduce the incidence of pale, soft, exudative meat. The data demonstrated the efficasy of dietary MgAsp supplementation as a method for improving meat quality and reducing the incidence of PSS (D´SOUZA et al. 1998).

B/ Inconsistent or no effect of Mg-supplementation on the PSS („inorganic forms")

The study (HAMILTON et al., 2002) was carried out in „**short-term**" feeding of **magnesium sulfate**-fortified diets during 2, 3 or 5 days prior to slaughter. During the study, animals were fed at a fixed level of 2.75 kg of a standard finisher diet/day; the fortified **diet contained 3.2 g/d of additional magnesium (0.12% of Mg supplemented in the diet) .** Results from this study suggest an **inconsistent effect of short-term feeding of magnesium** sulfate on muscle color and drip loss in pigs.

There is other „**short-term**“ example of supplemental Mg feeding from **magnesium sulfate** (300, 600, or 900 mg of elemental Mg /L of drinking water) for 2 days before slaughter. Pigs were not allowed access to feed (0.13% of Mg) for 15 h before slaughter but continued to have access to experimental water treatments. However, magnesium **did not improve pork quality** characteristics of practical significance in pigs without the halothane and Rendement Napole mutations(FREDERICK et al., 2006)

APPLE et al. (2005) used crossbred pigs to determine the PSS preventive effects of **long-term dietary** supplementation of **magnesium mica** (MM) with 2.5% MM, as-fed basis supplemented at the expense of corn (0.435% of Mg supplemented in the diet). Diets were fed during the early-finisher and late-finisher periods. At the conclusion of the 71-d feeding trial, **pork quality traits were not improved by dietary MM**. However, delaying postmortem glycolysis and elevating 0- and 45-min muscle pH by feeding finishing diets fortified with MM may benefit the pork industry by decreasing the incidence of PSE pork in pigs subjected to short-duration, routine stressors.

The important challenges remaining before magnesium supplementation can be used to improve pork quality throughout a wide section of the industry are to clarify the most appropriate dose, duration, and source of magnesium (PETTIGREW and ESNAOLA, 2001).

Magnesium supplementation is thought to reduce pre-slaughter stress through a reduction in the release of stress hormones, including cortisol and the catecholamines, however a **definitive mechanism has not been established**. Further work in this area is needed to evaluate the potential benefits of increased dietary magnesium levels in pig diets on reducing the incidence of PSS, including an examination of the effects of diet composition, sex of the animal, pig genetics and stress susceptibility, pre-slaughter handling protocols, and the optimal level (Mg-dose) and duration of magnesium supplementation (HOUSE, 2001).

However, is well known from the published data that PSS results from a mutation in a calcium/channel gene that is inherited as an autosomal dominant trait, usually in Landrace pigs. It seems that this genetic cause can be enhanced by Mg-deficiency. In the feed ration of **growing pigs is very large Ca : Mg ratio** (NRC 1988; **13 : 1,** NRC 1998; 12: 1), compared with the human, ruminant, horse diets- there is this ratio at the level about **3 : 1**. So, the susceptibility to the Mg-deficiency is very high in the swine diets (HLÁSNÝ, 1999).

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Malignant hyperthermia (MH) or porcine stress syndrome(PSS)

According to the literature sources;

a/ description and etiology;

- hypermetabolic and hypercontractile syndrome, when triggered by anesthesia or stress, produces a sustained increase of intracellular calcium levels within skeletal muscle fibers
- it results from a mutation in a calcium- channel gene that is inherited as an autosomal dominant trait, usually in Landrace pigs
- elevated intracellular Ca increases muscular glycogenolysis and heat production and muscle tone

b/ clinical signs and biochemistry;

- the initial clinical signs are fine muscle tremor such as rapid tail tremor
- tremor progress to muscle rigor, animal is reluctant to move

- blanching and erythema followed by cyanosis are evident in white-skined pigs due to peripheral vascular constriction
- tachycardia (up to 200 beats/ min.), open mouth breathing, hyperventilation, tachykardia develops early and continues until serum K^+ reaches cardiotoxic levels
- increased metabolic utilization of glycogen causes a rapid rise blood and muscle lactate levels and a low pH of muscle
- plasma catecholamine is increased (responsible for concurent hyperglycaemia)
- the main plasma electrolyte changes are increases in potassium and phosphate
- muscle contracture and hypermetabolism develop rapidly as a direct result of this uncontrolled and sustained increase in myoplasmic Ca^{2+}
- evidence indicates that active Ca^{2+} transport at the level of the sarcoplasmic reticulum is moderately inhibited
- elevated myoplasmic Ca^{2+} levels stimulate excitation

c/ the PSS induction;

Experimentally, the PSS can be induced by inhalation of anesthetics agents as halothane:

- halothane influences myocardial performance by its affect upon Ca^{2+} dependent mechanisms
- decreases the binding and availability of Ca^{2+} at superficial membrane sites in myocardial cells and may also affect intracellular Ca^{2+} dependent inotropic processes
- halothane is known to sensitize the myocardium to catecholamines
- epinephrine is contraindicated during halothane anesthesia because of the risk of inducing cardiac arrhythmias or ventricular fibrilation

Depolarizing muscle relaxants, such as succinylcholine, and alpha-adrenergic agonists also may initiate or potentiate the PSS.

1.Treatment:

According to the literature sources:

-supportive treatment includes fluid therapy and management of acidosis through ventilatory support and administration of bicarbonate.

- magnesium sulfate (50%) appears to reverse the syndrome in some pigs: it is recommended that incremental doses of 1 g be slowly injected intravenously until heart rate and muscle tone are reduced.

2.Prevention

According to the described mechanism (professor Bečka):

a/ **low doses of Mg** during longer period:

Ehrenberger et al.(l992) found that prolonged administration (**throughout the fattening period**) of low dosed Mg-Asp-hydrochoride (5 mg of Mg/ kg BW) reduced the metabolic disorders that are typical features of the PSS (pH, water-binding power and meat conductivity).

b/ **high doses of Mg** during a short period:

Schaefer et al. (1993) reported that meat from pigs supplemented with MgAsp short- term (40 g Mg/kg BW- **only 5 days before slaughter**), also exhibited reduced the signs of PSS. The similar results were found (D´Souza et al.1998), when pigs (mean live weight 77 kg) in the MgAsp diet treatment were supplemented with 40 g of MgAsp per pig per day for 5 days before transportation to the abattoir.

Pigs fed the MgAsp supplemented diet had:

- higher plasma Mg levels
- lower plasma norepinephrine levels

- lower lactic acid in the m.longissimus thoracis (LT)
- higher the muscle pH in the LT muscle at 40 min and 24 h after slaughter
- no PSE carcasses compared to control pigs

Data from this experiment suggest that plasma catecholamines, in particular norepinephrine, do not increase to an extent in MgAsp supplemented pigs, and that the dietary MgAsp is a method for reducing the incidence of PSS (D´Souza et al. 1998).

Conclusions

Dietary magnesium supplementation has reduced the effect of stress by reducing:

- plasma cortisol and catecholamine concentrations
- neuromuscular stimulation by antagonizing calcium and reducing the secretion of acetylcholine by motor nerve impulses (Hubbard, 1973: Hagiwara et al., 1974)
- release of the catecholamines from nerve terminals and from the adrenal glands (Classen et al.,1983)

The sympatikotony in PSS is restored by "long term lower" , or by "short term higher" Mg-supplementation before slaughtering. However, this mechanism described according to the „**BEČKA authonomic nervous system function**“ at the example of the PSS prevention and the PP treatment- seems to bee useful about other diseases treatment in animals. But also in human medicine- see examples of the Mg2+ treatment different effects dependent; (a) on the Mg2+ dose and (b) on duration of the Mg2+ parenteral application („Controversy surrounds the efficasy of parenteral Mg in clinical practice“).

Controversy surrounds the efficasy of parenteral Mg in clinical practice

The **autonomic nervous system** inervates smooth muscles inducing two effector reactions: **excitation and inhibition**. Generally, when a given organ is inervated by both sympathetic and parasympathetic fibers, the effects is reciprocal: that is, if the **sympathetic excites, the parasympathetic inhibits**. However, according to professor BEČKA (1935) findings, there are important relationships about the actions of Mg, OH, Ca, and H ions.

Long time stable- balanced tonicity (stimulation) of both (parasympaticus and Extracellular Ca ions in a minimum concentration of about 4 p.mil. are absolutely necessary for the release of acetylcholine (Ach) during neuromuscular transmission. If the exracellular Ca ions falls , or if the Mg ions rises, the amount of Ach released will be less and may be insufficient to cause normal neuromuscular transmission - so, neuromuscular block may occur (HUBBARD, 1974). Because Ca2+ is normally low in most cells (less than 10 -8 M), only a small amount of Ca2+ needs to muscle enter to significantly increase Ca2+. This is especially true for smooth muscle cells that have small internal volumes compared with their surface area.

Extra- and intracellular magnesium levels have previously been shown to be genetically controlled in humans and in the mouse. To further study this genetic regulation, mice were selected from a heterogeneous population, for low (MGL mice) and high (MGH mice) red blood cell (RBC) magnesium values (HENROTTE et al., 1997). These values diverged rapidly in the two strains, to reach a stable difference between the 14th and 18th generations. MGL mice also exhibited significantly lower plasma, kidney, and skull bone magnesium contents and higher urinary magnesium excretion and total brain weights. Moreover, in stressful conditions, MGL mice displayed a more aggressive behavior that the control MGH strain. Altogether, MGL mice showed a more restless behavior, a higher rectal temperature, and much higher brain (+17%) and urine (+200%) **noradrenaline levels than the MGH animals.** These strains, thus, constitute a new animal model for the study of magnesium

metabolism and its relationships with catecholamines, stress sensitivity, and aggressive behavior.

By a variety of mechanisms **Mg affects both the intracellular and extracellular free calcium level.** This may be the major reason why parenteral Mg, exerts anti- arrhythmic, and antithrombotic effects (McCARTY, 1996: SEREBRUANY et al., 1996).Several studies have investigated the role of Mg on acetylcholine- induced relaxation in isolated blood vessels with **some conflicting results**. Early studies have shown that Mg is required for acetylcholine - induced relaxation of canine coronary arteries since relaxation is markedly inhibited in absence of extracellular Mg (ALTURA and ALTURA, 1987: KU and ANN, 1991). **Other studies reported lowering Mg does not modify acetylcholine- induced relaxation** (FARAGO et al., 1991). In contrast with LAURANT and BERTHELOT (1998)other findings, some others report that **increasing Mg concentrations attenuates acetylcholine** - induced relaxation in feline cerebral arteries (FARAGO et al., 1991). It has been shown that acetylcholine - induced relaxation is improved in aortae from mineralocorticoid- salt hypertensive rats fed a Mg- supplemented diet (LAURANT et al., 1995).

However, there can be explanation from professor PhDr.,MUDr. et MVDr.h.c. Jan BEČKA (Prague 28.2.1889; Mauthausen 25.2.1942), about „conflicting results“. He unjustly franks with the lesser known scientists engaged in the action of Mg2+ and Ca2+ on the autonomic nervous system. He concluded (1929-1935), that the tonicity of the parasympathetic nervous system is maintained (long term „enterally“) by Mg2+ and OH-: and that of the sympathetic system by Ca2+ and H+ (homeopatic doses). However (short-term „parenterally“),overdosage of Ca2+ (and H+) causes the inhibition of the sympathetic and the parasympathetic nervous system action prevails. Similarly, overdosage of the Mg2+ (and OH-) causes the inhibition of the parasympathetic and the sympathetic nervous system prevails. So, he considered that the actual control is a negative feedback mechanism, and, importantly, professor Becka discovered that this mechanism is influenced by the dosage of Ca2+ and Mg2+ in connection with the acid-base state of animals (HLÁSNÝ,2000).

Puerperal paresis (PP) of cows results in acute depletion of serum ionized Ca2+, which is necessary for the efficiency of acetylcholine release in the nerve endings, so the prasympaticotony prevails. This action is also supported by higher blood Mg2+ which causes the inhibition of the parasympathetic nervous systém. There is well known PP of cow treatment; if Ca2+ is parenterally „overdosed“- the tendency to the parasympaticotony is introduced and cow is quickly recovered (HLÁSNÝ, 2000a).

However, diverse magnesium salts (enteral or parenteral), may have different effects about calcium losses by faeces, urine and influence on acid-base status; which differs **according to the nature of the anions (BEČKA, 1936; 1936a).**

Magnesium salts and therapeutic effects

Marginal primary Mg deficit affects a large proportion of the population (l5 to 20 %), in keeping with the daily mean Mg intake slightly over 4 mg/kg day versus the Mg RDA of 6 mg/kg day (DURLACH and MARESCHI, l990).

Adequate Mg levels are required in order to sustain an appropriate performance level, because of its key role in energetic metabolism, in the stabilization of membranes, and in muscle contraction. Hormonal changes found during prolonged exercise, such as increases in catecholamines, thyroid stimulating hormone, glucagon and corticosteroids, and a decrease in plasma insulin, inducing Mg deficit by several mechanisms. Magnesium plays key roles in cell function :"**Magnesium can play an intristing role**. We are still told that its laxative action is due to hyperosmosis caused by the presence of Mg-salts in the intestinal lumen. However, Claude Bernard already indicated that this is not a correct hypothesis. As he stated in 1857: Why would MgSO4 when given subcutaneously, act as a purgative through the intestine, and not at the spot where it has been i.v.injected ?" (CHARBON, 1995).

Diverse magnesium salts may samely be used for atoxic physiological nutritional

supplementation, but pharmacological doses of Mg salt may induce toxicity which differs **according to the nature of the anions.** For example studie of the effects of MgCl2 and MgSO4 on the ionic transfer components through the isolated amniotic membrane has shown important differences. MgCl2 interacts with all the exchangers, while the effects of MgSO4 are limited to paracellular components. Mainly MgCl2 increases the ionic flux ratio of this asymetric human membrane while MgSO4 decreases it, with all the possible deleterious fetal consequences (BARA et al., 1994). It seems therefore necessary to determine the therapeutic ratio (LD50/ ED50) of the various available salts before pharmacological use. The best choice is the salt with greatest margin of safety that is to say with the largest therapeutic ratio. This logical prerequisite is lacking in most protocols: MgSO4 is used simply because it is the routine without any partcular justification , and this might partly account for the letal effects observed. The selection of a particular magnesium salt among others should take into account reliable pharmacological and toxicological data and the comparative therapeutic ratio of the various salts particularly: the larger its value the greater the safety margin. Diverse magnesium salts may samely be used for atoxic physiological nutritional supplementation, but **pharmacological doses of Mg salt may induce toxicity which differs according to the nature of the anions.** For example studie of the effects of MgCl2 and MgSO4 on the ionic transfer components through the isolated amniotic membrane has shown important differences. MgCl2 interacts with all the exchangers, while the effects of MgSO4 are limited to paracellular components. Mainly MgCl2 increases the ionic flux ratio of this asymetric human membrane while MgSO4 decreases it, with all the possible deleterious fetal consequences (BARA et al., 1994).

The results with patients suffering coronary artery disease and underwent bicycle stress test (SMETANA et al., 1995) clearly suggest that **Mg-therapy suppress catecholamine secretion.** The other parameters did not reveal remarkable differences comparing the data of group receiving 600 mg/ day Mg over a period of 3 weeks and the placebo group.

The purpose of LAURANT et al. (1994) study was to determine the effect of dietary Mg supplementation on blood pressure and cardiovascular function of normotensive (NT) and mineralcorticoid -salt hypertensive (HT) rats. The rats were pair-fed for 5 weeks on a purified diet containing either normal (0.15% Mg) or Mg -supplemented diet (1.0% Mg). Magnesium supplementation significantly **lowered blood pressure levels in hypertensive rats, but not in NT rats**. Heart rate was not affected in either case.

The lowering effect of Mg on blood pressure was associated with a decrease in "in vivo" cardiovascular reactivity to noradrenaline and angiotensin II. Dietary Ca supplementation lowers blood pressure in many forms of genetically mediated and experimentally induced hypertension (AYACHI, 1979). It has been suggested that **both vagal and sympathetic nerve activity are controlled** by the anterior hypothalamic area (MIYAJIMA and BUNAG, 1985). By enhancing norepinephrine release from nerve terminals in anterior hypothalamic area of NaCl sensitive spontaneously hypertensive fed rats, **dietary Ca may increase the firing of sympathoinhibitory neurons and thus reduce sympathetic outflow and blood pressure** (OPARIL et al., 1991). Sodium ions can affect nerve terminals by altering Ca ions handling (AVIV and LASKER, 1990), and Ca ion contributes to the uptake and release of norepinephrine at nerve terminales (KEEN and BOGDANSKI, 1970).

Dietary magnesium supplementation has reduced the effect of stress by reducing plasma cortisol and catecholamine concentrations. Magnesium may reduce neuromuscular stimulation by antagonizing calcium and reducing the secretion of acetylcholine by motor nerve impulses (HUBBARD, 1973: HAGIWARA et al., 1974). Magnesium may also reduce the release of the catecholamines from nerve terminals and the adrenal glands (CLASSEN et al., 1983).

Heart rate was affected in the connection with the exercise of horses where mares were fed **with 2O mg Mg-asparate-hydrochloride per kg BW/day over a period of 8 weeks**. After the first 4 weeks the mares were transported to an other farm, where they passed a 28 days training period. At the begining (ECGl) and at the end of the training period (ECG2) an

electrocardiogram was recorded. Heart rate (HR) of the Mg group determined from ECG1 at rest (63) and ECG2 after exercise (93) were significantly lower than those of the control group (82 and l08, respectively). During the standardized tests HR increased significantly in Mg and placebo group by 84 % and 33 % in ECG1 and by 69 % and 108 % in ECG2,respectively. The observed differences between both groups **might be caused by the regulating effect of Mg on the vegetative nervous system** (FRISCHMUTH et al.l992).

Magnesium deficiency in dogs has been shown to increase coronary tone and potentiate coronary vasoconstriction (TURLAPATY AND ALTURA, 1980). The influx of Ca ions to anoxic arterioles results in vascular spasm. In animal studies, Mg antagonizes Ca ion entry, thereby promoting vasodilatation and alleviating the effect of severe hypoxia on the brain, liver, and kidneys (TURLAPATY and ALTURA, 1978: WHITE et al., 1983). In vitro, the addition of **physiological concentrations of Mg** significantly reduced coronary spasm induced by prostaglandin F alpha 2 in human coronary arteries (KIMURA et al. 1989).

In most cases magnesium and potassium deficiency occur simultaneously and individual K-deficiency is nearly unknown. The combined K/Mg deficiency is primarily a deficiency of the cell, because K and Mg are the main representative cations of the cell. Magnesium deficiency is an increasing and very important problem in industrial societies today, which is always followed by potassium deficiency. Because it is impossible to correct this potassium deficiency by giving potassium, it is called "refractory potassium deficiency". This may seem strange at first sight but will become clear from the key position of magnesium. Mg regulates the Na/K pump at the cell membrane by activating membranous Na/K - ATPase, the enzyme which splits the ATP-Mg complex. The resulting energy is used for the transport of 3 Na ions out of and 2 K ions into the cell. Mg with its ATPase is therefore responsible for the electrolyte concentration gradients in the cell. During Mg-deficiency the Na/K pump is not activated optimally - the transport of potassium into the cell is less effective and cellular potassium decreases, whereas cellular sodium increases, because sodium can not longer be removed from the cell at a sufficient rate. Under ischaemic conditions with ATP deficiency or excessive adrenergic stimulation Mg leaves the cell. Presumably the Na/Ca exchange, whereby 3 Na ions are exchanged by one Ca ion, is also regulated by Mg. Sufficient extra- and/or intracellular Mg blocks Ca influx, whereas with low extra- and/ or intracellular Mg the Ca influx increases. **Ca overload of the cell will follow from Mg deficiency as well as from an insuficient Na/Ca exchange**. This is a start of a vicious circle with increased vascular and myocardial contractility and **additional oxygen and ATP consumption**, reduced vascular perfusion, vascular and coronary spasm, and tetanic hyperexcitability of striated and smooth muscle. the reduced membrane potential approaches the fibrilation threshold and induces electric instability of the cell with dysrhythmias. In this situation giving potassium is not successful. The cellular electrolyte imbalance can be **restored only by giving potassium with an additional Mg supply**. The aim is to improve the Na/K pump and the Na/Ca exchange by Mg activation to restore the former trancellular gradients of Na and K, to remove the calcium overload with its deleterious consequences, and to restore the cellular ATP-magnesium energy potential. this procedure has been confirmed many times clinically by measuring plasma and muscle electrolytes obtained at biopsy or by the parameters of the ischaemic and energeic situations (SCHROLL, 1995).

Almost all mammalian arteries and arterioles are surrounded by sympathetic adrenergic nerve axons. Exceptions are the aorta of some species (BEVAN, 1980) some fine pial vessels (HILL, 1986), and pulmonary arteries of some species (McLEAN , 1986). Large bundles of symphatic nerve axons frequently follow the patways of larger distributing arteries. The resting membrane potentials of arteriol and arteriolar smooth muscle, when determined in vitro, have been found to be in the range of 60 to 75 mV, with e few exceptions (EDWARDS, 1988), the resting membrane potentials were stable. The observed values of resting membrane potential of arteries and arterioles reswult from their membranes being more permeable to K ions than to other ions. The concentrations differences and the resting fluxes of ions across the cell walls of arterial smooth muscles have been estimated. As with all sells arterial muscle

cells maintain large ionic gradients across their membranes. The cell Na^+ (10- 20 mmol/l) is much lower than that of the extracellular fluid (ECF) Na^+ (150 mmol/l). The cell K^+ is much higher (130 - 160 mmol/l) than the K^+ of the ECF (3- 5 mmol/l). The cell Cl^- (140 mmol/l) is higher than that of many other excitable cells**. The free cell Ca^{2+} is maintained at a very low level (10^{-6} to 10^{-8} mol) compared with the ECF Ca^{2+} (2 mmol/l)**. These concentrations gradients give rise to a series of electrochemical gradients , the equilibrium potentials (E_{ion}) of which are described by the NERNST equation for each ion: the approximate potentials are :E Na = + 50 mV / E k = - 90 mV ; E Cl = - 20 mV / E Ca= more than 150mV.

There is general agreement that resting arterial membranes have a higher permeability to K^+ than they do to Cl^-, Na^+ , or Ca^{2+} (CASTEELS, 1981). Where tested, arterial smooth muscles , with the exception of some fine cerebral arterioles, are depolarized when ECF K^+ is increased. In most arterial smooth muscle preparations, the graphs relating log ECF K+ over the concentration range of 5- 20 mM, and membrane potential were non linear (CASTEELS, 1981). As ECF K+ was reduced slightly, the resting membrane potential became more negative but further reductions caused depolarization. In an extreme example, fine cerebral arterioles are hyperpolarized when ECF K^+ is increased (EDWARDS, 1988). Many of the paradoxial effects on membrane potenttial, produced by reducing ECF K^+ , may be explained by a closure , or resseting , of K^+ - selective channels "by the changed ECF K^+". The membranes of many excitable cells contain K^+ - selective channels that are either directly or indirectly activated by an increase in cell Ca^{2+}. (HILLE, 1984). Although they are voltage dependent, these channels **are only opened in the absence of Ca^{2+} by large depolarizations.**

In contrast then are opened explosively at even quite negative potentials when Ca^{2+} is increased. Other reports indicate that channels can be further subdivided on the basis of their sensitivity to Ca^{2+}. The channels of secretory cells are activated **by low (10^{-8} M) concentrations of Ca^{2+}** (PETERSEN, 1974) while those of **skeletal muscle require higher concentrations (10^{-6} M)** for their activation (MAGLEBY and Pallotta, 1983). Most excitable cells have Ca channels in some areas of their membranes. Well- known examples are those found in cardiac muscle cells, secretory cells, and nerve terminals (HILLE, 1984). Calcium channels like Na channels, are activated by membrane depolarization and allow Ca^{2+} to enter the cell. They are normally selective for Ca^{2+}, but their selectivity is lost when Ca^{2+} is greatly reduced : they then allow invard Na+ movement (ALMERS, 1984). Because Ca^{2+} is normally low in most cells (less than 10^{-8} M), **only a small amount of Ca^{2+} needs to muscle enter to significantly increase Ca^{2+}**. This is especially true for smooth muscle cells that have small internal volumes compared with their surface area. Some Ca channels, like Na channels rapidly inactivate during maintained depolarization but others barely do so (HILLE, 1984). In some the inactivation is brought about by the accumulation of intracellular Ca^{2+} (ECKERT and Tillotson, 1981). All Ca^{2+} channels are blocated by Cd^{2+} or Mn^{2+}. Barium ions are invariably good substitutes for Ca^{2+} as inward charge carries. The entry of Ca^{2+} through voltage- dependent Ca channels may also be modulated by transmitter or transmitter- like substances. An example is the increased entry of Ca^{2+} into ventricular muscle during beta-adrenoceptor activation (REUTER, 1983). This contrasts with the decreased entry of Ca^{2+} into sympathetic ganglion cells during alpha- adrenoceptor activation (HORN and McAfee, 1980).

At many synapses specializations of the membrane properties of the target cell often occur at or (on..) near the synaptic region. An example of this is the concentration of Ca channels on the dendritic processes of central neurons (LLINAS and SUGIMORI, 1980), and of some sympathetic ganglion cells (HIRST and McLACHLAN, 1966). Several observations suggest that the membrane properties of vascular smooth muscle are changed by a generalized

sympathetic denervation: the membrane potential is less negative and the cells are more excitable. These changes have been attributed to changes in Na pump activity (FLEMING, 1987) but they may relate only indirectly to the sympathetic innervation: when single mesenteric arteries were denervated, their resting membrane potential was found not to alter (HILL, 1985). Fine arteries are very insensitive to norepinephrine,often requiring concentrations of norepinephrine in excess of 10^{-6} M to produce maximal alpha- mediated concentrations (HIRST AND LEW, 1987). In contrast most distributing arteries produce maximal contractions to concentrations a 100 times lower. These observatioons indicate that the **larger vessels are more likely to be affected by physiological concentrations (generally much less than 10^{-6} M) of circulating catecholamines** (HIRST AND LEW, 1987).

Contraction of the **smooth muscle cells in the walls of the blood vessels** and the consequent reduction of tissue perfusion is **initiated when the cytoplasmic free Ca concentration rises above 0.1 mmol/ litre** (BOLTON, 1979). Increases in endogenous vasoconstrictors, together with hypoxia and ischaemia, resulting in increased permeability on the cell membrane to extracellular Ca (PHILLIPS et al., 1983: KARAKI et al., 1979) and mobilization of Ca from intracellular Ca pools, are possible reasons for this increase in cytoplasmic Ca concentration. Peripheral arterial dilatation caused by Mg(SO)4 could be caused by an indirect curare-like action on the neuromuscular junction and sympathetic ganglia by retarding the release of acetylcholine or by a direct action reducing the reactivity of the smooth muscle to sympathomimetic amines and non-sympathomimetic vasopressors (LEVOWITZ et al.,1970: FROHLICH et al.,1962).

Magnesium and brain

Magnesium sulphate have been used for many years to prevent and treat eclamptic seisures (KATO and SMOJEN, 1969: LUCAS et al., 1995). However, despite magnesium sulphate´s empiric success in obsterics, its mechanism of action is still **not completely understood and has been the basis for considerable controversy.** Neurologists have condemned the use of magnesium sulphate as a therapy for preeclampsia- eclampsia claiming that it does not treat eclamptic conculsions (FISHER et al., 1988: DONALDSON, 1988: DONALDSON, 1986: KAPLAN et al., 1988).

In the central nervous system (CNS), magnesium ion (Mg2+) has two major functions, the stabilization of synaptic connectivity and widespread enhancement of neurochemical enzymatic functions. Mg2+ has been shown to affect guanine nucleotide binding proteins (G proteins) in several ways : **nanomolar concentrations** of Mg2+ are required for GTPase activity (GILMAN, 1987: HIGASHIJIMA et al., 1987), **micromolar concentrations** of Mg2+ are required for receptor- mediated activation of G proteins (GILMAN, 1987: GIERSCHIK et al., 1988**), millimolar concentrations of Mg2**+ increase the affinity of various types of receptors for agonists, an effect thought to result from increased receptor - G-protein coupling (HULUME et al., 1983: BIRNBAUMER et al., 1990), voltage- dependent-Ca2+ channel (AUGUSTINE et al., 1987) and N-methyl-D- aspartate (NMDA) receptor operated ionic channel (CRUNELLI and MAYER, 1984: NOWAK et al., 1984). The inhibitory effects of **millimolar concentrations of Mg2**+ on neurotransmitter release have been already been demonstrated by in vivo microdialysis experiments (OSBORNE et al., 1991: OKADA et al., 1996: 1998).

Excitatory amino acids, such as glutamate and aspartate, are major neurotransmitters in the mammalian central nervous system. It is now generally accepted that these amino acids are primarily responsible for normal excitatory synaptic transmission (WATKINS and EVANS, 1981). These neurotransmitters produce their effects by interacting with specific receptors on the cell surface, the excitatory amino acid receptors (MONAGHAN et al., 1989). Five receptor subtypes have been identified and are classified into two groups : (1) ionotropic receptors: N- Methyl-D- Aspartate (NMDA), Kainate, AMPA and AP4 and (2) metabotropic receptor (ACPD**). Overstimulation of the NMDA receptor as well as other excitatory amido acid receptors results in neurotoxicity and neuronal injury.** These receprors are

considered as the final common pathway for many acute and chronic neurologic conditions (McDONALD et al, 1988). The **most well characterized excitatory amino acid receptor subtype is NMDA receptor which also is permeable to Ca ions** (FAROOQUI and HORROCKS, 1991).

An important consequence of NMDA receptor activation is the influx of Ca ions into neurons. Excessive NMDA receptor stimulation is thought to be an important factor in neuronal cell damage, mediated by excessive calcium entry into the cell (OLNEY, 1989: McMASTER et al., 1991).

Acute stroke is the third largesta cause of mortality and the largest cause of disability in most Western societies. Therapeutic trials in ischaemic stroke have explored two broad strategies: enhancing blood flow to ischaemic tissue, most successful with pharmacological reperfusion by thrombolysis: and neuroprotective therapies designed to interrupt the metabolic events responsible for the progression of compromised brain tissue to irreversible infarction.

Large numbers of stroke patients have been randomized into clinical trials to date- for example almost 3500 in thrombolytic trials, and **many more in neuroprotective trials- but not widely applicable acute therapy has yet been found** (MUIR, 1998).

The toxicity of the N-methyl-D- aspartate (NMDA) applied directly to neuronal culture **is attenuated by physiological magnesium concentrations** in culture media (ASCHER and NOWAK, 1984), **whilst reduction of magnesium concentration has the converse effect** (ROSE et al., 1990). Physiological extracellular magnesium concentrations produce voltage dependent block of NMDA ion channel conductance (NOWAK et al., 1984), **whilst increasing extracellular (Mg2+)** within the physiological range , and to potentially attainable supraphysiological levels**, impedes NMDA receptor opening in a non- competitive manner** (SCHMIDT and TAYLOR, 1988: DAVIES and WATKINS, 1977: HARRISON and SIMMONDS, 1985: AULT et al., 1980).

Studies have demonstrated that magnesium can protect against NMDA - induced neurodegeneration, brain injury, and convulsions in rats (Mc DONALD et al., 1990: WOLF et al., 1990). Parenteral magnesium sulphate had a definite protective action on central nervous system O2 toxicity (KATZ et al., 1990). It reduces seizure duration and electroencephalogram amplitude in convulsions secondary to oxygen toxicity. A neuroprotective effect of Mg has been demonstrated even when Mg was administered 24 h after an ischemic episode (TSUDA et al.,1991).

Proposed mechanisms for magnesium´s suppressive action on the NMDA receptor are: (1) Mg2+ enters the channel and blocks the passage of more permeable ions, such as Ca2+ , in a voltage- dependent manner (2) Mg2+ competes with Ca2+ uptake presynaptically, reducing calcium dependent neurotransmitter release. This generalized inhibition of neurotransmitter release could also account for Mg anticonvulsant effects (KATZ and MILEDI, 1969).

Using autoradiography (HALLAK, 1998) has studied the effect of peripherally administered Mg treatment on the NMDA receptor channel complex in the rat central nervous system. These studies included three different protocols:

Short- term administration: 270 mg of magnesium sulfate (i.p.) followed by 27 mg/kg every 20 min. for 4 hours

Prolonged adm.: 270 mg of magnesium sulfate (i.p.) every 4 hours for 24 hours

Chronic adm.: 270 mg of magnesium sulfate (i.p.) every 12 hours for a total of 2 weeks

HALLAK (1998) found, that magnesium sulfate enters the cerebrospinal fluid and brain after systemic administration. The significant rise in brain Mg concentrations was associated with an elevation of the seisure threshold and a marked resistance of the animal to electrically and NMDA stimulated hippocampal seisures. Short term (4h) magnesium sulfate administration results in increased inhibition of the ion channel. This effect was continued also with prolonged treatment (24h), along with decreased sensitivity of the NMDA receptor-channel complex to its agonists, glutamate and glycine. **However, chronic inhibition by Mg results in up regulation of the receptor population.**

ROTHMAN (1983) showed that 10 mM mgnesium prevented anoxic neuronal death in cultured fetal rat hippocampal neurones, thereby concluding that synaptic activity mediated

anoxic neuronal necrosis and **leading subsequently to the excitoxic hypothesis (ROTHMAN, 1984)**. Whilst **magnesium at these high concentrations** is a blocker of all synaptic activity, **physiological magnesium concentrations have more specific activity to prevent presynaptic glutamate release.** Removal of magnesium from artificial CSF superfusing mouse neocortical slices induces spontaneous depolarisations and release of glutamate, whilst both of these effects are abolished by reintroduction of Mg in concentrations of 250 uM to 1 mM (SMITH et al., 1989).

In rat hippocampal slice preparations, **high magnesium concentrations (10 mM**) prevented anoxic loss of electrical function of hippocampal CA1 neurones (CLARK and ROTHMAN, 1987: KASS et al., 1988), and dentate granule cells (KASS et al., 1988), and attenuated anoxic loss of tissue ATP (KASS et al., 1988). SCHANNE and colleagues (1993) found that **4mM magnesium to protect against ischaemic ATP** and phosphocreatine loss in artificial CSF superfusate from which calcium had been removed.

Neuronal free calcium concentrations correlates with the likelihood of irreversible ischaemic cell death (EIMERL and SCHRAMM, 1994: CHOI, 1985)., and free intracellular calcium increases may result from calcium entry via the NMDA ion channel and voltage - gated calcium channels, and release from endoplasmic reticulum and other intracellular stores. **Magnesium competes with calcium at voltage- gated calcium channels both intracellularly and on the cell surface membrane** (ISERI and FRENCH, 1984). It may thereby impede calcium- dependent presynaptic release of glutamate and prevent neuronal calcium overload via voltage- gated channels during ischaemia. Magnesium also enhances mitochondrial buffering of raised intracellular free calcium ions (FAVARON and BERNARDI, 1985), and prevents release of intracellular calcium stores from endoplasmic reticulum (PARSONS et al., 1997).

White matter ischaemia has been studied by WAXMAN´s group using an isolated rat optic nerve preparation. After anoxia, the optic nerve loses its compound action potential rapidly, and the influence of different agents upon action potential recovery has been assessed. In this model, post- anoxic recovery is unaffected by inorganic or synthetic calcium channel antagonists with the exception of magnesium (STYS et al., 1992). **Magnesium in concentrations of 10 mM enhances action potential recovery significantly** (STYS et al., 1990), probably through effects upon the sodium- calcium exchange pump (STYS et al., 1991). Both magnesium sulphate and magnesium chloride infused intravenously (IV) reverse the vasoconstrictor effects on rat carotid arteries of endothelin 1, neuropeptide Y and angiotensin II (KEMP et al., 1992: KEMP et al., 1993) in doses that produce plasma concentrations of 2.4- 2.7 mmol/L. In slightly higher doses , with plasma levels of 3.8- 4.6 mmol/L, the constrictor effects of endothelin 1 were abolished entirely (KEMP et al., 1993), although in other species, endothelin 1- mediated vasoconstriction of cerebral vessels has been more resistant to magnesium sulphate IV (TORREGROSA et al., 1994).

MgSO4 administered intraperitoneally 15 min after NMDA injection **produced dose-dependent reduction of infarcted brain tissue 5 days post- insult** (McDONALD et al., 1990). Single doses of up to 4 mmol/ kg afforded significant protection, confirming the ability of systemically administered magnesium salts to exert therapeutic effects on the NMDA receptor complex specifically.

Two studies in Glasgow have involved 85 patients with stroke (MUIR and LEES, 1995). The **first examined the tolerability of MgSO4** given in a regime identical to that in the LIMIT-2 study in AMI (WOODS and FLETCHER, 1994), a loading dose of 8 mmol being followed by 65 mmol over 24 h (roughly 3 mmol/h). Serum levels rose from a baseline mean of 0.76 mmol/L to 1.42 mmol/L, attaining maximal concentration only at the end of the 24 h infusion. No adverse cardiovascular effects were found, and a trend towards improved survival over 3 months post-stroke was seen.

A **second trial at the same centre** controlled 25 patients in a multiple- dose randomisation study to explore the safety and tolerability of different koading infusions. Doses of 8, 12 and 16 mmol were used, each followed by 65 mmol over 24 h. Magnesium concentrations after loading infusions of 8, 12 and 16 mmol were 1.22, 1.33 and 1.84 mmol/L respectively. **Since the 16 mmol group had achieved doubling of baseline serum Mg concentration within 15 min, this dose was selected for full efficacy study in a**

multicentre trial. Of note, hyperglycaemia was not evident in the stroke patients in either Glasgow study (MUIR, 1998).

There are multiple mechanisms by which therapeutic infusion of magnesium salts to raise serum levels to supraphysiological pharmacological concentrations could exert a beneficial effect in cerebral ischaemia. **Safe and tolerable concentrations in cerebral fluid and brain are likely to be able to influence NMDA receptor opening**, thereby interventing at the site of excitoxic injury most consistently effective in reducing the volume of experimental cerebral infarction. Magnesium also may reduce presynaptic glutamate release of calcium ions from endoplasmic reticulum, enhances mitochondrial calcium buffering, increases regional cerebral blood flow to ischaemic tissue, and antagonises the vasoconstrictive effects of several mediators including endothelin 1. It is not known which of these effects is of relevance, but magnesium reduces histological infarct volume in standard animal models of focal cerebral ischaemia, and also reduces neuronal loss in several other models of cerebral ischaemia.

In contrast to many other potential neuroprotective drugs being developed for stroke, there is substantial clinical experience with magnesium infusions. Trials in pregnancy confirm that **doses that elevate serum concentrations of magnesium approximatelly 2-3 times physiological can exert pharmacological effects in the CNS** (MUIR, 1998: Department of Neurology, Institute of Neurological Sciences, Southeren General Hospital, GLASGOW G51 4TF, SCOTLAND: KEITH W. MUIR)

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- Mg2+ enters the channel and blocks the passage of more permeable ions, such as Ca2+ , in a voltage- dependent manner
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MgSO4 administered intraperitoneally 15 min after NMDA injection produced **dose-dependent reduction of infarcted brain tissue 5 days post- insult** (McDONALD et al., 1990). **Single doses of up to 4 mmol/ kg afforded significant protection**, confirming the ability of systemically administered magnesium salts to exert therapeutic effects on the NMDA receptor complex specifically. Brain, cerebrospinal fluid or serum magnesium concentrations were not reported, but brief spells of apnoes in animals of the highest dose group suggest that levels were higher than may be attainable safely in clinical use.

In a rat global cerebral ischaemia model (20 min forebrain ischaemia followed by reperfusion), direct injection of magnesium chloride to the hippocampus reduced death of CA1 neurones even when given 24 h after onset of ischaemia (TSUDA et al., 1991). **The dose used was large (50 mM) and the results are therefore of uncertain significance to human therapeutics**. A French group found infusion of 2.5 mM magnesium to reduce glutamate and aspartate release in response to forebrain ischaemia in a similar model: identifical effects were obtained with dizocilpine, but not with an AMPA antagonist (GHRIBI et al., 1995).

Cerebral vascular smooth muscle cells when exposed to low Mg ions undergo rapid potent contractile responses. The mechanism for the latter effects of Mg ions are,however, not fully understood. Therefore, ZHANG et al (l992) determined the **effects of lowering Mg ions** stepwise on the distribution of Ca ions in single VSMCs cultured from canine cerebral arteries. Their results suggest that: l/Mg ions regulates intracellular free Ca ions in cerebral VSMCs, probably by modulating Ca ions entry across plasma membranes and/or release from intracellular stores, 2/ the level of ionized Mg ions probably plays an important role in regulation of cerebral vascular tone, cerebral blood flow and its distribution (ZHANG et al., l992).

Acute myocardial infarction (AMI) and HEMOSTASIS

Heart disease is the main cause of death today. Half of these deaths are associated with cardiac arrhythmias and sudden deaths. Magnesium can produce rapid vasodilatation, hypotension **and the opposite effects occur with low Mg levels**. Magnesium is a calcium competitor in heart ventricular muscle due to inhibition of Ca movement into the cardial cell. It may be possible to reduce the doses of Ca antagonists by supplementing them with Mg ions. In the pilot experiments NASTOU et al. (1994) observed that, after a 10-day period of Mg-supplementation, patients who used Ca - antagonists to control hypertension showed a decrease in systolic blood pressure of about 20 mm Hg.

The data obtained are consistent with the hypothesis that Mg ions play important regulatory roles in cardiovascular cellular dynamics. Mg ions appears to be pivotal in regulation of cardiac haemodynamics, vascular tone, vascular activity, lipid metabolism and prevention of free radical formation. Mg ions exerts important actions on control of Ca ions : uptake, subcellular content and distribution in smooth muscle, endothelial cells and cardiac muscle cells (ALTURA and ALTURA, 1995b). **The ionizable Ca and ionizable Mg ratio** appears from data of ALTURA and ALTURA (1995a), to be an important guide for signs of peripheral vasoconstriction, ischaemia or spasm and possibly atherogenesis.

Extracellular as well as intracellular Mg levels modulate Ca exchanges at various levels in cardiac cells, and numerous experimental models indicate both a decrease in myocardial Mg and an increase in myocardial Ca levels in heart failure. In all these processes, the key role of sarcolemmal and sarcoplasmic transmembrane **Ca fluxes and of intracellular free Ca levels for both the contraction and relaxation of cardiac cells** has been emphasized. In patients with congestive heart failure, low RBC Mg levels have been found in patients dying from sudden cardiac death, as well as in patients presenting with atrial fibrilation and ventricular rhythm disturbances (LASSERRE, 1995).

The observations of HUTZELMANN et al.(1992) indicate the same situation in competitive fencing athlets that obtained in a single blind study placebo for 28 days, and then 18.6 mmol Mg-oxide for 28 days. **Mg-supplementation lowered significantly heart rate** and significantly increased Mg concentration in plasma-erythrocytes and decreased plasma lactate concentration.

It is well known that the magnesium is correlated with cardiovascular function and the hypertension could be associated with low serum magnesium levels (ALTURA et al., 1984). **Other reports contain contradictory results**, suggesting that Mg deficiency could exert a normotensive or hypertensive effect (DURLACH et al., 1989).

Controversy surrounds the efficasy of parenteral Mg in clinical practice

Despite a wealth of clinical experience with the use of parenteral Mg salts in the treatment of acute coronary events, the mechanism of action remains unknown (THEL and O´CONNOR, 1995: DURLACH and RAYSSIGUIER, 1993).

In animals, high levels of extracellular Mg in vitro, as well as intravenous supplementation ex vivo, are associated with a progressive DOSE dependent inhibition of platelet aggregability *(HERRMAN et al., 1970: HERZOG et al., 1993).*

The data on the association between **Mg and platelets in humans are confusing**. While in vitro Mg decreases platelet aggregation (RAVN et al., 1996) and reduces platelet degranulation and surface antigen expression (GAWAZ et al., 1994), other reports have indicated that Mg is essential for platelet agglutination (SATOH et al., 1993) thrombin and collagen activation (MATSUNO et al., 1993) and even could substitute for calcium in supporting aggregation (PEERSCHKE, 1985). The effect of parenteral Mg on platelet function in the setting of AMI is entirely unknown. It is conceivable, that these "prime" platelets from AMI patients may respond differently than those of normal volunteers (SEREBRUANY et al., 1998: SEREBRUANY et al., 1997).

This controversy arises because of apparent conflicting results from clinical trials. Most recently, the LIMIT-2 trial (2 316 patients) showed a **significant mortality benefit** (WOODS,et al., 1992: 1994), whereas the ISIS-4 trial (54 824 patients) found **no benefit**

(ISIS-4, 1995). A strong argument can be made that the ISIS-4 patients did not benefit because **Mg was administered after the critical processes producing myocardial reperfusion** injury had already occurred. In LIMIT-2, Mg was given prior to the likely occurrence of reperfusion. In ISIS-4, Mg was given after the likely occurrence of reperfusion. Other observers point to methodological differences between these trials that may explain the discordant results, thus leading to the **need to reexamine the claim that Mg therapy is a useful adjunct in the treatment of AMI** (ANTEMAN, 1995: LeLORIER et al., 1997: BORZAK et RIDKER, 1995).

Proponents of Mg therapy have suggested that the potential benefit was not seen in ISIS-4 becuse **Mg was administered too late.** The beneficts of parenteral Mg in an expanding array of clinical conditions, including acute myocardial infarction (AMI), may be directly related to an improved hemostatic profile (SEREBRUANY et al., 1998)

Mg deficiency is considered a risk factor for the development of cardiovascular diseases including atherosclerosis, ischaemic heart diseases and hypertension (ALTURA and ALTURA, 1995: ARSENIAN, 1993). Mg deficiency has been implicated in the aging process (COSTELLO and MOSER VEILLON, 1992: DURLACH et al., 1993: RAYSSIGUIER et al., 1993) and may increase the frequency of cardiovascular diseases which are the most common cause of morbidity and moratlity in the elderly (BILATO and CROW, 1996: LAKATTA and YIN, 1982).

Numerous experimental studies have shown that **changes in extracellular Mg concentration can affect vascular reactivity ,blood flow and blood pressure**. In isolated blood vessels, the **decreasing extracellular Mg concentration increases vascular tone** and reactivity to many agonists, whereas **increasing extracellular Mg concentration has the opposite effect** (ALTURA and ALTURA, 1986: ALTURA et al., 1987).

High and low Mg concentrations did not influence norepinephrine- induced concentrations of isolated aortae from either adult or aged rats. The effects of **varying Mg concentrations on in vitro catacholamine - induced concentration are controversial.** Early studies have shown that reactivity to norepinephrine decreases when Mg concentration is above 12 mM (FUJIWARA et al., 1978), whereas it decreases or does not change when Mg is reduced or removed (FUJIWARA et al., 1978: HOWELL and CARRIER, 1986: RAHMANI et al., 1990).

Vascular reactivity and the **effect of various Mg concentrations** on it, LAURANT and BERTHELOT (1998) studied in aortic rings from adult (4 month-old) and aged (24 month - old) male rats. They found that contraction induced by CaCl2 of the aortae incubated in high potassium PSS containing 1.2 mM Mg was greater in aged than in adult rats. **Low Mg (0.1 mM) decreased CaCl2 - induced contraction** in the aortae from adult rats more than in those from aged rats. **High Mg (4.8 mM) attenuated CaCl2- induced contraction** in the aged but not in the adult rats. Low Mg did not modify acetylcholine- and sodium nitroprusside - induced relaxation in adult and aged rats. **With high Mg acetylcholine**- and sodium nitroprusside - induced relaxation was increased in both groups. The increasing effect of high Mg on acetylcholine- induced relaxation was however greater in aorta from aged rats.

LAURANT and BERTHELOT (1998) concluded that their results support the recommendation that Mg administration could be increased in the elderly to prevent cardiovascular diseases . They found **that high and low Mg concentrations did not influence norepinephrine**- induced concentrations of isolated aortae from either adult of aged rats. However, the effects of **varying Mg concentrations on in vitro catecholamine-induced contraction are contraversial.** In early studies have shown that reactivity to norepinephrine decreases when Mg concentration is above 12 mM (FUJIWARA et al., 1978), whereas it decreases or does not change when Mg is reduced or removed (HOWELL and CARRIER, 1986). LAURANT and BERTHELOT (1998) emphasise that the reasons for the discrepancy between eged and adult rats are UNCLEAR but may be related to an altered vascular Ca homeostasis in aged blood vessels (MALONEY and WHEELER-CLARK, 1996). **High Mg decreased the senzitivity to CaCl2 in isolated aortae from aged rats, but not from adult rats**, suggesting the presence of an inhibitory effect of Mg on Ca influx in aortic smooth muscle cells from aged rats. It is established that Mg modulates vascular tone by interfering with Ca utilization in the vascular sooth muscle cell. Mg affects Ca influx and Ca

release from internal stores suggesting that **Mg is able to regulate the activity of vascular smooth muscle cells by competing with Ca** (ALTURA et al., 1993: ALTURA et al., 1987) .

Several studies have shown that the inhibitory **effect of Ca entry blockers decreases with age** in isolated blood vessels (Van OVERLOOP et al., 1993: WANSTALL et al., 1988: WANSTALL and O´DONNELL, 1989). Early studies have, however, reported that **high Mg potentiates the inhibitory effect of Ca antagonists** on Ca - induced contraction of blood vessels (TURLAPATY et al., 1981). Since aortae from aged rats were senzitive to the inhibitory effect of Mg on Ca influx, it could be suggested that **Mg exerts beneficial effects, as Ca antagonist , on vascular tone in aged blood vessels.**

Several studies have investigated the role of Mg on acetylcholine- induced relaxation in isolated blood vessels with **some CONFLICTING results**. Early studies have shown that Mg is required for acetylcholine - induced relaxation of canine coronary arteries since relaxation is markedly inhibited in absence of extracellular Mg (ALTURA and ALTURA, 1987: KU and ANN, 1991). **Other studies reported lowering Mg does not modify acetylcholine- induced relaxation** (FARAGO et al., 1991). In contrast with LAURANT and BERTHELOT (1998)other findings, some others report that **increasing Mg concentrations attenuates acetylcholine** - induced relaxation in feline cerebral arteries (FARAGO et al., 1991). It has been shown that acetylcholine - induced relaxation is improved in aortae from mineralocorticoid- salt hypertensive rats fed a Mg- supplemented diet (LAURANT et al., 1995). **Mg inhibits NO synthase activity of cultured endothelial cells , in a dose - dependent manner** (HOWARD et al., 1995). However, this same studie demonstrates that NO released under basal or agonist - mediated conditions **is not affected by a wide range of Mg concentrations** (HOWARD et al., 1995). In view of these conflicting data , it seems that the relationship between extracellular Mg and No activity is **not well UNDERSTOOD** and suggests that there are differential effects of Mg on agonist- induced NO release.

Physiological magnesium concentrations have significant anticonstrictor effects against prostaglandin F2 alpha and serotonin in isolated post-mortem human middle cerebral arteries (ALBORCH et al., 1992), although magnesium was slightly less potent than some dihydropyridine calcium antagonists. Pia vessels also constrict in response to EAAs, and intravenous or intra- arterial **magnesium chloride infusion in rats caused dose-dependent pial vessel relaxation** in doses of 15, 150 or 300 umol (HUANG et al., 1994). Magnesium sulphate IV reversed basilar artery vasoconstriction in a rat model of subarachnoid hemorrhage at mean plasma levels of 4.32 mmol/L (RAM et al., 1991).

Hypermagnesaemia can depress insulin levels with consequent hyperglycaemia, and neuroprotective beneficts may thereby be masked. It has been suggested that magnesium chloride has a greater propensity to cause hyperglycaemia than does magnesium sulphate (MARINOV et al., 1996), but such a proposal is based upon the **different vascular effects of various magnesium salts on arteriolar and venular constriction** (NISHIO et al., 1988), and remains an unproven, if attractive hypothesis with respect to glycaemic control. This hypothesis offers an **explanation for the failure of some investigators to find neuroprotective effects,** for example ROFFE et al. (1996) study of mice after permanent middle cerebral artery - MCAO , in which 1 mmol/kg intraperitoneally immediatelly after ischaemia and 1 h later failed to reduce histological infarction assessed at 24 h. Co-administration of insulin reduced cerebral oedema significantly, but uncontrolled hyperglycaemia in the magnesium chloride/ no insulin group was associated with increased oedema and infarct volume. Similar hyperglycaemia with magnesium chloride infusion was reported by BLAIR et al.(1989), who also failed to find evidence of neuroprotection by pretreatment magnesium chloride 5mmol/kg in a rat global forebrain ischaemia model despite high peak plasma concentrations of 5.22- 6.29 mmol/L.

MARINOV and colleagues (1996) produced the middle cerebral artery reperfusion (MCAO-r) by the intraluminal suture technique in rats, with 1.5 or 2 h of ischaemia followed by reperfusion and histological assessment. **Intra- arterial magnesium sulphate was infused over 10 min pre- ischaemia in doses of 30 mg /kg or 90 mg /kg.** Treatment produced dose- dependent reduction in histological infarct volume, the maximum effect being 60 per cent reduction in the higher dose group with shorter (1.5 h) ischaemic period before reperfusion. In this study, plasma Mg^{2+} rose from 0.74 to 1.49 mmol/L in the higher dose

group. The study design excluded rats without cortical infarcts from analysis, thereby probably **underestimating the neuroprotective effects of the 90 mg/kg dose since 6 of 18 animals in this group developed only striatal infarction. No effects on blood pressure, heart rate or blood glucose were found.**

Using intravenous magnesium chloride 1 mmol/kg in two doses , pre-ischaemia and at reperfusion after 90 min, another group found 24 per cent reduction in histological infarct volume in an intraluminal suture MCAO- reperfusion model: this was not statistically significant, but magnesium had an additive effect when combined with the free radical scavenger tirilazad in this study, and rats had an improved neurological status (SCHMID-ELSAESSER et al., 1997).

After permanent MCAO by ligation in rats, CHI et al. (1990) reported significantly increased blood flow to the ischaemic hemisphere after infusion of 16 mg/kg/ min MgSO4 for 30 min (total dose of 480 mg/kg- 1.95 mmol/kg). Blood magnesium levels increased from 0.86 to 3.21 mmol/L and there was a **14 per cent reduction in heart rate: blood pressure was unaffected.**

Within the 1982- 1985 years , nine reports (McCARRON et al.,1982 and 1984: ACKLEY et al.,1983: HARLAN et al.,1984 and 1985: NICHMAN et al., 1984: GARCIA-PALMIERI et al., 1984: GRUCHOW et al.,1985: REED et al.,1985) have identified an association between a lower consumption of dietary calcium and a higher risk of hypertension in the United States. These studies have included data from a variety of sources representing local, regional, and national surveys that include a representative sample by age, sex, race, geographic and ethnic considerations. However accumulated evidence suggests **that both an excess of Ca as well as a Ca deficiency may contribute to hypertension** (RESNICK et al., 1986). When levels of Ca in body tissues are analysed: increased, decreased or unchanged concentrations are found in hypertensive compared with normotensive subjects (KESTELOOT and GEBOERS, 1982: McCARRON, 1982). In vitro, **varying amounts of Ca may potentiate both contraction and relaxation of smooth muscle** (BOHR, 1963: OVERBECK, 1984).

Experimantal work in animals has shown that **Mg is an important regulator of vascular tone.** However, the relation between blood pressure and Mg in experimantal research is complex and **not fully understood**. In some but not all studies hypertension has developed in Mg-deficient rats, and in other studies Mg has prevented the blood pressure rise in spontaneously hypertensive rats (SHR). The evidence from epidemiological research of a role for **magnesium in the development of human hypertension is inconsistant**. A fall in blood pressure in relation to i.v. magnesium infusion is regularly observed and i.v. magnesium is clinically used in eclampsia. peroral magnesium added in **nutritional doses** to patients with untreated hypertension in several small studies has not affected blood pressure significantly. However, in recent larger study a significant fall in blood pressure of a few mm Hg was observed. If the patients are Mg-depleted after long term thiazide therapy or treated with beta blockers a more substantial fall in blood pressure may occur. Peroral magnesium in **pharmacological doses** has repeatedly been observed to lower blood pressure. **A dose-dependent blood pressure lowering effect** of peroral Mg in a dose up to 40 mmol without side effects has been described. The pathophysiological background may involve several mechanisms such as interference with the raa systems, **catecholamines, prostacyclins or with other ions such as sodium, potassium and calcium**. Recent studies indicate abnormalities in cellular ion handling resulting in **high free intracellular calcium and low free intracellular magnesium** as a common mechanism contributing to the pathophysiology behind so-called metabolic syndrome (WESTER, 1995).

By a variety of mechanisms Mg affects both the intracellular and extracellular free calcium level. This may be the **major reason why parenteral Mg, similar to the established calcium channel blockers, exerts anti- arrhythmic, and antithrombotic effects** (McCARTY, 1996: SEREBRUANY et al., 1996).

Despite a wealth of clinical experience with the use of parenteral Mg salts in the treatment

of acute coronary events, **the mechanism of action remains unknown** (THEL and O´CONNOR, 1995: DURLACH and RAYSSIGUIER, 1993). If parenteral Mg is indeed a vital element in protection against myocardial reperfusion injury and thrombosis, then it should target platelets, the coagulation cascade, and favorably affect hemostasis in general. In animals, high levels of extracellular Mg in vitro, as well as intravenous supplementation ex vivo, are associated with a progressive DOSE dependent inhibition of platelet aggregability (HERRMAN et al., 1970: HERZOG et al., 1993). **However, data on the effects of Mg deficiency on platelets are contradictory in animals.** Platelets from Mg deficient and control calves and rats show no differences in ADP (adenosine diphosphate breakdown)-induced platelet aggregability (STEVENSON and YODER, 1970), which was significantly increased in Mg-deficient swine.

There is agreement that parenteral Mg has an inhibitory effect on platelet aggregation in swine (SEREBRUANY et al., 1996), hamsters (RISHI et al., 1990) , dogs (CHANG et al., 1985), and rabbits (RENAUD et al., 1983).

The **data on the association between Mg and platelets in humans are confusing**. While in vitro **Mg decreases platelet aggregation** (RAVN et al., 1996) and reduces platelet degranulation and surface antigen expression (GAWAZ et al., 1994), other reports have indicated that **Mg is essential for platelet agglutination** (SATOH et al., 1993) thrombin and collagen activation (MATSUNO et al., 1993) and even could substitute for calcium in supporting aggregation (PEERSCHKE, 1985).

With increasing concentration of Mg, a cell is able to increase its performance. With increasing concentration of calcium , the cell needs more energy to maintain the Ca gradient between the intra - anb extracellular space. If all binding sites for Mg are completely saturated, the cell is able to export the calcium via the Na^+ / ^{2+}Ca exchange without consuming energy. The intracellular concentration of magnesium is a major determinant of whether calcium is exported out of the cell by energy - consuming mechanisms or by Na / Ca exchange. Therefore , the success of a treatment with magnesium is better the higher the influx of Ca. High influx of Ca is seen during an action potential (especially in the heart during tachycardia), whereas low influx is seen at cell membranes of young people. With this method it is possible to study the interaction of Mg and Ca with strophosid and verapamil (HUNGER, 1995).

Experimental studies have shown that alterations of Mg have little effect on the cardiac action potential unless Ca has been reduced or eliminated from the bathing solution (SHINE, 1979). When **extracellular Ca is decreased, the concomitant lowering of Mg will exaggerate** the lengthening of the action potential plateau, which could precipitate arrhythmias. An increase in extracellular Mg blocks the voltage-dependent l- type calcium channel which in cardiac cells primarily involves the sinus and atrioventricular nodes. Enhancement of Ca flow through L- type Ca channels is also thought to be responsible for early afterdepolarizations, which can result in triggered activity and ventricular arrhythmias.Clinically, **acute administration of parenteral Mg prolongs the PR interval**, sinoatrial conduction time and increases the atrioventricular nodal refractory period during sinus rhythm in patients with and without cardiac disease (DiCARLO et al., 1986: PERTICONE et al., 1992: KULICK et al., 1988).

Magnesium and DIABETES

Individuals **with diabetes mellitus are at an increased risk of developing Mg deficit mostly due to renal losses, in particular during diabetic ketoacidosis- DKA** (ROFFI et al., 1994). Being an intracellular cation as potassium (K), Mg responds similarly to changes in the extracellular acid- base status as happens with K. **During acidosis, there is a shift of both K and Mg from the intracellular to the extracellular space and the opposite phenomenon occurs with reversal of the acidotic state.** Serum concentrations of total Mg (tMg) during ketoacidosis before initiation of treatment may be either low, normal or slightly elevated. It was found that the decline in serum tMg in patients treated for DKA who received no Mg

during the first twelve hours of therapy was twice that of patients who received Mg (MARTIN et al., 1958). Similarly ROFFI et al. (1994) found only a slight increase in serum tMg in children newly diagnosed with IDDM who were also acidemic with levels ranging from 0.82 to O.91 mmol/L (1.99 to 2.21 mg/dL) as compared to the controls who had 0.82 to 0.89 mmol/L (1.99 to 2.16 mg/dL).

The causes of Mg deficit in diabetes mellitus are probably multiple. Mg deficit can occur either in insulin- dependent (Type I) or in non- insulin - dependent (Type II) diabetes mellitus (MATZ,1993: MATHER et al., 1979: Am.Diab. Assoc., 1992). Proposed **mechanisms for Mg deficit in diabetic patients**, include hypermagnesuria, decreased intestinal Mg absorption, reductiom in bone Mg levels and cellular Mg depletion secondary to insulin deficiency. ROFFI et al. (1994) found a positive correlation between urinary Mg excretion and both glukosuria and hydrogen ion activity. Thus,patients presenting in DKA , a situation in which the effects of both glucose driven osmotic polyuria and increased blood hydrogen activity coexist, are at a particularly high risk of developing hypermagnesuria and, consenquently, Mg depletion. Magnesium losses during DKA have been calculated to be in the range of 0.25 to 0.5 mmol (0.5 TO 1.0 mEq /6.08 to 12.16 mg/ of elementar Mg) per Kg of body weight (ATCHLEY et al.,1993: BUTLER, 1950).

The depletion of body K during DKA even in the presence of normal or high serum K concentration has been well recognized, to the point that K supplementation has become standard practice in the management of fluids and electrolytes in DKA. **Magnesium, on the other hand, has longly been ignored** (MARTIN et al., 1958), although it has been used in adults (MATZ, 1992). In theory, several consequences of Mg deficit may add to the morbidity and even mortality of DKA. Refractory hypokalemia, hypocalcemia and hypophosphatemia are recognozed alterations associated with Mg deficit (BERKELHAMMER and BEAR, 1985). **The capability of Mg deficit to induce cardiac arrhythmias has been debated** (SURAWICZM, 1989). Magnesium is also known to play a role of a second messenger for insulin action (NADLER et al., 1993). Current recommendations from the American Diabetes Association do not warrant supplementation to diabetic patients unless Mg deficit is documented (MARTIN et al., 1958). Furthemore, with few exceptions (MATZ, 1992**) most of the standard protocols for managem)ent of DKA do not include routine administration of Mg.**

A modification of extracellular Mg ion (Mg) has been shown to have profound effects on secretagogue- evoked secretory responses in the isolated rat pancreas. **Elevated (Mg) inhibited Ca mobilization and secretory responses whereas a low (Mg) has a opposite effect**. The results (SINGH et al. 1995) indicate that secretagogue - evoked Mg transport (both releas and efflux) is dependent upon extracellular Na ions and moreover cytosolic Ca ions seems to regulate the transporter. Low Mg levels increase the activity of endocrine glands,i.e. pancreas and adrenal medulla. Since on the other hand adrenaline inhibits insulin synthesis and secretion, the net action of Mg deficiency upon pancreatic and serum insulin would be of interest. Therefore, PORTA et al.(l990) estimated the Mg-asparate supply in rats which were stressed under severe stress. They concluded that **high Mg levels suppress insulin secretion**, low levels promote both insulin synthesis and secretion to such an extent, that even during severe stress pancreas and serum insulin contents are unusually high. **Adrenaline´s suppressive effects are obviously overruled by local Mg depletion.** Since long term stress per se also leads to Mg depletion, the "reversed" influence on insulin could curb adrenaline secretion triggered by liver glycogen downfall (PORTA et al.,l990).

Magnesium, *BURNS* and BONE

Magnesium depletion is a focus of attention in the pathophysiology of severe burn injury for several reasons. First**, serum Mg concentration is low following burns** (KLEIN et al., 1997), raising the question of whether there is total body Mg depletion or a redistribution of Mg to the intracellular compartments. Second, **burn patients are hypocalcemic secondary to hypoparathyroidism and possibly also to an intracellular accumulation of Ca.** Moreover, these patients demonstrate renal resistance to exogenous parathyroid (PTH)

hormone. Hypocalcemia due to decreased PTH secretion and renal resistence to PTH administration have been reported with Mg depletion (ANAST et al., 1976: RUDE et al., 1976). **Finally**, and perhaps most importantly, burn victims have been shown to lose bone mass following thermal injury (KLEIN et al., 1995) due in part to decreased bone formation (KLEIN et al., 1993: KLEIN et al., 1995a) and also to increased bone resorption (KLEIN et al., 1998a). The postulated pathophysiology of the effects of burn injury on bone metabolism were shown in the schematic diagram illustrating the **pathophysiology of burn injury to bone, where also the role of CORTICOSTEROIDS is important** (KLEIN and HERNDON, 1998).

The deficit in bone formation and the reduced bone density may last for years (KLEIN et al., 1995: KLEIN et al., 1997a) and may increase the risk of post- burn fractures and reduce the peak bone mass of this group of patients, putting them at increased risk for adult onset osteoporosis (KLEIN et al., 1995).

The most commonly observed manifestations of chronic Mg depletion on bone and calcium metabolism are hypocalcemia associated with hypoparathyroidism and end-organ resistence to exogenous PTH administration (ANAST et al., 1976: RUDE et al., 1976).

RUDE et al.(1976) in a study of 17 hypomagnesemic patients, found that while Mg infusion produced a rapid rise in PTH, de rise of serum Ca concentration was delayed for days. Moreover, **in contrast to the report of ANAST et al (1976) urinary cyclic AMP response to PTH- extract was blunted.** The authors hypothesized that since Mg was involved in intracellular reactions generating cyclic AMP, Mg deficiency may result in imparied cyclic AMP generation in both the PTH- glands and in PTH target tissue, therefore explaining both the defect in PTH secretion and in end- organ responsiveness to PTH.

Interestingly, hypermagnesemia has also been shown be CHOLST et al.(1984) and by SLATOPOLSKY et al. (1976) to also produce hypocalcemia, hypoparathyroidism, and end-organ PTH resistance. **These findings suggest that both Mg deficiency and Mg excess may be involved in either the upregulation of the PTH-gland calcium- sensing receptor**, the downregulation of the renal PTH receptor, or both. Furthemore, should the existence of such a control mechanism be documented, it would imply that a tightly- controlled range of circulating Mg is necessary for normal functioning or expression of calcium- sensing and/ or PTH receptors and would be consistent with the tight control exerted by the renal tubules over circulating levels of ionized Mg (BROADUS, 1996)

Two-thirds of total body Mg is deposited in bone. Mg is reported to be located on the crystal surface, not within the hydroxiapatite lattice structure with only a small quantity normally exchangeable with the extracellular fluid compartment (BROADUS, 1996). However, it remains unknown as to the availability of bone Mg in cases of total body Mg depletion. Thus, although the total bone Mg content may be less than 2 oer cent of the total bone calcium content, minor adjustments in the exchangeable Mg pool in bone could potentially exert a larger effect on the total bone Mg than a change of similar magnitude in exchangeable Ca would have on the bone Ca pool. If Mg in matrix is important for the complexation of Ca, then bone Mg depletion could be in part responsible for defective bone matrix calcification and reduced bone mineral density seen in burn patients. It is in the investigation of the pathophysiology, of the burn injury to bone that the role of Mg , to date understudied, becomes critically important (KLEIN and HERNDON, 1998).

These authors found that children and adults who are severely burned develop Mg depletion, hypocalcemia , hypoparathyroidism and renal resistance to the administration of exogenous PTH. **This *same spectrum of findings were seen wit both Mg depletion and hypermagnesemia.*** They reported that in a group of ten children burned at least 30 per cent of total body surface area that 70-80 per cent of serum levels of ionized Ca and Mg were low. In three of the patients studied when serum Mg returned to normal, retention of a standard Mg infusion was abnormally high in two of them, suggesting persistence of Mg depletion despite normal serum Mg levels. Mg intake in these children conforms to the recommended dietary intake for age suggesting that excessive Mg losses may contribute to the observed Mg depletion. These losses are through the burn wound and possibly through abnormal intestinal secretion. Increased metabolic rate seen in burn patients may also promote intracellular Mg uptake to support the increased energy requirements of cells. It is hypothesized that since Mg

is an important cofactor in the production of cyclic AMP, Mg deficiency may block intracellular cyclic AMP generation in PTH- cells to block the secretion of PTH- hormone and in renal tubular cells to block the renal generation of cyclic AMP and phosphate excretion. However, while Mg administration may improve PTH secretion and hypocalcemia in non-burned patients, preliminary data in burned children suggest that the cause of hypocalcemia and hypoparathyroidism is more complex (KLEIN and HERNDON, 1998*).* **There is much controversy about the role of Mg deficit in the physiopathology of senile osteoporosis** (STENDIG-LINDBERG et al., 1993), in immunodepression of aged persons (GUNTHER et al., 1992) and in oncology.

Magnesium and aging

The importance of magnesium in the physiopathology of ageing has been very differently evaluated (DURLACH et al., 1993: DURLACH and BAC, 1997).In the human, magnesium absorption decreases with age. Around the age of 70, it becomes two-thirds of what is usually is with people around 30 (SEELIG, 1981). Magnesium exchangeable pools are reduced in elderly patients (ALFRAY et al., 1974). In some particular cases , urinary Mg leakage may be increased (MOUNTOKALAKIS, 1987), but usually urinary Mg excreation decreases (SIMECKOVA et al., 1996) or remains normal (LOWIK et al., 1993).

Among the biological bases of ageing, it seems particularly important to highlight the fact that senescence appears to be a condition of decreased adaptability to stress (PARNETTI et al., 1990). The aged related alterations in brain function particularly concern hippocampal pyramidal neurones. This part of the limbic system exerts an inhibitory influence on the **hypothalamo- pituitary- adrenal axis activity**. Hippocampal ageing induces a state of hyperglucocorticism. Hippocampus injury could in turn provoke new imbalance of the hypothalamo- pituitary- adrenal axis with "glucocorticoid cascade" (SAPOLSKY et al., 1986: SAPOLSKY,1986: KERR et al., 1991: LANDFIELD et al., 1992: SAPOLSKY, 1996: 1996) inducing a state of hyperadrenoglucocorticism. These changes could be attained through neuronal influences on the binding capacity of the adrenocorticoid receptor in the hippocampus (DeKLOET et al., 1991: ROTHUISEN et al., 1991: Van EEKELEN et al., 1991).

An indirect proof of age **related hypothalamic alteration** may rely on the disruption of circadian rhythm for plasma cortizol and melatonin in elderly subjects (OLSSON et al., 1989: SHERMAN et al., 1985: SHARMA et al., 1989). The best proof of the association with ageing between decreased hypothalamo- pituitary sensitivity and negative feedback regulation by glucocorticoid relies on dynamic investigation, and mainly on the dexamethazone suppression test. Older subjects in all diagnostic categories (normal ageing, dementia, depression) have higher post dexamethazone plasma cortizol levels. **A chronic stressful state exists in the ageing process.** The increased stress susceptibility is closely related to the ageing process itself and not so much to any particular age- related pathological conditions such as depression or dementia (PARNETTI et al., 1990: GEORGOTAS et al., 1986: STUCK et al., 1988).

Ageing induces peripheral and central hypoactivity of adrenergic receptors (RASKIND et al., 1988). This decreased sensitivity may modify Mg movements through cell membrane . They seem **linked with beta adrenergic receptors**, in particular which might be atypical (DURLACH et al., 1998).

Among the various diseases which may induce secondary magnesium deficit and which are frequently observed in elderly subjects**, diabetes mellitus appears as one of the main causes of Mg depletion in aged people** (DURLACH et al., 1993). Insulin resistence in ageing appears as a first step befora non insulin dependent diabetes (PAOLISSO et al., 1992). When glucose tolerance becomes impaired in older subjects a significant negative correlation may be observed between plasma and /or erythrocyte Mg concentrations, fasting blood sugar and basal insulinemia (DeLEEUW et al.,1992: PAOLISSO et al., 1992: HUA et al., 1992).

Today, it appears **difficult to assess the importance of magnesium deficit in the development of insulin- resistence in ageing**. Eyperimental and clinical data showed that magnesium deficit could bring about either diabetogenic or insulin- like effects . For example in vitro and ex vivo data showed in rats that insulin receptor activity was decreased (CARRASCOSA et al., 1989) both during ageing and in case of magnesium deficiency. **But**

conversely in marginal Mg deficiency in rats slightly enhanced the peripheral insulin sensitivity was observed (DURLACH et al., 1998)! PAOLISSO´s studies in the human (1992) because of several biases fail to demonstrate the notion of an insulin- resistance due to Mg deficiency in ageing (DeLEEUW et al., 1992).

Heated zealots like P.Delbet (DELBET, 1963) have seen in magnesium a sort of panacea **which may play the role of elixir vitae preventing all the hazards of senility**. Intellectual functions, sexual potency and skin quality are stimulated by mere oral magnesium supplementation. But, on the other hand, most of the general reviews concerning nutrient requirements and electrolytic abnormalities in the elderly (DURLACH et al., 1993) have overlooked certain data concerning the magnesium status of ageing!

Between these two extremes, it is today possible to find a balance. It seems now well established that **magnesium does not constitute an elixir vitae**. Reversely magnesium deficit appears as able to play a role in the physiopathology of ageing (DURLACH, 1988: LOWIK et al., 1993: SINGH et al.,1996: SINGH et al., 1996). This clinical notion relies on a large experimental backgroud (RAYSSIGUIER et al., 1996: CLASSEN et al., 1994). First of all the seminal paper by O.HEROUX et al. (1977) showed that chronic marginal magnesium deficiency reduced lifespan in rats (HEROUX et al., 1977). **Magnesium deficit accelerates ageing** through its various effects on the neuromuscular, cardiovascular and endocrine apparatus, kidney and bone, immunity , anti- stress and anti- oxidant systems (DURLACH, 1977: DURLACH et al., 1997).

In developed countries, magnesium intake is marginal in the entire population whatever the age: around 4 mg/ kg/ day instead 6 mg/ kg/ day recommended to maintain balance of this mineral and good health (SEELIG,1981: GALAN et al., 1997). The high prevalence of the marginal magnesium deficiency in 15 to 20 per cent of the population seems consistent with the estimation of nutrient deficiency using probability analysis (DURLACH et al., 1998). These data are particularly relevant to the health of aged persons. However, the elderly population is extremely heterogenous: diseases, handicaps, physical or psychological impairments expose to more severe nutritional deficiencies (HEGSTED, 1989: SCHNEIDER et al., 1986). **Thus marginal Mg deficiency is observed in elderly people** as well as in the whole population (PENNINGTON and YOUNG, 1991: ABDULLA and REIS, 1991), in free living ageing groups (VIR and LOVE, 1979) as well as in institutionalized elderly patients, although it is more pronounced in the latter (ABDULLA,1976: GREEGER,1977: CLASSEN et al., 1989: THOMAS et al., 1989), whether in America, Australia or Europe. **A positive correlation between energy intake and magnesium intake is always observed** (HORVATH, 1989).

Magnesium and other functions

Hypermagnesaemia is associated with sedation, muscle relaxion, hyporeflexia, decreased excitability (STONE and PRITCHARD, 1971: LIPSITZ, 1971: AYROMLOO et al., 1982: RASCH et al.,1982), and calcium and potassium disturbances (LIPSITZ,1971: STONE and PRITCHARD, 1970: DURLACH and DURLACH, 1984). The manifestations **of Mg intoxication** reflect its ability to decrease central nervous system excitability by suppressing neuronal firing and inhibiting the release of acetylcholine in the peripheral neuromuscular junction. One of the most important cellular functions of Mg is to control cell membrane permeability either through is plasticization role in the cell membrane , inducing structural and electrostatic changes, or through its effect on membrane APP-ase dependent pumps (GUNTHER,1981). Therefore, **its intracellular deficiency is thought to be responsible for a rise of calcium (and sodium) in the cell and for a loss of potassium (and phosphorus).** Without any systemic regulatory response, magnesium deficiency would be associated with hypocalcemia and hyperkalaemia. **Magnesium excess is usually associated with hypercalcemia and hypokalaemia** (KRISHNAN et al., 1993: DONOVAN et al.,1980: MORDES,1977: MACINTYRE et al., 1963). Frequent monitoring of magnesium, calcium, and potassium is thus critical during management of persistent pulmonary hypertension

(PPHN) with Mg(SO)4 treatment ,respiratory depression is induced by hypermagnesaemia (DONOVAN et al., 1980: GREEN et al.,1983).

LIPMAN et al.(1987) have shown that a **continuous infusion of Mg(SO)4 can control sympathetic crises and supress catecholamine release**, which may occur in infants with persistent pulmonary hypertension of the newborn (PPHN). Pulmonary vasoconstriction is dependent on the availability of calcium to the affected cells (BOHR, 1977). The use of Ca channel blockers to induce vasodilatation can affect cardiovascular haemodynamics by a complex interplay of effects which include systemic arterial vasodilatation, a negative ionotropic effect, and reflex phenomena. Magnesium, which may act as a Ca blocker (LEVINE and COBURN, 1989) antagonizes Ca ion entry into smooth muscle cells, promoting vasodilatation (TURLAPATY and ALTURA, 1978).

Magnesium has a negative inotropic effect in heart muscle which is the consequence of a competitive antagonism against Ca. VIERLING et al.(l992) found that this effect is due to a concentration- dependent diminution of the Ca inward current by a blockade of Ca channels. In Mg-free solution the intracellular Ca strongly increased after Na withdrawal and decreased after readdition of Mg. This correlates with an increase and decrease in resting force in papillary muscles. In accordance with these results, a remarkable augmentation of Ca efflux (by 250%) was observed, if Mg ions (l.2 mM) was added to a Mg and Na free solution. So, in heart muscle, **an increase in ECF-Mg can reduce intracellular Ca by two independent mechanisms.** This may have important implications for the therapeutic effects of Mg in cardiac diseases (VIERLING et a.,l992).

Of particular relevance for airway diseases , applied Mg has been shown to relax smooth muscles of the bronchial system, to inhibit cholinergic neuromuscular transmission and to stabilize mast cells. Evidence exists of a bronchodilatating activity of Mg in asthmatic airways. Therefore with the respect to these findings, SMETANA et al. (1995) investigated the **effect of i.v. (after 3 days**) and p.o. administered Mg **(after 30 days)** in patients with bronchial hyperreactivity in a clinical trial. The result of this study indicate a beneficial effect of Mg therapy on the lung function, especially with i.v. administration (serum Mg 1.98 mmol/l) compared with the p.o. group (serum Mg 0.80 mmol/l).

Hyperglycaemia is known as an etiologic factor of acute pancreatitis. FRICK et al.(1995) have shown an upregulation of calcium processing proteins and pancreatic damage in the hyperglycemic environment in experimental studies of acute pancreatitis. In 1971 HOLTMEIR posed a hypothesis that there might exist a causality between plasma Mg deficiency and acute pancreatitis in humans, **for hypomagnesemia causes oversensitivity of the digestive system muscular coat (tunica muscularis) spasm , which in turn leads to dyskinesis, and disruption of the digestive system and pancreato- biliary sphincter dysfunction.** The first observation of Mg ion concentration behaviour during acute pancreatitis among humans were made in 1952 by EDMONDSON et al., and showed a short lived reduction of plasma magnesium ion concentration among 20 per cent suffering from acute pancreatitis independent of the type of disease.

A relationship between magnesium and pyridoxine has been observed in numerous metabolic functions. These two substances are involved in many physiological functions, participating in more or less closely connected steps: because of their functional proximity , associations between the two frequently have synergistic effects (KUBENA et al., 1988). For example, magnesium is known to be necessary to activate the phosphorylation of vitamin B6: a relationship between these nutrients has been observed in neurological disfunction , e.g. , autism (MARTINEAU et al., 1985: 1986). Deficiencies of either of these nutrients during reproduction may impair reproductive suuccess , as well as growth and development of offspring (KIRSKEY et al., 1975: KUBENA et al., 1983: 1983a).

Today obstetrics is a field were intravenous pharmacological magnesium therapy is frequently used (DURLACH et al., 1994: BENNETT and EDWARDS, 1997). **But its indications remain controversial.** A critical and comprehensive review of tocolytic agens to stop preterm labor concludes that the only effective drugs are the prostaglandine inhibitors. An analysis of randomized placebo - controlled clinical trials showed that parenteral

magnesium is no better than placebo (HIGBY et al., 1993). **The evidence that supports the use of MgSO4 for tocolysis is weak** (BENNETT and EDWARDS, 1997). Several randomized trials showed that it is no better than placebo at delaying pre-term delivery (BENNETT and EDWARDS, 1997) and when used in praeeclampsia, parenteral Mg has no effect on the length of spontaneous (WITLIN et al., 1997) or induced (ATKINSON et al., 1995) labour.

The main indication of parenteral Mg in obstetrics is praee klampsia. Two recent large trials (LUCAS et al., 1995: The Eclampsia Trial, 1995) established that MgSO4 was better than phenytoin or diazepam at reducing the risk of seizures and improved both maternal and neonatal outcome. But until these two trials preference was given to anticonvulsans which seemed to be the major treatments of preeklampsia as thea appeared to be more efficient and better tolerated in mother and fetus and to have lesser side effects on fetal heart tracings particularly (DURLACH et al., 1994).

Another possible indication for giving parenteral magnesium to women in preterm labour has been suggested (NELSON and GRETHER, 1995). A retrospective epidemiological studie showed that antenatal exposure of very low birthweight (less than 1500 g) infant to maternal pharmacological Mg supplementation reduced the incidence of cerebral palsy at age 3 or more. This hypothesis agrees with the many reports of a **neuroprotective role for Mg** (BAC et al., 1996: MUIR, 1998). It has stimulated several investigations whether MgSO4 was really cerebroprotective. **Two studies found no protective effects** and instead suggested cofounding factors that might have accounted for the apparent results of the earlier studies (SCHENDEL et al., 1996: PANETH et al., 1997).

In order to check whether antenatal exposure to maternal pharmacological Mg supplementation had **cerebroprotective effects on premature children**, several trials were conducted. One was MAGNET (The Magnesium and Neurologic Endpoints Trial) a randomized controlled double- blind trial. But an interim analysis showed that MgSO4 given to mother in preterm labour before 34 weeks was associated **with a significant increase in neonatal mortality. This trial was therefore discontinued** (MITTENDORF et al., 1997).

But other researchers criticizing the methodology of MAGNET and therefore unconvinced by the reasons for terminating the trial (BENICHOU et al., 1998: CROWTHER et al., 1998: LEVENO, 1998: GRETHER et al., 1998), pursued their own research which resulted in three other randomized trials on the same important subject being presently run: PREMAG TRIAL in France: ACTO MgSO4 (Australian Collaboration Trial of MgSO4) in Australia: BEAM (Beneficial Effects of Antenatal Magnesium trial) in the U.S.

Differences between the effects of antenatal magnesium therapy on premature infants **might be due to the dosage of MgSO4**! For example the mediane dose of tocolytic magnesium administration during MAGNET **is twice as high as the PREVENTIVE dose** used in ACTO MgSO4 and BEAM (MITTENDORF et al., 1998). **There is a dose-responsive between exposure to MgSO4 and mortality** (REYNOLDS et al., 1996). These different dosages of the magnesium supplement could **explain the BENEFICIAL or DELETERIOUS effects of magnesium** maternal PHARMACOLOGICAL antenatal administration (MITTENDORF et al., 1998).

These very interesting studies once again highlight the possible side effects of pharmacological infusion of MgSO4 on the fetus.DURLACH (1995) has been insisting for many years that this magnesium salt seemed to be the worst **toxicologically and pharmacologically.** Strangely enough in all these important clinical trials it is the one which has been routinely used although nowhere can be found any sort of justification for that choice (DURLACH, 1995).

Increases stress susceptibility , histamine reactions, growth reduction and the pathophysiological cosequences of a disturbed Ca metabolism are among the sequels of severe Mg deficiency (GUNTHER, 1981). On the other hand, **pharmacological Mg doses** are applied for **supression of uterine contractility**, treatment of pre-eclampsia and certain types of cardiac arrhythmia (CLASSEN et al., 1995).

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