Streß Reactions Modified by Magnesium Status

By *Hans-Georg Classen*
Institute of Food Technology Department of Pharmacology and Toxicology of Nutrition University of Hohenheim

Zusammenfassung

Im Verlauf des Generellen Adaptations-Syndroms, das durch Stressoren ausgelöst wird, kann die Widerstandskraft des Körpers entweder erniedrigt (Stadium der Alarm-Raktion bzw. Stadium der Erschöpfung) oder erhöht sein (Stadium der Resistenz). Ausgeprägte Mg-Mangelzustände können als starker Stressor zu Thymus-Involution führen; ein mäßiges Mg-Defizit kann u. a. die Schleimhaut des Magens gegenüber anderen Stimuli sensibilisieren und die Ausbildung von Streß-Ulzera begünstigen. Obwohl im Verlauf eines chronischen marginalen Mg-Mangels die Resistenz des Körpers unter besonderen Bedingungen erhöht sein kann, sollten Mg-Defizite ausgeglichen werden, auch im Hinblick auf ihre Beteiligung bei verschiedenen Adaptationskrankheiten. Die Hemmung akuter Streß-Reaktionen (wie die Entstehung von Streß-Ulzera, Herznekrosen oder Folgezustände von sozialem Streß) durch eine Mg-Therapie bei Tieren ohne deutlichen Mg-Mangel lassen ebenso wie vielversprechende Beobachtungen aus der Klinik vermuten, daß der Gesundheitszustand durch einen optimalen Magnesium-Status günstig beeinflußt wird.

Summary

In the course of the General Adaptation Syndrome, elicited by stressors, the resistance of the body can be either decreased (Stages of Alarm Reaction or of Exhaustion) or increased (Stage of Resistance). Severe Mg-depletion can act as a strong stressor inducing involution of the thymus, and moderate Mg-deficiency can —among other adverse reactions — sensitize the gastric muscosa to superimposed stimuli and provoke stress ulcers. Although evidence is given that continued exposure to marginal Mg-deficiency can increase resistance under special circumstances, Mg-deficits should be corrected for, also with respect to their involvement in several diseases of adaptation. The inhibition of acute stress reactions (e.g., development of peptic ulcers and cardiac necroses as well as manifestations of social stress) by Mg-therapy in animals without overt Mg-deficit, together with promising clinical observations, suggest benefical health effects provided by optimal Mg-status.

Résumé

Au cours du syndrome général d'adaptation, qui est déclenché par des agents stressants, la capacité de résistance de l'organisme peut être ou bien abaissée (stade de la réaction d'alarme ou stade de l'épuisement) ou bien accrue (stade de la résistance). Des états de déficit marqué en Mg, de même qu'un agent stressant intense, peuvent entraîner une involution du thymus; un déficit modéré en Mg peut en particulier sensibiliser la muqueuse de l'estomac envers d'autres stimuli et favoriser l'apparition d'ulcères de stress. Bien qu'au cours d'un déficit marginal chronique en Mg la résistance de l'organisme puisse être accrue dans certaines conditions, les déficits magnésiques doivent être compensés, également en considération de leur participation à diverses affections d'adaptation. L'inhibition des réactions aiguës de stress (telles que la formation d'ulcères de stress, de nécroses cardiaques ou d'états consécutifs à un stress social) par un traitement par le Mg chez des animaux sans déficit marqué, ainsi que des observations prometteuses sans déficit marqué, ainsi que des observations prometteuses en clinique permettent de supposer que l'état de santé est influencé favorablement par un état optimal du Mg.

1. Stress, biological stress reactions and factors modifying the response to stressors

In 1976, *Hans Selye* [45] has recommended the following definition for stress: "Stress is the nonspecific response of the body to any demand made upon it"; consequently, all endogenous or exogenous agents — which can, however, neet not be noxious — but that make such demands, are called "stressors". These stimuli are usually subdivided into somatic stressors (e.g., forced muscular work, starvation, noise, exposure to cold or heat, toxic amounts of drugs like adrenaline or insulin) and psychological stressors (e.g., fear, joy, rage, sorrow, frustration, isolation). On combined exposure, the effects of different stressors are usually additive in proportion to their relative potency. Despite obvious specific actions (e.g., adrenaline increasing, insulin lowering blood glucose; joy being perceived as positive, fear as negative), very different stressors will uniformly evoke considerable nonspecific responses, known as the General Adaptation Syndrome (G.A.S.) [45].

These findings are taken into consideration in all modern biological research: Control receive placebo preparations or sham operations, whenever possible, which shall allow to defferentiate between unspecific and specific effects of the treatment under investigation. Problems may arise, however, when the role of ingredients present in normal food shall be studied by changing their concentration: the ideal placebo equivalent of a diet poor in NaCl should taste as fade and unpleasant as does the verum diet, but it should contain normal NaCl concentrations. Only these conditions allow to distinguish exactly between specific effects of low NaCl intake and unspecific reactions, e.g., due to decreased appetite and food consumption, leading to loss of body-weight and finally to lowering of blood-pressure. Similarly, unspecific stress reactions might interfere when feeding experimental animals magnesium (Mg)-deficient diets; in this connection, any behavioral studies concerning the preference of avoidance of such diets have been reported in literature so far.

What kind of biological stress reactions are known? In comprehensive animal studies *Selye* [45] has shown that on exposure to noxious agents and conditions, rats regularly exhibit bleeding gastrointestinal ulcers, an atrophy of the thymus gland and lymph nodes and enlarged adrenals within 24 h. This triad is symptomatic for Stage I of the G.A.S., called **Alarm Reaction**. It is obvious that at this stage, the resistance of these ani-

mals against all kinds of stressors is decreased compared to (unstressed) controls. — On continued exposure to stress the typical pathological signs disappear, so far as they are reversible, in the surviving animals: they have become adapted to the situation. Compared with (untrained) controls they are now more resistant against the causative stressor: Stage II of the G.A.S. or **Stage of Resistance.** It is a very important fact that at this stage resistance os also increased against quite different stressors, a phenomenon called crossresistance. — Finally the acquired adaptation can be lost again (and also when "training" is unterrupted); the signs of the alarm reaction reappear, but now they are irreversible, and the individual dies: Stage III of the G.A.S., called **Stage of Exhaustion.**

Alarm reactions lead to a stimulation of central nervous and neurohumoral mechanisms (e.g., the limbic system involving the hypothalamus; liberation of diverse releasing factors; activation of the pituitary-adrenocortical axis and the sympathetic system). A number of more or less typical biochemical, circulatory and other physiological parameters are changed directly or indirectly and can be used as quantitative measures of the reaction: In peripheral blood the concentrations of STH, ACTH and other glandotropic hormones, of vasopressin, gluco- and mineralocorticoids, thyroid and gonadal hormones, catecholamines and beta-endorphin are usually elevated, which in turn induce specific metabolic and circulatory alterations and affect electrolyte metabolism as well [45, 49]. Decreased blood-Mg levels are described only exceptionally, e.g., in rats [34] or sheep [47] following exposure to cold; in female turkeys under hyperthermia [25]; in horses under physical stress [26]; in sheep after infusions of adrenaline [41] or after severe burns, probably as the result of direct loss of Mg [2]. In acute infectious illnesses, serum-Mg generally remains at normal or high-normal concentrations despite negative Mg-balances [2]. Usually, the administration of toxic amounts of hormones or drugs as well as asphyxia or severe blood-loss immediately lead to (unspecific) hypermagnesemia due to acidosis and cell damage, e.g. in cats [7], or rats even after Mg-depletion [8]. Such elevated Mg-levels could be regarded as a self-protecting mechanism as will be shown later. — Corresponding to the respective blood-levels, typical urinary excretion patterns are also well kown [45, 49]. For example, *Lehr* and coworkers have related urinary Mg-loss to the degree of myocardial injury induced by stress hormones [30].

On the other hand it is important to realize that there is any reliable parameter indicating the degree of adaptation: hence a stage of resistance can only be assumed when the response to a stressor is apparently weaker in "trained" than in "untrained" animals.

Maladaptation to stress together with various conditioning factors (which should not possess measurable stressor effects) play the decisive pathogenic role in the development of the so-called diseases of adapation; most frequently descussed under this aspect are shock, gastrointestinal diseases (e.g., peptic ulcers; ulcerative colitis), cardiovascular diseases (particularly cardiac necroses and hypertension) and neuropsychiatric diseases [45]. Numerous experimental studies and clinical reports have shown that under the influence of conditioning or "risk" factors — which may be exogenous (dietary factors, treatment with certain hormones and drugs) or endogenous (genetic predisposition, age or sex) — a normally well tolerated degree of stress can become pathogenic by potentiating stressor effects. This selectivity of damage is comparable to that in different chains, in each of which mechanical stress of identical tension will break the particular link that has become weakest as a result of internal or external factors [45]. — There is abundant evidence that actual Mg-status — which can be deficient, normal, optimal or excessive — plays an important role in pluricausal stress diseases. However, when normal Mg-intake is changed, e.g., by feeding rats special deficient diets, it must be kept in mind that such an intervention must not in each case be regarded only as a conditioning and potentiating factor. As will be shown, acute severe Mg-deficiency produced in young rats can act as a strong stressor eliciting typical signs of an Alarm Reaction. On the other hand it seems as if animals could — to a certain degree — become adapted to chronic marginal Mg-deficiency. Theoretically, at this stage, the level of resistance should be increased not only to the causative, but also to other stressors. — Finally the Stage of Exhaustion should be achieved in chronic Mg-depletion, too.

It must be admitted that it is often difficult, if not impossible, to decide whether an unphysiological Mg-status must be regarded as a conditioning factor, or as a stressor having elicited one of the three stages of the G.A.S. However, with these possibilities in mind, some contradictory findings could be interpreted.

2. Alarm Reactions elicited or modified by acute magnesium depletion

In rats clinical sings of Mg-deficiency largely depend on the initial age, respectively body-weight of the animals, the Mg-content of the diet and the duration of exposure. In contrast to weanling female rats (about 40 g b.w.), exhibiting typical erythema, moderately increased excitability and an exponential decrease in serum-Mg, adult ones (of about 250 g b.w.) remained completely normal from the clinical point of view, and serum-Mg decreased in a linear fashion, when these animals received a marginal Mg-deficient diet of 135 ppm Mg during 28 days [4, 29]. On the other hand, a diet containing only 50 ppm Mg led to the occurrence of severe convulsions already after two weeks in weanling rats (of about 40 g b.w.), and mortality amounted to 21% [31]. Therefore the remainder received drinking-water supplemented with 2 mmol Mg

according to *Günther* and *Ising* [18]. Convulsions ceased and there was no more mortality till day 21 when the animals were sacrificed (n = 15). In these animals the weight of the thymus glands was significantly decreased, compared to controls, taking into consideration either the absolute, or the organ weights related to body-weight [31]. — When the experiment was repeated with 2 mmol of Mg added to the drinking-water right from the beginning, neither convulsions nor mortality were observed. Under these conditions the weight of the thymus glands did no longer differ from that of the controls [32]. Generalizing, it can be concluded that acute severe Mg-depletion can act as a powerful stressor producing a typical symptom of the stress triad, namely involution of the thymus gland, which is certainly due to an overstimulation of the pituitary-adrenocortical axis.

As outlined above, gastric ulcers also develop during the stage of Alarm Reaction. Is has been noted be *Selye* [45] that the gastric mucosa of rats and other species is markedly sensitized by acute and complete starvation to superimposed stressors such as cold, restraint or trauma. Neither marginal Mg-deficiency of 3 weeks duration (without leading to convulsions) nor starvation during 18 to 42 h caused gastric lesions in young rats when applied separately. However, when applied together, 60% of the rats (n = 15) exhibited 1 to 5 small, fresh gastric ulcers [31]. The question whether additive stressor or potentiating effects are responsible for these lesions cannot be answered at this point. — Anyway, these observations could be confirmed by additional experiments: 41 female weanling rats (about 38 g b.w.) were kept on a Mg-deficient diet (50 ppm Mg) during 21 days and received drinking-water with 2 mmol Mg (= deficient group) respectively 30 mmol Mg (= controls). After 24 h of starvation (with deionized water ad libitum) the animals were subjected to an 18 h immobilization stress. As shown in **Tables 1 and 2**, gastric lesions were significantly aggravated by Mg-deficiency with regard to qualitative macroscopical estimation and to quantitative microscopical examination, considering both surface and depth of the ulcers and performed under blind conditions.

Severity of gastric lesions

Group	n	body-weight before restraint and starvation	0 no ulcers	1 1 to 2 small ulcers	2 3 to 5 small ulcers	3 several large ulcers	4 multiple large ulcers
Controls: Starvation + Restraint	20	148 ± 10	6	5	7	2	—
Mg-deficiency + Starvation + Restraint	21	127 ± 11	1	3	11	2	4

Table 1: Aggravation of gastric ulcers, produced by starvation plus immobilization, by marginal Mg-deficiency (according to [32]: Macroscopical examination.

Gastric ulcerations

Group	n	total surface (µm)	total depth (µm)
Controls:		2295,60 ± 207,80	1343,35 ± 121,91
Starvation + Restraint	20	2688,57 ± 185,82	
Mg-deficiency + Starvation + Restraint	21	49 4965,43 ± 429,32	2688,57 ± 185,82

Table 2: Same experiment as in Table 1: Mean and standard error of total surface and total depth of gastric ulcers (Microscopical estimation).

Again the question must remain open whether Mg-depletion together with starvation must be regarded as additive stressors or as conditioning factors, potentiating the effect of restraint. Further experiments are planned involving the study of components of gastric juice and gastric mucosa, since according to *Selye* [45] the causation of peptic ulcers does not depend upon the presence of the pituitary or the adrenals; they not only occur after hypophysectomy or adrenalectomie but are even aggravated in the absence of the pituitary-adrenal axis. Curiously, a great excess of glucocorticoids can also provoke peptic ulcers or at least condition the mucosa for their production during stress [45].

As outlined earlier the third symptom of the stress triad is an enlargement of the adrenals indicating overstimulation. Biochemical parameters have proven that the secretion of catecholamines is indeed increased after Mg-depletion: *Johnson* has shown that in rats adrenal levels of epinephrine decrease after 8 days of deficiency by 23% and by 46% after 12 days [24]. Correspondingly, the urinary excretion of adrenaline (calculated per milligram of creatinine) increased after 14 weeks in male rats (150 g b.w.) by 50 and about 70%, when the animals were fed a marginal (80 ppm Mg in the diet plus 2 mmol Mg in drinking-water) or a pronounced deficient (40 ppm Mg in the diet) regimen in the experiments of *Günther* and *Ising* [18]. The secretion and urinary excretion of steroids has not been measured under comparable conditions. However, to our surprise, *Root* and *Duckett* have reported in Montreal 1976, that in adult male rats kept on a Mg-free diet for 3 weeks, serum and pituitary levels of FSH, TSH, GH, LH and prolactin, determined by radioimmunoassay remained unchanged [42]. Nevertheless it can be assumed that central nervous reactions to acute stress are modified by Mg-depletion: *Chutkow* and *Grabow* [5] have shown that in young rats kept on an only 12 ppm Mg containing diet, brain-Mg decreased exponentially by 2% after 2 days and by 6 to 7% after 7 days. At this time the animals, previously insensitive to noise stimuli, rapidly exhibited convulsions of increasing severity and frequency after reexposure to this stressor. Although brain levels of norepinephrine, dopamine and 5-hydroxytryptamine were not affected by

Mg-depletion [6] it is possible that the turnover of central neurotransmitters is altered, since in rats, kept under comparable conditions, the acute toxicity of amphetamine has been found to increase by 100% [21]. The whole body of changes occurring during acute Mg-depletion should somehow sensitize organs against stressors. In our laboratory *Vormann* [51] has shown that in female rats (initial b.w. of about 75 g) kept on a 50 ppm Mg containing diet during only 6 days, myocardial Mg was already decreased by 4% whereas Ca and Na where increased by 33% respectively 14%. Under these conditions 50 µg adrenaline being uneffective in controls, led to a further elevation of cardiac Ca, and 200 µg adrenaline produced necroses within 7 hours. — Clinical implications of Mg-deficiency, e.g. with regard to pluricausal cardiovascular, respectively neuropsyiatric diseases have been extremely well reviewed by *Seelig* [44] and *Durlach* [13], and *Ising* et al. [22] have recently reported that susceptibility to noise is increased under these conditions in workers. These subjects will also be discussed during this Symposium.

Discussing stress reactions it is of particular interest whether evidence is given to suppose that also other stages of the G.A.S. can be achieved in animals kept on Mg-deficient diets.

3. The General Adaptation Syndrome elicited by marginal magnesium-deficiency

Heroux and coworkers [19] have conducted a relevant outstanding long-time experiment on 192 male Sprague-Dawley rats with an initial age of 5 weeks and a body weight of 85 to 100 g: Controls were fed a semipurified diet containing 520 ppm Mg and were kept at physiological temperature (28 °C) or chronically exposed to cold stress of 6 °C. Another two groups were also kept at 28 °C or 6 °C, but in addition received a diet suboptimal in Mg (100 ppm), leading to typical skin alterations in 50% of the animals during the first 69 days and to reduction of growth. — Hearts were histologically examined for fresh necroses on days 69, 240 and 517. On these days certain animals were exposed to even more severe stress by exposure to −20 °C for 4 hours and then also examined. As can be seen from the occurrence of fresh necroses, summarized in Table 3, Mg-deficient animals exhibited reduced resistance on day 69, especially after exposure to the additional stress of −20 °C. — On day 240, no marked differences could be seen when comparing the 4 groups: some unspecific Stage of Resistance must have been achieved. One could even speculate that at this time resistance against severe cold stress was increased in both groups kept at 6 °C, independent of Mg-supply. This would mean that cold adapted Mg-deficient rats are more resistant than controls kept on physiological temperature and normal Mg-supply!

On day 517, finally, the group kept on Mg-deficient diet plus low temperature had obviously turned to the Stage of Exhaustion: Before the, exposure to additional stress, only 44% of the animals had survived (as compared to 71 −93% in the other groups) and none of the rats of this group survived exposure to −20 °C for 4 hours.

	Day 69		Day 240		Day 517	
	Before	After −20 °C	Before	After −20 °C	Before	After −20 °C
Control 28 °C:	0/6	4/8	1/8	5/7	2/6	3/7
(520 ppm Mg) 6 °C:	0/7	1/8	1/5	1/7	0/4	1/6
Mg-depletion 28 °C:	1/8	7/7	1/8	5/7	0/5	4/6
(100 ppm Mg) 6 °C:	5/8	7/8	1/7	2/8	2/4	—

Table 3: Acute cardiac necroses of rats exposed to different stressors, according to *Heroux* et al. [19]

These observations fit very well into *Selye's* concept of the G.A.S. and might be even helpful to explain that in man severe hypomagnesemia associated with a significant Mg-deficit may be totally asymptomatic and remain undetected clinically as stated by *Flink* [17]. Nevertheless, the increased susceptibility to stress during the Stage of Alarm Reaction as well as reduced longevity clearly indicate that Mg-supply should be optimal. Thus under certain circumstances, Mg-treatment should be expected to be beneficial.

4. Stress-Reactions modified my magnesium therapy

The efficacy of a Mg-therapy depends above all on the route of administration, the dose, the actual Mg-status, and the Mg-compound used. Toxic symptoms and pharmacological effects of excess Mg have been reviewed by *Mordes* and *Wacker* [36] and *Ebel* et al. [14] and can be easiest observed after parenteral administration of overdoses, or, in the presence of acute or chronic renal failure, also after oral intake. However, in the absence of either renal or intestinal diseases, hazardous hypermagnesemia is rather unlikely to result, even after excessive oral ingestion [36]; hence this route of administration should be preferred whenever possible. In Montreal, five years ago, we have already reviewed the importance of the actual Mg-status and the role of the anion with respect to enteral resorption [8, 9]: Briefly, all Mg-salts so far examined are equally well absorbed in Mg-deficient animals; in addition *Vormann* has shown that hypermagnesemia observed in rats after single oral doses of 125 mg/kg and 250 mg/kg Mg reached about twofold the levels in Mg-deficient than in control animals [51] indicating different intestinal absorption mechanisms after Mg-depletion. — On the other hand, chloride containing compounds are better absorbed in animals with well balanced Mg-status. Since Magnesium-Aspartate-Hydrochloride*) (MG-Asp.-HCl) is equipotent with regard to its uptake, but less toxic than $MgCl_2$, we

* Magnesiocard®, Manufacturer: Verla-Pharm, D-8132 Tutzing/Obb. All doses mentioned in the text refer to Mg++.

prefer the former. In rats with well-balanced Mg-status a linear correlation between log Serum-Mg and orally applied dosis of Mg-Asp.-HCl could be estalished, r = 0,96 [28] within pharmacological dose ranges; the LD_{50} on oral application being 1021 (933 — 1117) mg/kg Mg.

The question was whether in animals without Mg-deficiency acute stress reactions can be inhibited by Mg-therapy. In 1973, *Szelenyi* reviewing the significance of Mg in gastro-intestinal disorders has mentioned own unpublished experiments in which "the frequency of ulcer occurrence as well as the severety of the ulceration (produced by restraint) was remarkably mitigated in the animals pretreated by Mg" ("long-term administration of Mg-aspartate and Mg-orotate") [48]. Any further details are reported. — In the experiments of *Vasku* et al. [50] young rats of 62 g b.w. received repeated i. p. injections of 50 mg Mg-aspartate plus 50 mg K-aspartate (corresponding to about 55 mg, respectively 2.3 mmol Mg per kg b. w.) all 2 days and were then subjected to 17 h immobilization stress; unfortunately; the duration of the whole experiment was not reported, and electrolytes were measured either. From macroscopical and microscopical observations these authors conclude that the electrolytes administered had practically no influence on bleedings and erosions of the gastric mucosa. However thymolysis and lympholysis were markedly inhibited. — *Schulz-Baldes* [43] produced stress in rats by unilateral adrenalectomy or i. p. injections of 5 mg/kg histamine. At a dose of 400 mg/kg $MgSO_4$ i.p. (corresponding to about 55 mg, resp. 2.3 mmol Mg/kg b.w.), applicated 2 to 3 h prior to the stressors, the histamine induced response was slightly inhibited as judged by 15% lesser decrease in adrenal ascorbic acid concentrations. — In view of these contradictory results and bearing in mind that in human therapy considerable amounts of Mg are used for the treatment of gastrointestinal disorders [10], of which 2 to 20% can be absorbed [3], we decided to study this question again [35]: Female Sprague-Dawley rats (90 to 120 g b.w.) were maintained on standard laboratory chow; stress ulcers were produced by 18 h immobilization preceded by 24 h starvation. In order to exclude local reactions or interactions, Mg (as Mg-Asp.-HCL) was administered by the s.c. route. The LD_{50} was established to be 432 (317 — 587) mg Mg/kg b.w., s.c. 8 mmol Mg (corresponding to about 194 mg) per kg b.w. were injected s.c. at the beginning of the stress period, and twice 4 mmol Mg per kg b.w. at 6 and 12 h. In additional experiments (in which no mortality was observed) it was shown that under these conditions maximal increases in serum-Mg occurred 70 min after the injections; levels reaching 11.8; 5.1 and 4.5 mmol/l Mg, respectively. Between the injections serum-Mg markedly decreased but didn't fall down to the normal range. — As shown in Tables 4 and 5 this Mg-therapy revealed significant protective effects against the development of stress ulcers, considering macroscopical examination of gastric lesions as well as the quantitative microscopical estimation of both surface and depth of the ulcers and performed under blind conditions. The weights of the thymus glands, however, remained uneffected.

Severity of gastric lesions

Group	n	body-weight	0 no ulcers	1 1 to 2 small ulcers	2 3 to 5 small ulcers	3 several large ulcers	4 multiple large ulcers
Controls: Starvation + restraint	16	102 — 112	2	1	5	3	5
Mg-therapy + Starvation + restraint	14	102 — 112	3	3	6	2	0

Table 4: Beneficial effect of Mg-therapy on the development of gastric ulcers according to [35]: Macroscopical examination

Gastric ulcerations

Group	n	total surface (µm)	total depth (µm)
Controls Starvation + restraint	15	3692 ± 621	1108 ± 203
Mg-therapy + starvation + restraint	14	1446 ± 416	521 ± 144

Table 5: Same experiment as in Table 4: Mean and standard error of total surface and total depth of gastric ulcers: Microscopical estimation.

Taking also into consideration the results obtained in Mg-deficient rats it can be concluded that Mg-status profoundly influences the manifestation of acute stress with regard to the stress triad.

In modern livestock breeding, social stress occurs above all when animals are put together in groups for fattening or after having brought forth youngs, or during transportation, e.g., to the slaughter-house. Surprisingly good effects of Mg-Asp.-HCl, added to normal feed at a concentration corresponding to an additional uptake of 40 mg Mg^{++} per kg b.w., were observed in pigs being especially sensitive to stress: In young animals of 20 to 35 kg b.w., kept together in groups of 5 or 6 for fattening, cannibalism (i.e., ear and tail biting) stopped within 24 h in 50% and was obviously reduced in 25% of about 1400 pigs. Comparable good results are assumed in some hundred sows, also grouped together, and were observed in 90 sows under controlled conditions, concerning the time coming on heat. Harmonizing effects were also observed in about 1500 heifers and some horses. During transportation to the slaughter-house only one of 750 pigs died of sudden cardiac arrest; without treatment at least 1% succumbed animals are to be expected. In these experiments Mg-Asp.-HCl was superior to $MgCl_2$ and Mg-asparatate [37]. The observations were confirmed

by serum-Mg being elevated by about 10% [37] and by cardiac Mg being increased by 1.6% whereas cardiac Ca was lowered by 6.6% after oral administration of daily 40 mg/kg Mg during 14 days (n = 42) [38]. Comparable electrolyte alterations were observed in rats fed Mg-Asp.-HCl [28]. Today this compound is available in Switzerland as feed additive*).

In Finland *Nuoranne* has reported that since 1969 Mg-content has been raised by 20 to 30%, using MgO or $MgSO_4$, in pig feed assuming that bruxism, splay leg and leg weakness in these animals are pathognomonic symptoms of Mg-deficiency, because animals fed a Mg-deficient diet exhibited similar changes [39]. Since 1972 all industrial pig foods in Finland have been supplemented by a considerable amount of Mg, and from indirect clinical evidence *Nuoranne* and coworkers conclude that this Mg-supplementation has a favourable effect on disorders, a great part of which they assume to be functional failures of muscle tissue. Amelioration of cannibalism was also mentioned [40]. — It seems unproven and unlikely that pig feed are generally deficient in Mg (even in pigs receiving a Mg-deficient diet, serum-Mg was not decreased) leading to clinical signs of Mg-deficiency; however the reported benefical effects of abundant doses of Mg added to feed fit well into the concept of our group (although under the aspect of Mg-therapy).

Mg-salts have been shown to have a depressive action when applied directly to nerval tissue [16]. The question is, however, whether in animals with a normal Mg-balance, the minute, if any [9], amounts penetrating the blood-cerebrospinal fluid and blood-brain barriers on systemic application [20, 27] are sufficient to elicit central nervous effects. *Somjen* and coworkers have clearly shown that there is no narcotic action of Mg administered to humans by the i.v. route [46]. Neither is there a sedating effect in cats; but *Krämer* et al. using animals with chronically implanted electrodes showed that the cortical response to striatal stimulation was diminished and that amygdaloid projections to the hippocampus and the hypothalamus were inhibited when serum-Mg levels were increased from 1.8 to 3.6 mval/l by oral application of Mg-Asp.-HCl [27]. These findings suggesting tranquillizing effects of excess Mg may help to interpret beneficial effects on acute stress reactions mediated by the central nervous system. In addition, peripheral actions of Mg-therapy must be considered which can mainly be explained as Ca^{++}-antagonistic effects together with the prevention of the loss of functional Mg. In experiments on rats it has been shown that Mg-loss, myocardial Ca-overload and fiber necrosis — produced by toxic amounts of catecholamines — can be prevented by Mg-Asp.-HCl [23, 51, 52] (see also *D. Lehr*, this Symposium). — Concerning the interrelations between Mg-status and the development of stress ulcers, central-nervous tranquillizing effects could be discussed together with peripheral, Ca-antagonistic actions, since calcitonin also prevents the development of stress ulcers in rats [1]. However, further studies are necessary for better understanding the underlying mechanism [5].

Good therapeutic effects in man after oral Mg-therapy were reported e.g., by *Fehlinger* [15], *Matusczyk* [33], *Davis* and *Ziady* [12] and *Classen* [11], who treated patients with tetanic syndrome, vegetative disorders, cardiac disturbances, or children with functional nervous disturbances. For further literature compare *Seelig* [44] and the proceedings of this Symposium. It is to be hoped that in man, too, these promising observations are confirmed by controlled studies under double-blind cross-over conditions.

* Manufacturer: ufa-med, CH-6210 Sursee.

References

[1] *Bates, R. F. L., Barlet, J. P.:* Horm. Metab. Res. **6**, 332—333 (1974).
[2] *Beisel, W. R., Pekarek, R. S.:* Intern. Rev. Neurobiol. Suppl. **1**, 53—82 (1972).
[3] *Bertram, H. P., Zumkley, H.:* Krankenhausarzt **52**, 416—424 (1979).
[4] *Blanc, Ch., Classen, H. G.:* Magnesium-Bull. **2**, 68—71 (1980).
[5] *Chutkow, J. G., Grabow, J. D.:* Amer. J. Physiol. 223, 1407—1414 (1972).
[6] *Chutkow, J. G., Tyce, G. M.:* J. Neural Transmission **44**, 297—302 (1979).
[7] *Classen, H. G., Marquardt, P., Späth, M., Schumacher, K.-A.:* Pharmacology **5**, 287—294 (1971).
[8] *Classen, H. G., Ebel, H., Schumacher, K.-A., Marquardt, P., Späth, M., Helbig, J.:* Magnesium in Health and Disease. Spectrum Publications, Inc. 521—535 (1980).
[9] *Classen, H. G., Marquardt, P., Späth, M., Ebel, H., Schumacher, K.-A.:* Arzneimittel-Forsch. 23, 267—271 (1973).
[10] *Classen, H. G.:* Magnesium-Bull. **1**, 1—8 (1979).
[11] *Classen, O.:* Magnesium-Bull. **2**, 124—125 (1980).
[12] *Davis, W. H., Ziady, F.:* S. Afr. med. J. **53**, 591—593 (1978).
[13] *Durlach, J.:* Neurological manifestations of magnesium imbalance. In: Handbook of Clinical Neurology. Vol. **28**, North Holland, Oxford (1976).
[14] *Ebel, H., Classen, H. G., Marquardt, P., Späth, M.:* Münch. Med. Wschr. **117**, 1243—1248 (1975).
[15] *Fehlinger, R.:* Magnesium-Bull. **1**, 152 (1979).
[16] *Feldberg, W.:* J. Physiol. (Lond) **140**, 20 P (1958).
[17] *Flink, E. B.:* Magnesium deficiency and magnesium toxicity in man. In: A. S. Prasad (Ed.): Trace Elements in Human Health and Disease, Vol. II. Acad. Press, New York, San Francisco, London (1976) p. 1—21.
[18] *Günther, T., Ising, H.:* Magnesium-Bull. **1**, 115—117 (1979).
[19] *Heroux, O., Peter, D., Heggtveit, H. A.:* J. Nutr. **107**, 1640—1652 (1977).
[20] *Hilmy, M. I., Somjen, G. G.:* Amer. J. Physiol. **214**, 406—413 (1968).
[21] *Holl, J. E., Resurrecion, A.V.A., Park, L. E., Caster, O.:* Res. Comm. Chem. Path. Pharmacol. **22**, 501—512 (1978).
[22] *Ising, H., Dienel, D., Günther, T., Markert, B.:* Int. Arch. Occup. Environ Health **47**, 179—190 (1980).
[23] *Jacob, R., Classen, H. G.:* Magnesium-Bull. **1**, 125—130 (1979).

[24] *Johnson, C. J.* (1965) cited in 44.
[25] *Kohne, H. J., Jones, J. E.:* Poultry Science **54**, 2034—2038 (1975).
[26] *Kossila, V., Tanhuanpää, E., Peltonen, T., Virtanen, E.:* Ann. Agric. Fenn. 15, 322—329 (1976).
[27] *Krämer, W., Holm, E., Dreyer, S., Meyer, J. B., Behari, J. R., Fischer, B.:* Magnesium-Bull. **1**, 49—52 (1979).
[28] *Krieger, G., Classen, H. G.:* Magnesium-Bull. **1**, 191—194 (1979).
[29] *Laidig, A., Classen, H. G.:* Magnesium-Bull. **2**, 72—75 (1980).
[30] *Lehr, D., Irene, S., Paino, B., Lehr, K.:* Magnesium loss in ischemic myocardial injury. 7th Int. Congress of Pharmacology, Paris, 1978.
[31] *Mangler, B.:* Der Einfluß eines alimentären Magnesium-Mangels auf die Entwicklung von Stress-Ulcera und die Elektrolytverteilung im Herzmuskel. Diplomarbeit, Univ. Hohenheim (1981).
[32] *Mangler, B., Fischer, G., Classen, H. G.:* See this Symposium
[33] *Matusczyk, H.:* Magnesium-Bull. **1**, 106—108 (1979).
[34] *McGee, J. H., Savory, J.:* Clin. Chem. **19**, 642 (1973).
[35] *Mesmer, H., Fischer, G., Classen, H. G.:* Arzneim. Forsch. **31**, 389—391 (1981).
[36] *Mordes, J. P., Wacker, W.E.C.:* Pharmacological Rev. **29**, 273—301 (1977).
[37] *Niemack, E.-A., Stöckli, F., Classen, H. G., Helbig, J.:* Magnesium-Bull. **1**, 28—34 (1979).
[38] *Niemack, E.-A., Stöckli, F., Husmann, E., Sonderegger, J., Classen, H. G., Helbig, J.:* Magnesium-Bull. **1**, 195—198 (1979).
[39] *Nuoranne, P. J., Eläinlääkari, Suomen, Lehti:* **80**, 258—268.
[40] *Nuoranne, P. J., Raunio, R. P., Saukko, P., Karppanen, H.:* Brit, J. Nutr. **44**, 53—60 (1980).
[41] *Rayssiguer, V.:* Horm. Metabol. Res. 9, 303—314 (1977).
[42] *Root, A. W., Duckett, G. E.:* Effect of short-term magnesium-deficiency upon pituitary function in intact and castrated adult male rats. 2nd Int. Symp. on Magnesium. Montreal (1976).
[43] *Schulz-Baldes, J. G.:* Arzneim. Forsch. **15**, 835—837 (1965).
[44] *Seelig, M. S.:* Magnesium Deficiency in the Pathogenesis of Disease. Plenum Medical Book Comp., New York—London (1980).
[45] *Selye, H.:* Stress in Health and Disease. Butterworths Boston — London (1976).
[46] *Somjen, G., Hilmy, M., Stephan, C. R.:* J. Pharmacol. Exptl. Ther. **154**, 652—659 (1966).
[47] *Sykes, A. R., Field, A. C., Slee, J.:* Anim. Prod. **11**, 91—99 (1969).
[48] *Szelenyi, I.:* World Rev. Nutrition and Dietetics 17, 189—224 (1973).
[49] *Ursin, H., Baade, E., Levine, S.:* (Editors): Psychobiology of Stress. Academic Press, New York — San Francisco — London (1978).
[50] *Vasku, J., Urbanek, E., Dolezal, S.:* Arzneim. Forsch. **16**, 559—565 (1966).
[51] *Vorman, J.:* Magnesium-Bull. **2**, 123 (1980).
[52] *Walcher, K., Classen, H. G.:* Magnesium-Bull. **2**, 86—89 (1980).