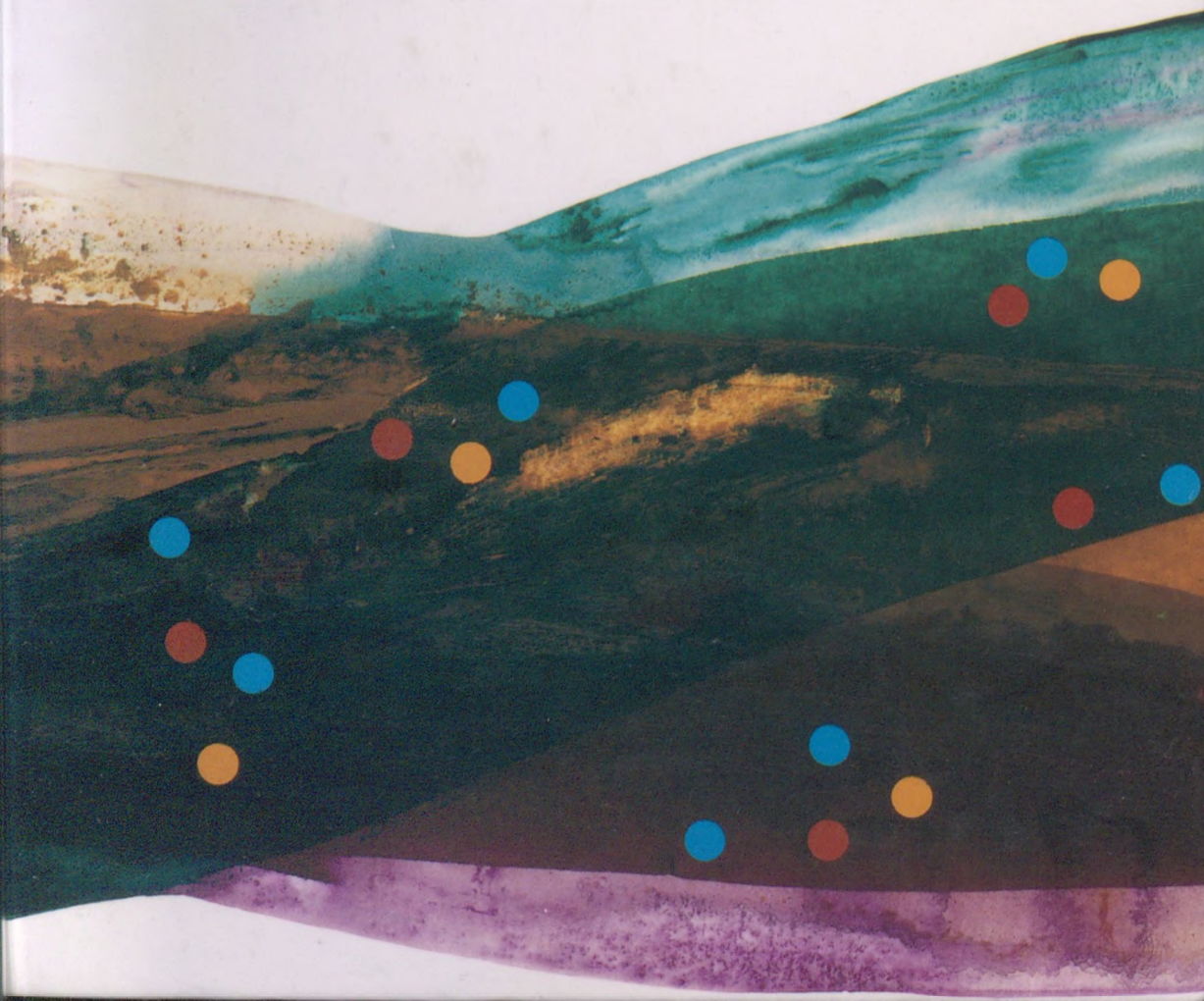


MAGNESIUM IN BIOLOGICAL SYSTEMS

Environmental and Biomedical Aspects

**Edited by T. Fazekas
B. Selmeczi
P. Stefanovits**



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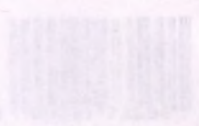
Magnesium in biological systems

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Foreword

The history of magnesium can be broken down into several successive chapters. The early historical period from the 18th century to the first quarter of the 20th century mainly involved the development of chemical and pharmacological knowledge. The next stage began in 1926, when the essential character of magnesium was acknowledged. The early part of the modern period, up to the 1960s, established the basis of our present knowledge at physiological, epidemiological and clinical levels.

The modern period began in 1971 with the *First International Symposium on Magnesium* held in Vittel, France; 350 participants from 52 countries contributed to the publication of 2 weighty volumes of Proceedings, corresponding to a compilation of more than 25,000 references, which still offer a wide range of valuable data.

In this multinational context, Hungarian magnesium research occupied an exceptional position. With 2 general reviews and 6 original communications, Hungary came ahead of 29 other countries, just behind France, the USA, Canada and Germany. If the ratio between the number of researchers and the national population was taken into account, Hungarian magnesium research deserved to be ranked first! Its originality and variety were established at that time, and this was later confirmed.

At the closing ceremony of the First International Symposium on Magnesium, three wishes were expressed: to create an international association establishing permanent links between international magnesium researchers, to organize international and national meetings and to ensure the publication of highly specialized papers. The *International Society for the Development of Magnesium Research* (SDRM) was thus born. *Magnesium Research* is its official organ. SDRM has since organized regular international and national meetings. Hungarian magnesium research, promoted by János Rigó, a member of the Editorial Board of the *Magnesium Research*, has regularly provided noteworthy participation in these various meetings, with the appreciated help of the magnesium team of the *Magyar Általános Orvosok Tudományos Egyesülete* (MAOTE) under the leadership of Vilma Kuti. Five Hungarian Magnesium Symposia were subsequently organized, one in Győr in 1975 by Vilma Kuti, one in Szombathely by Frigyes Morvay, one in Kazincbarcika in 1989 and two in Balatonszéplak in 1992 and 1994, all by Sándor A. Kiss. As President of SDRM, I had the privilege to participate in all these symposia and may testify to their quality. It is impossible to highlight all the aspects of this many-sided research, but it must be stressed that it has applied to such different fields as agronomy, phytophysiology and plant biochemistry, where Hungarian research was seminal under the guidance of

Sándor A. Kiss. His book *Magnesium fertilization, magnesium in biology* (1983) and his papers – particularly those published in *Magnesium Research* – epitomize the achievements of Hungarian magnesium research in this field. I also wish to express my deep appreciation of the contribution of Hungarian magnesium researchers who demonstrated the importance of a sufficient magnesium intake during pregnancy. Among these researchers, I will mention only a departed friend: Zoltán Melles.

Akadémiai Kiadó, the Publishing House of the Hungarian Academy of Sciences now decided to publish an English version of this volume. I am sure that this book, which exemplifies the dynamism of Hungarian magnesium research, will achieve all the success it deserves.

JEAN DURLACH

President, SDRM

Editor-in-Chief, *Magnesium Research*

1. Primary magnesium sources

The sources of magnesium for living organisms are rocks, soils, air and water. These are primary sources, though they may sometimes also be secondary since there is a cycle between them.

Soils are formed through the weathering of rocks, during which significant changes occur in the amount and form of magnesium present. Similarly, the magnesium in water is released from rocks and soil. However, magnesium may be transferred back to the soil from groundwater. On the other hand, in the course of the great geological cycles, magnesium-containing rocks may accumulate in sea deposits or in shallow lakes through evaporation. An analogous transfer occurs between air and water or between rock and air.

The non-living components of Nature provide the sources of magnesium for living organisms. They are therefore called primary sources, even if these sources may be secondary or tertiary in consequence of the material cycling of minerals.

1.1. Magnesium-containing minerals and rocks

Numerous magnesium-containing minerals are known; they are grouped into two main classes: silicates and other magnesium salts (sulphates, chlorides and carbonates). Within the silicates, further subdivision is necessary: primary silicates and clay minerals.

In the crystal structure of primary silicates, magnesium neutralizes the excess negative charges of SiO_4^{4-} tetrahedra in different geometric arrangements. On the basis of the differences in geometry of the linkages of the silicon-oxygen units in the SiO_4^{4-} tetrahedra, the following types of silicates are distinguished: nesosilicates, cyclosilicates, phyllosilicates, sorosilicates, and tectosilicates. Further silicate variations are provided by the aluminosilicates, in which the silica tetrahedra are bound to aluminium octahedra, in which iron or magnesium may substitute the aluminium as central ions of the crystals. Magnesium-containing minerals include mica, chlorites, amphiboles, augites, pyroxenes, granates, talc, and serpentines. In the crystals of secondary silicates, which are generally sorosilicates, magnesium often substitutes aluminium or in other cases is present as brucite (MgOH_2) sheets between silica tetrahedra sheets.

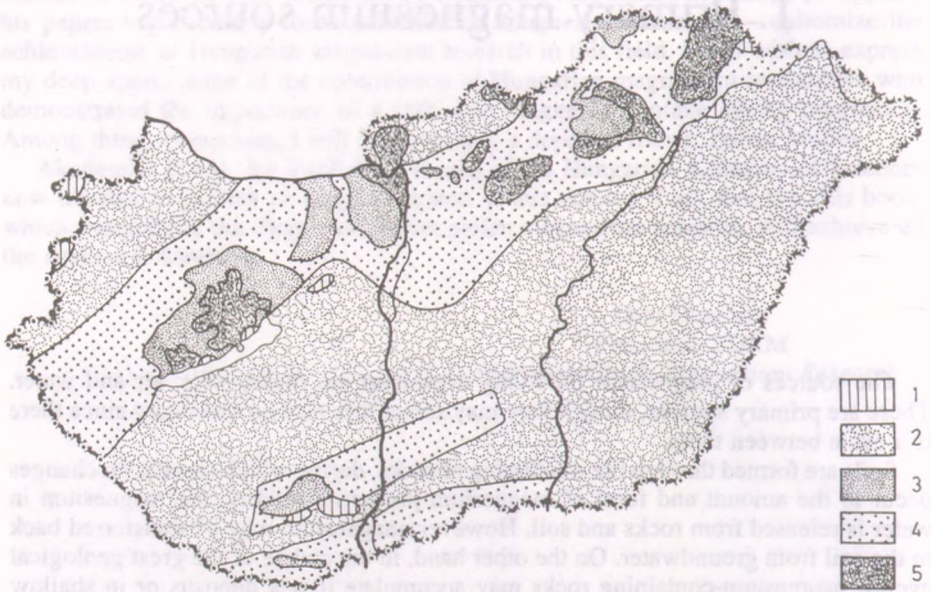


Fig. 1.1. Sketch of geological structure of Hungary (Korim, 1979)

1. Precambrian-Palaeozoic surface rocks; 2. Precambrian-Palaeozoic ranges covered with basin sediments; 3. Mesozoic surface ranges (mainly limestone and dolomite); 4. Mesozoic ranges covered with basin sediments; 5. Neogene volcanic rocks

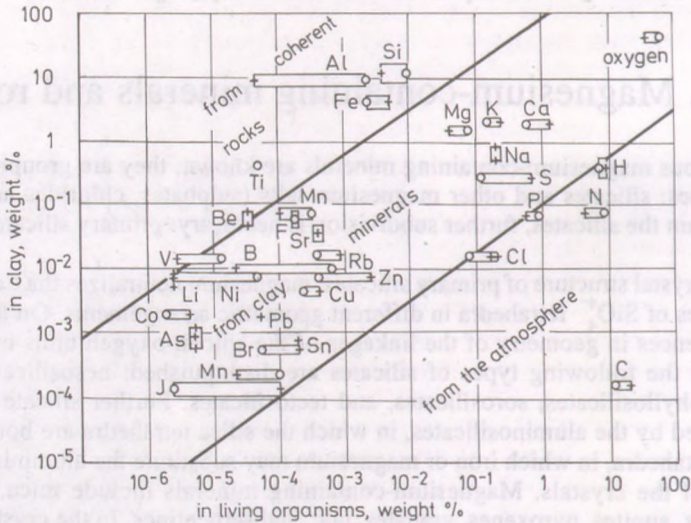


Fig. 1.2. The amounts of different elements in living beings and dead materials (Szádeczky-Kardoss, 1975)

o = plants; + = human organisms

These minerals, and also smectites, vermiculite and soil chlorites, belong in the group of clay minerals because their size does not exceed 0.002 mm.

The group of magnesium salts includes kieserite ($\text{MgSO}_4 \cdot \text{H}_2\text{O}$), magnesium chlorides (bischofite, $\text{MgCl}_2 \cdot 6\text{H}_2\text{O}$, and carnallite, $\text{KMgCl}_3 \cdot 6\text{H}_2\text{O}$), magnesium carbonate (magnesite, MgCO_3) and dolomite [$\text{CaMg}(\text{CO}_3)_2$].

Magnesium-containing rocks are distinguished on the basis of their origin as eruptive (volcanic) or calcareous rocks. The magnesium content of eruptive (volcanic) rocks and of biotite-granite is variable, but never exceeds 2–6% expressed as MgO . Dolomite, which occurs widely in calcareous rocks in Hungary, contains 20% magnesium, expressed as MgO (Fig. 1.1).

Loess and loess-like deposits, which cover most of the surface of the country, contain 1–2% MgO , while sands contain less.

In clays, which are considered to be sedimentary minerals, the different elements occur in much the same ratios as in living organisms (Fig. 1.2; Szádeczky-Kardoss, 1975).

The release of magnesium through weathering

Magnesium bound in silicates can be released only if the structure of the minerals is broken down. Generally, silicates containing divalent iron decompose more rapidly. If the iron is oxidized to iron(III), this opens the way for the release of magnesium. The released magnesium may be incorporated into new minerals or be leached from the site of weathering.

The release of magnesium from calcareous rocks depends on the pH conditions, and the carbon dioxide content and concentration of the solution. The rate of decomposition of dolomite generally depends on the calcium content of the rock. The more the calcium, the more rapid the decomposition. If weathering occurs on the surface and if there is a vegetation cover, then weathering and soil formation occur together. In this case, the weathered rock provides the parent material for soil formation.

1.2. Magnesium in soils

Magnesium occurs in soils in three forms: in the lattices of primary and secondary minerals, adsorbed on exchange sites, and in the soil solution. These forms are in equilibrium and may undergo interchange, depending on the concentration conditions and time available for transformation.

The most important magnesium-containing minerals in soils

The primary silicates belong in this group. Their amount and characteristics depend on the type of rock from which they originate. They do not play a significant role in the magnesium cycle, since their weathering or decomposition is very slow. Among

the soil minerals, biotite and chlorite are important because they occur widely. While biotite is usually found in alluvial deposits (e.g. Danube deposits) and in granite areas, chlorite occurs more often in metamorphic schist and Alpine sedimentary rocks. These minerals comprise the major magnesium supply in soils.

Other magnesium-containing silicates are the clay minerals, such as vermiculite, smectites, palygorskite and sepiolite. Depending on the conditions (the concentration and ion composition of the soil solution, the pH, reductive or oxidative processes,

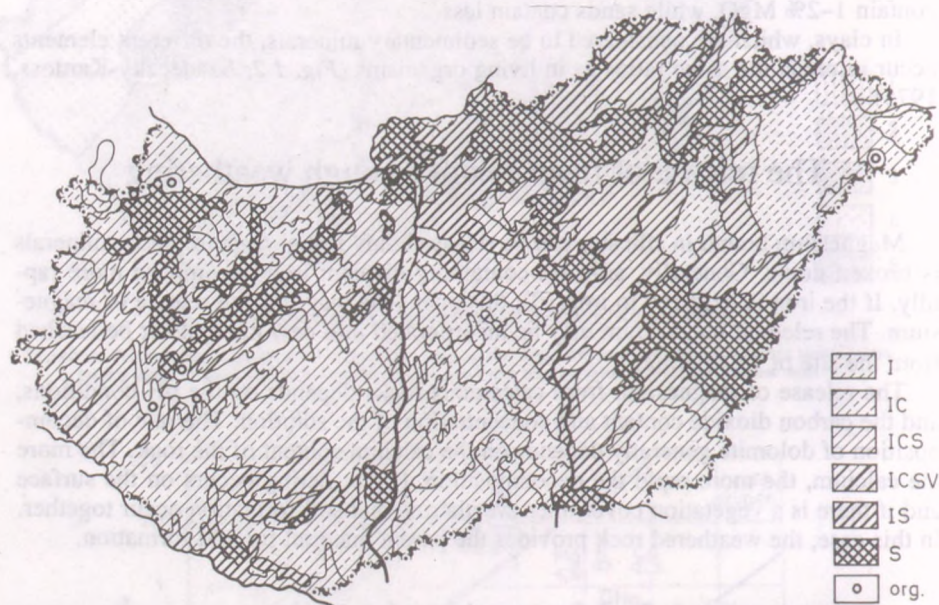


Fig. 1.3. Distribution of soil clay mineral associations in Hungary (Stefanovits and Dombóváriné, 1985)

I = illite, C = chlorite, seldom kaolinite; S = smectite; V = vermiculite; org. = organic soils

leaching or salt accumulation), magnesium may be readily released from magnesium-containing crystals. The weathering of minerals may lead to new clay minerals or complete decomposition, and the components may be leached into the groundwater. The distribution of these minerals is shown in Fig. 1.3 (Stefanovits and Dombóváriné, 1985).

A number of studies have been conducted on the release and absorption of magnesium by clay minerals. Darab and Reményiné (1978) suggested the transformation of montmorillonite to chlorite in soils on the Great Hungarian Plain. However, the presence of magnesium is favourable for the formation of montmorillonite, which is common in meadow and salt-affected soils in Hungary (Christensen and Doll, 1973).

Adsorbed magnesium

Another form of magnesium in soil is the adsorbed form on exchange complexes. Since most soil clay minerals are negatively charged, cations are adsorbed on their surface. The amount and nature of the cations adsorbed are determined by the adsor-

Table 1.1. Exchangeable cations of hydromorphic soils from the Great Hungarian Plain (Darab and Reményiné, 1978)

Soil type and location	Depth cm	Ca ²⁺	Mg ²⁺	Na ⁺	CEC	Ca ²⁺	Mg ²⁺	Na ⁺
		meq/100 g				CEC%		
Aquic Hapludert (Eutric Vertisol) Szarvas	0- 15	20.8	7.2	0.5	29.2	71.2	24.7	1.7
	15- 26	17.2	7.0	0.5	25.3	68.1	27.7	1.9
	26- 41	16.8	7.2	0.4	25.0	67.2	28.8	1.7
	41- 60	18.8	7.2	0.4	27.0	69.6	26.6	1.6
	60- 80	24.6	9.2	0.5	35.5	70.3	26.3	1.5
	80- 97	20.6	10.4	0.4	31.8	64.6	32.6	1.4
Typic Natraqoll (Mollic Solonetz) Szarvas	0- 23	20.3	12.2	0.7	34.0	59.7	35.9	2.3
	23- 60	9.9	13.6	0.2	26.2	37.8	51.9	7.6
	60- 88	7.7	17.6	5.4	31.4	24.5	56.0	17.6
	88-138	12.6	17.2	5.5	36.6	34.4	49.4	15.0
Typic Natrustoll (Mollic Solonetz) Ecsegfalva	0- 15	10.2	8.3	1.2	20.2	50.6	40.9	5.7
	5- 11	10.3	10.0	1.8	22.4	46.1	44.6	7.8
	11- 22	11.1	15.5	3.3	30.1	36.8	51.3	10.9
	22- 32	11.1	17.9	4.5	33.9	32.8	52.9	13.4
	32- 45	10.9	19.4	6.8	37.1	29.0	51.9	18.3
	45- 60	10.8	20.5	9.4	40.2	26.2	49.8	22.9

Table 1.2. Chemical compositions of clay fractions of hydromorphic soils from the Great Hungarian Plain (Darab and Reményiné, 1978)

Soil type and location	Horizon	Depth cm	SiO ₂	Al ₂ O ₃	Fe ₂ O ₃	CaO	MgO	Na ₂ O	K ₂ O
			%						
Aquic Hapludert (Eutric Vertisol) Szarvas	A ₁	0- 25							
	A ₂	40- 60	50.80	22.40	9.30	0.38	1.16	0.12	0.86
	B	80- 90							
	C	110-140	49.50	25.05	9.05	0.77	1.33	0.14	0.34
Typic Natraqoll (Mollic Solonetz) Szarvas	A	0- 25							
	B ₁	35- 55							
	B ₂	60- 90	47.90	27.10	9.30	0.49	1.13	0.09	0.74
	C	110-140	51.70	22.40	9.65	0.56	0.84	0.10	0.52
Typic Natrustoll (Mollic Solonetz) Ecsegfalva	A	0- 5	61.15	17.07	6.25	0.70	2.75	0.70	3.84
	B ₁	23- 32	52.67	20.20	8.74	0.66	3.50	0.33	4.08
	B ₂	61- 71	56.43	20.79	8.74	1.78	3.67	0.35	2.38
	C	87-100	48.22	19.54	7.71	1.15	1.56	1.89	3.10

bent, in this case the type of the clay mineral, and the conditions of the solution, e.g. its concentration, ion composition and pH, the length and extent of wetting and drying, and other physical and chemical conditions.

The effect of the nature of the clay mineral is exerted through selective adsorption. For a given concentration and ion composition of the solution, that ion which fits best into the crystal structure is preferably adsorbed. Magnesium may fit and be incorporated into the clay mineral structure through substitution for the aluminium ion or within brucite sheets in the interlayer space. If the adsorption conditions are the same for different ions, magnesium is adsorbed to a higher extent than other ions.

Hungarian scientists were among the first to draw attention to soils with higher proportions of adsorbed magnesium. The publications of Arany (1929, 1931, 1956) and Kreybig (1935, 1941, 1946) indicated the importance of adsorbed magnesium, and the later data of Máté (1955), Darab and Reményiné (1978), Morozova (1979)

Table 1.3. Exchangeable Mg^{2+} and related characteristics of forest soils developed on different parent materials (Stefanovits, 1971)

Soil type and location	Depth cm	Horizon	Clay %	Humus %	*Exch. Mg^{2+} S%	S meq/120g	V%
Typic Haplustalf (Haplic Luvisol) developed on loess Karád	0- 5	A ₁	12	3.2	26.3	10.5	44
	5- 22	A ₂	15	1.5	89.0	9.4	47
	21- 35	AB	21	1.2	34.5	11.8	57
	35- 70	B ₁	29	1.0	31.2	17.1	57
	70-100	B ₂	23	0.9	25.5	17.4	63
	100-150	C ²	15	0.8	19.7	19.0	100
Typic Haplustalf (Haplic Luvisol) developed on loess Hűvösvölgy	0- 5	A ₁	24	5.3	20.2	11.6	56
	5- 20	A ₂	14	1.0	36.9	4.2	31
	20- 60	B ₁	26	0.8	36.2	13.4	61
	60- 85	B ₂	26	0.4	28.8	16.0	66
	85-100	C	18	0.4	19.6	19.1	100
Typic Haplustalf (Haplic Luvisol) developed on andesite tuff Mátraháza	0- 12	A ₁	17	6.8	14.4	22.6	46
	12- 25	A ₂	22	1.8	14.6	12.1	42
	25- 50	B ₁	32	1.1	14.6	16.9	57
	50- 80	B ₂	35	0.7	19.6	25.9	77
	80-115	B ₃	34	0.7	21.5	24.1	66
	115-140	BC	35	0.7	21.3	26.7	72
Typic Albaqualt (Dystric Gleysol) developed on Quaternary loam deposit Szakonyfalu	0- 3	A ₁	-	29.0	22.5	11.2	13
	3- 20	A ₂	11	2.8	37.3	1.1	6
	20- 40	AB	22	0.9	50.7	2.7	15
	40- 60	B ₁	26	0.8	50.6	4.9	19
	60- 80	B ₂	30	0.6	39.6	7.8	24
	80-120	C	38	0.6	29.9	25.1	59
Typic Albaqualt (Dystric Gleysol) developed on Quaternary clay deposit Apátistvánfalva	0- 20	A _p	11	2.6	25.6	8.5	35
	20- 35	AB	26	0.5	29.7	9.1	39
	35- 50	B ₁	30	0.3	37.6	13.1	38
	50- 70	B ₂	42	0.3	40.1	17.8	43

* Mg^{2+} S% = % of Mg^{2+} within exchangeable basic cations.

Table 1.4. Exchangeable Mg^{2+} and related characteristics of four soils of the same catena developed on loess (Stefanovits, 1971)

Soil type and location	Depth cm	Horizon	Clay %	Humus %	*Exch. Mg^{2+} S%	S meq/120g	V%
Calcic Haplustoll (Calcic Chernozem) Dombovár	0–20	A _p	24	2.2	9.1	22.5	80
	20–50	A ₁	25	1.7	11.5	26.1	100
	50–80	B	23	1.1	11.4	18.4	100
	80–115	BC	19	0.7	13.3	15.4	100
	115–160	C	15	0.6	16.9	12.1	100
Typic Haplustoll (Haplic Phaeozem) Szabadi	0–16	A _p	18	2.4	12.9	18.1	84
	16–30	A ₁	23	1.3	12.9	19.3	82
	30–60	AB	25	0.9	11.3	20.7	85
	60–80	B ₁	22	0.6	10.1	23.2	100
	80–100	BC	18	0.4	13.0	17.1	100
	100–150	C	15	–	13.8	11.5	100
Typic Haplumbrept (Chromic Cambisol) Nagyberki	0–25	A _p	22	1.9	8.9	13.8	76
	25–45	B ₁	25	1.1	17.6	18.7	90
	45–65	B ₂	27	0.7	17.6	19.7	79
	95–110	C	12	0.4	12.9	12.8	100
Typic Haplustalf (Haplic Luvisol) Baté	0–25	A _p	17	1.5	11.5	10.7	73
	25–50	B ₁	31	0.9	19.3	15.5	62
	50–80	B ₂	27	0.6	21.5	18.5	86
	80–120	C	14	0.4	12.0	13.6	100

* Mg^{2+} S%=% of Mg^{2+} within exchangeable basic cations.

and Stefanovits (1956, 1963, 1971) supported this. According to Kreybig, "magnesium soils" are soils in which the adsorbed magnesium accounts for at least 30% of the four basic adsorbed cations (Ca, Mg, K and Na). In other words, magnesium supplies at least 30% of the basic saturation. Many of the meadow and salt-affected soils of the Great Hungarian Plain with high chlorite and smectite contents are "magnesium soils", as reported by Darab and Reményiné (1978) and shown in Table 1.1. Data from the same authors on the chemical analysis of the clay fractions of the soils given in Table 1.2 show that the clay fractions (which occupy half of the volume of the soils) contain 1–3% magnesium (expressed as MgO). If these data are compared with the values of exchangeable magnesium, which are 7–20 meq/100 g, the exchangeable magnesium is seen to account for only 10% of the total magnesium content. However, the exchangeable magnesium is important for living organisms, since this is the primary source of magnesium available for plants.

Not only meadow and salt-affected soils, but also the acidified forest soils may contain high amounts of exchangeable magnesium. The data of Stefanovits (1971) in Tables 1.3 and 1.4 indicate that the proportion of exchangeable magnesium increases with the increase of leaching and acidification. This proportion may exceed 30%. This is because magnesium can be incorporated into the crystal structure of clay minerals, whereas calcium cannot, and the loss of calcium through leaching is higher than that of magnesium.

Magnesium salts in soils

Magnesium salts in soils occur in the forms of sulphates or carbonates. While sulphates generally occur in hydromorphic soils, carbonates occur together with CaCO_3 . The data of Darab and Reményiné (1978) in *Table 1.5* indicate that the accumulation of magnesium sulphate may be rather high. Among carbonates, dolomite is the most frequent mineral which may occur beside CaCO_3 . The X-ray investigations of Stefanovits, Dombóváriné and Kónya (1989) revealed that in large areas of Hungary the soils contain dolomite (*Fig. 1.4*). The presence of dolomite and calcite in the carbonate accumulation horizons of chernozem soils (Calciustolls) is shown in *Fig. 1.5*.

In most of the literature dolomite has been regarded as a marine sediment (Szendrei, 1972, 1977). The geological studies of Miháltz (1967), Molnár (1979) and Molnár and Kuti (1985) suggested that dolomite might precipitate from the calcareous lacustrine deposits of the salt-lakes of the Great Hungarian Plain if the composition of the groundwater and climatic conditions favour this.

During the work of compiling the clay mineral association map of the country, X-ray studies demonstrated the recent precipitation of dolomite in the pseudomycellar carbonate accumulation (calcic) horizons of chernozem soils. As a consequence of the regular wetting and drying, there is a two-way flow of material in these soils.

Table 1.5. Data on water extracts of hydromorphic soils from the Great Hungarian Plain (Darab and Reményiné, 1978)

Soil type and location	Horizon	Depth cm	pH	CO_3^{2-}	HCO_3^-	Cl^-	SO_4^{2-}	Ca^{2+}	Mg^{2+}	Na^+	K^+
					meq/100g soil						
Aquic Hapludert (Eutric Vertisol) Szarvas	A	0– 20	7.0	–	0.50	0.25	0.80	0.30	0.30	1.11	1.15
	B ₁	40– 60	7.6	–	0.50	0.10	1.30	0.20	0.20	2.19	0.13
	B ₂	60– 80	8.6	0.42	0.75	0.12	1.94	0.15	0.15	3.45	0.01
	C	120– 140	8.4	0.42	0.75	0.12	2.29	0.10	0.25	3.66	0.01
Typic Natraqoll (Mollic Solonetz) Szarvas	A ₁	0– 15	7.6	–	0.06	0.05	0.22	0.19	0.09	0.22	0.02
		15– 26	7.5	–	0.32	0.05	0.30	0.15	0.08	0.22	0.01
	A ₂	26– 41	7.7	–	0.40	0.07	0.34	0.06	0.07	0.23	0.01
		41– 60	7.7	–	0.40	0.05	0.46	0.10	0.12	0.38	0.01
	B	60– 80	7.7	–	0.70	0.05	0.24	0.53	0.22	0.07	0.02
		80– 97	7.1	–	0.67	0.05	0.44	0.48	0.22	0.06	0.01
	C ₁	105– 120	7.7	–	0.65	0.05	0.30	0.45	0.23	0.13	0.02
	C ₂	130– 140	7.7	–	0.64	0.02	0.34	0.39	0.22	0.14	0.01
Typic Natrustoll (Mollic Solonetz) Ecsegfalva	A	0– 5	6.6	–	0.299	0.149	0.187	0.109	0.485	0.478	0.020
		5– 11	7.3	–	0.750	0.099	0.166	0.079	0.370	0.578	0.010
	B ₁	11– 22	7.4	–	0.650	0.099	0.104	0.039	0.263	0.660	0.010
		22– 32	7.5	0.039	0.960	0.149	0.124	0.039	0.263	1.000	0.010
	B ₂	32– 45	7.6	0.039	1.209	0.699	0.707	0.079	0.271	2.217	0.020
		45– 60	7.4	–	0.598	1.449	3.449	0.189	0.559	4.600	0.030
	BC	71– 86	6.8	–	0.349	2.349	27.668	7.799	12.845	8.757	0.069
	C	86– 100	7.3	–	0.550	2.498	8.900	1.237	2.779	7.557	0.090
		120– 130	7.3	0.039	0.659	2.301	2.301	0.379	1.324	6.400	0.030

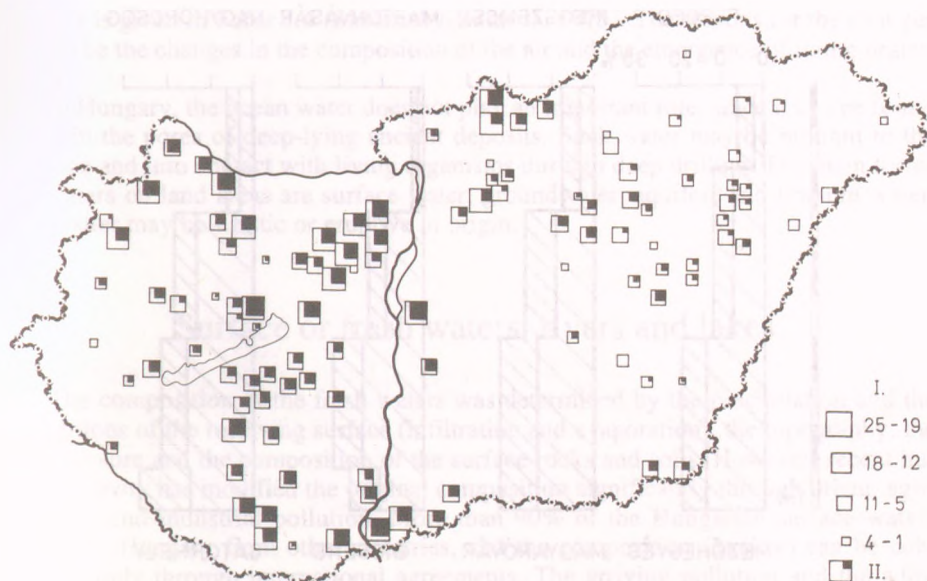


Fig. 1.4. Percentage of calcite plus dolomite in the calcareous horizons within 1 m depth of the soil profiles, and ratio of dolomite in the total

I = %calcite+dolomite; II = ratio of dolomite, on an areal basis

During the summer drying period, microcrystals of calcite and dolomite precipitate from the upward flowing soil solution. The degree of precipitation depends on the concentration and ion composition of the solution. This form of dolomite is readily available for plants.

1.3. Magnesium in water

Water is another important magnesium source for living organisms. There is a special cycle in the water of the oceans. In one part of the cycle, terrestrial rocks and soils release materials: in others materials are precipitated and deposited on the floor

Table 1.6. Proportions of different cations in the ancient and present oceans (Szádeczky-Kardoss, 1975)

Time	References*	Mg	Ca	Na	K
Ancient oceans	Conway	13	23	47	17
Ancient oceans	Ronov	14	29	40	7
Present oceans	Goldberg	11	3	83	3

* In Szádeczky-Kardoss, 1975.

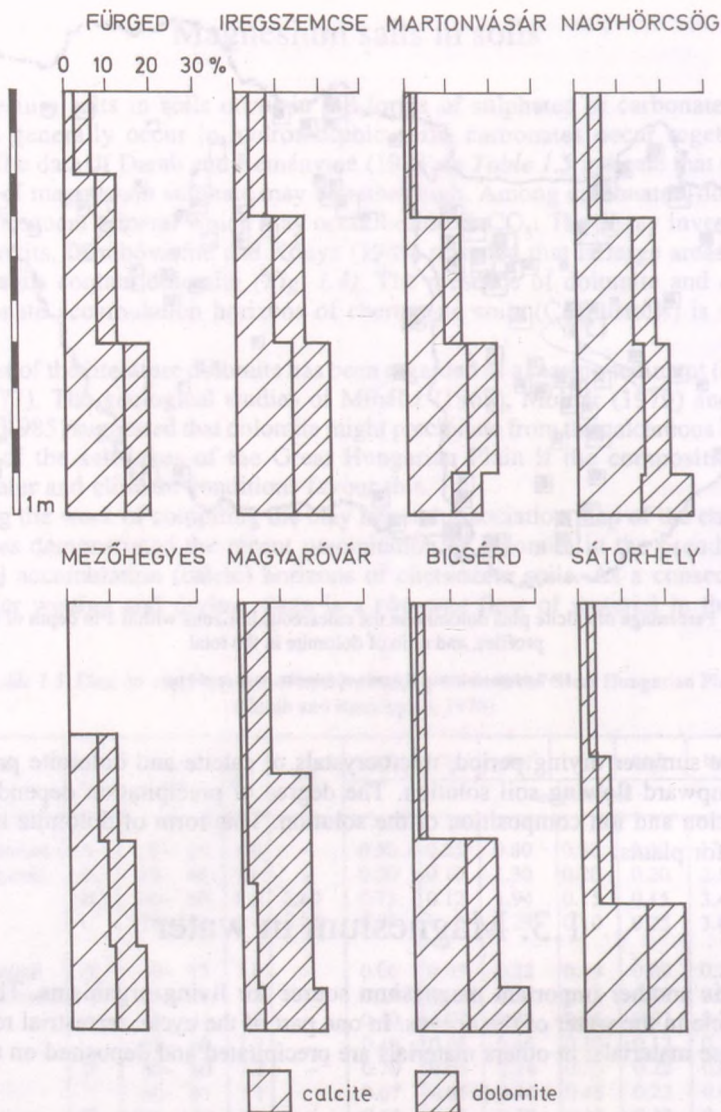


Fig. 1.5. Distribution of calcite and dolomite in profiles of chernozem soils (Calciustolls) (Stefanovits, Dombóváriné and Kónya, 1989)

of the ocean. However, there is not a real equilibrium between the two processes, since there may be a release from ocean deposits and water is accumulating in the form of ice at the Poles, while the water of the oceans is evaporating and they are becoming more concentrated.

During the evolution of the Earth, the composition of the ocean waters has changed significantly. The difference in composition of the waters of the ancient and present

oceans is given in *Table 1.6* (Szádeczky-Kardoss, 1975). The reasons for the changes might be the changes in the composition of the air and the emergence of living organisms.

In Hungary, the ocean water does not play an important role, since it can be found only in the pores of deep-lying ancient deposits. Such water may be brought to the surface and into contact with living organisms through deep drilling. The main forms of waters on land areas are surface water, groundwater, aquifers and fracture water. The latter may be karstic or eruptive in origin.

Surface or fresh waters, rivers and lakes

The composition of the fresh waters was determined by the precipitation and the conditions of the receiving surface (infiltration and evaporation), the topography, the temperature and the composition of the surface rocks and soils. However, recent human activity has modified the original composition significantly through urban, agricultural and industrial pollution. More than 90% of the Hungarian surface waters arrive in Hungary from other countries, and the composition (quality) can be controlled only through international agreements. The arriving pollution and the additional pollution within the country determine the quality and the magnesium content of the surface waters. Since most of the Hungarian drinking water supply is based on surface waters, these are very important magnesium sources for living organisms.

The magnesium content and in general the quality of the water varies from place to place. The average concentration is 15–25 mg/dm³ (the upper limit of magnesium for the best drinking waters is 50 mg/dm³). If the drinking water consumption in Hungary is 2–4 dm³/day/head, this means a daily consumption per person of 30–100 mg of magnesium.

Groundwaters

Groundwaters play a significant role in the cycle of nutrients for living organisms. The drinking water supply was and in many rural areas still is obtained from wells. The drinking water requirements of grazing animals are satisfied from groundwater wells. Groundwater is also an important source for plants, since in at least one-third of the area of Hungary the roots of crops can reach the groundwater and take up essential ions. The quality of the groundwater determines to what degree it can serve as a source of magnesium for all the living organisms.

The groundwater conditions of the country are well known from the map by Rónai (1989). A simplified sketch of the map, showing only the magnesium contents, is given in *Fig. 1.6*. The composition of the groundwater varies as much as that of the soils in the different areas. However, this is natural since there is direct contact and a direct relationship between these two components of the environment. The close relationship between the compositions of the soil and the groundwater is supported by the data in *Table 1.7*, obtained from analyses of soils and groundwaters from the same locations (Darab and Reményiné, 1978).

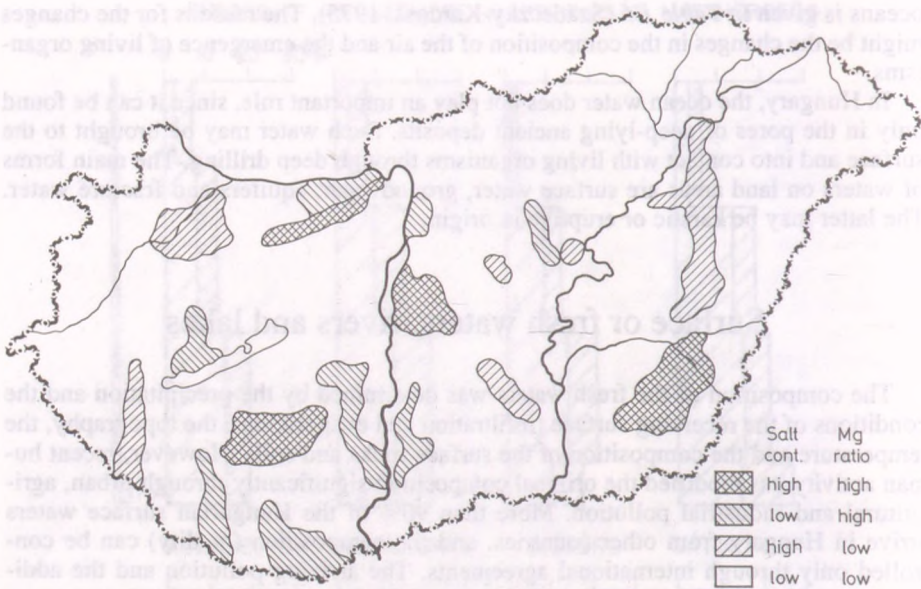


Fig. 1.6. Magnesium contents of groundwaters (adapted from Rónai, 1989)

It can be concluded that groundwater is both a direct and an indirect source of magnesium for living organisms. It is a direct supply through the drinking water, and an indirect supply through the soil, plants and animals.

The composition of tap water is very different from that of natural mineral waters; the differences in concentration may be even two orders of magnitude.

Table 1.7. Chemical compositions of ground waters under hydromorphic soils of the Great Hungarian Plain (meq/dm³) (Darab and Reményiné, 1978)

Soil type	pH	CO ₃ ²⁻	HCO ₃ ⁻	Cl ⁻	SO ₄ ²⁻	ΣAnions	Ca ²⁺	Mg ²⁺	Na ⁺	K ⁺	ΣCations
Aquic Hapludert (Eutric Vertisol) Szarvas	7.8	—	10.5	5.3	24.0	39.9	5.3	17.6	17.03		39.9
Typic Natraqoll (Mollic Solonetz) Szarvas	8.1	0.3	8.7	1.8	6.8	17.6	8.5	4.0	5.5	0.01	17.9
Typic Natrustoll (Mollic Solonetz) Ecsegfalva	—	1.20	79.9	33.6	47.4	90.2	3.5	25.6	59.2	0.13	88.4

Some groundwater are considered to be mineral waters and have become well known. Most of them are "bitter" mineral waters, e.g. the *Hunyadi János* from the Budapest area, the *Ferenc József*, *Apenta*, and *Mira* from Tiszajenő and the *Igmánd* bitter mineral waters from the Nagyigmánd-Kocs area. The mineral waters called "cservicek" from Parádsasvár in the Mátra Hills, and also the mineral waters of Balatonfüred and Kékkút are groundwaters.

The bitter waters always have a high magnesium content.

Aquifers

Aquifers are generally found in Tertiary sand, sandstone and stratified limestone formations of valleys in sedimentary areas. Most of these artesian aquifers are disconnected from new water sources and their ages may be several millions of years. They can be reached only through deep drillings. In most cases, such deep drillings have been related to fuel surveys. However, the direct objective of the deep drilling is sometimes to obtain mineral water. The magnesium contents of aquifers vary from place to place, as may be seen in Fig. 1.7. The most famous aquifer mineral waters of the country are from Hajdúszoboszló, Debrecen, Gyula, Karcag, Cserkeszőlő and Bükkészék.

Fracture and karst waters

The waters from fractures in limestone and dolomites contain a significant amount of magnesium. The mineral waters of Budapest, Hévíz, Harkány, Miskolc, Eger, Mezőkövesd, Visegrád and Zalakaros belong in this group. Figure 1.8 by Korim (1979) shows the important mineral water sources in Hungary. The highest magnesium content was found in the fracture water from Tamási, which contained 164 g/dm³ magnesium.

Mineral waters

Mineral waters as magnesium sources may be classified as calcium magnesium hydrocarbonate or as sulphate mineral waters. Their importance is discussed on the basis of studies by Zajkás (1979). Of the calcium magnesium hydrocarbonate waters, those at Budapest, Harkány, Kékkút, Székesfehérvár and the so-called *mohai Ágnes* and *Parád (Szent István)* are very important.

Of the sulphate mineral waters (with Glauber salts and bitter salts) *Mira*, *Hunyadi János* and *Igmánd* contain a significant amount of Glauber salt besides magnesium sulphate, while magnesium sulphate is the dominant salt in *Apenta* and *Ferenc József*.

Unfortunately, the compositions of karst and fracture waters are not constant because drilling introduces contamination from the layers above.

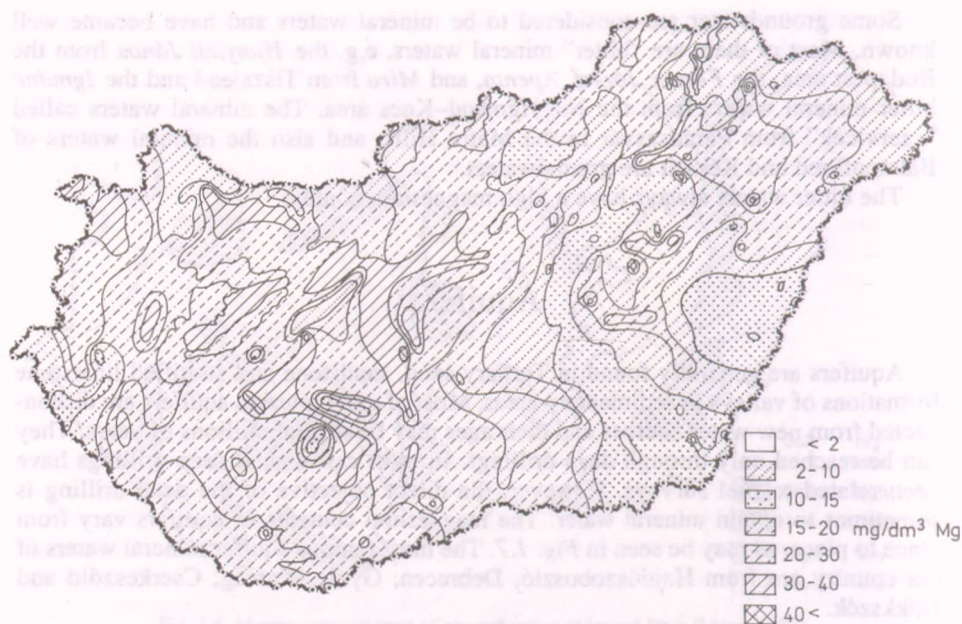


Fig. 1.7. Magnesium contents of aquifers (Tóth, 1982)



Fig. 1.8. Distribution of significant sources of mineral water in Hungary (Korim, 1979)

1.4. Magnesium in dust pollution

The dust in the air may be a source of magnesium. The smoke emitted from coal-fired power-plants and industrial plants, agricultural machines and transportation increases the dry dust content of the air. The quantity and the composition, including the magnesium content of the dust, are determined by the source.

Quantity and composition of atmospheric dusts

Several sets of data are available on different sources of dust pollution in Hungary. *Table 1.8* gives data of Kovács et al. (1989). It should be mentioned that a proportion of the pollution may arrive from other countries. One interesting example is dust from the Sahara Desert, which has coloured the snow surface several times. The highest external magnesium-containing dust pollution arrives with north winds from the magnesite-processing plants in Slovakia.

Table 1.8. Composition of dust pollution in Hungary

	Solid pollutants (dust) kiloton/year				
	1980	1985	1986	1987	1988
Power-plants	220.0	129.0	124.1	97.8	84.5
Other heating systems	3.2	2.2	1.9	1.5	1.3
Industry	239.1	232.9	224.6	217.9	205.5
Agriculture and forestry	6.9	8.5	7.6	8.4	7.1
Transport	19.4	10.8	11.2	11.6	11.6
Urban pollution	75.8	94.3	85.3	84.6	87.0
Service industry	12.2	13.9	8.9	11.8	10.8
Total	576.6	491.6	463.3	433.6	407.8

As concerns the sources, the emission from coal-fired Hungarian power-plants and cement factories are the most important pollutants. Another source of magnesium in dust is metallurgical and rock grinding plants. The data in *Table 1.9* illustrate the above statements and show the differences in dust pollution above different urban areas.

The information available on magnesium present in the environment through atmospheric pollution is limited as compared with the information relating to rocks, soil and water.

Table 1.9. Atmospheric dust pollution in different urban areas in 1988
(Kovács et al., 1989)

Location	Dust deposited g/m ² /30 days	Location	Dust deposited g/m ² /30 days
Tolerable limit 16			
Lábatlan	51	Salgótarján	10
Várpalota	37	Orosháza	10
Dunaújváros	29	Kazincbarcika	9
Vác	26	Győr	9
Sajószentpéter	17	Szeged	9
Ajka	16	Komló	8
Dorog	14	Nyíregyháza	8
Békéscsaba	14	Beremend	8
Tatabánya	13	Pécs	7
Miskolc	13	Sopron	6
Ózd	11	Debrecen	6
Pét	11	Budapest	6
Székesfehérvár	11	Tiszaszederkény	6
Kecskemét	11	Gyöngyös	5
Szolnok	10		

References to Chapter 1

- Arany, S. (1929): Summary of data of soils liming and the magnesium content of the salt affected soils of Hungary. *Mezőgazd. Kut.* **2**, No. 1, 1. (In Hung.)
- Arany, S. (1931): Study of the behavior of magnesium in soils. *Mezőgazd. Kut.* **4**, No. 12, 439. (In Hung.)
- Arany, S. (1956): Contribution to the role of magnesium in the formation of alkali soils. *6th Congr. Int. de la Science du Sol.* Paris, Vol. **B**, 655.
- Christensen, D.R., Doll, E.C. (1973): Release of magnesium from soil clay and silt during cropping. *Soil Science* **116**, 59.
- Darab, K., Reményiné, M. (1978): The characteristics and micro-mineral composition of magnesium containing soils. *Agrokémia és Talajtan*, **27**, 357. (In Hung.)
- Homonnai, A., Hock, B., Csanády, M., Csáki, F. (1989): *Study of the Stage of the Environment of Hungary*. Institute of Environment Management, Budapest, 39. (In Hung.)
- Korim, K. (1979): The geological relations of mineral waters. In: Borszéki, B. (ed.): *Mineral and Thermal Waters*. Mezőgazdasági Kiadó, Budapest, 118. (In Hung.)
- Kovács, E., Szepesi, D., Gács, I., Fekete, J., Várkonyi, T. (1989): The air. In: Bulla, M. (ed.): *Studies on the Stage of the Environment of Hungary*. Institute of Environment Management, Budapest, 77. (In Hung.)
- Kreybig, L. (1935): Vorkommen, Eigenschaften und wirtschaftlicher Wert von Magnesium und Kaliböden in Ungarn. *Trans. III. Int. Congress Soil Sci. Oxford*, Vol. 1, 353.
- Kreybig, L. (1941): The distribution, characteristics and farming value of magnesium and potassium soils of Hungary. *1933-35 Report, Inst. of Geology*, Budapest. (In Hung.)
- Kreybig, L. (1946): *The Distribution of Magnesium and Potassium Soils of Hungary*. Publication of the Inst. of Geology, Budapest. (In Hung.)

- Máté, F. (1955): The accumulation of magnesium on the exchange complex of meadow soils of the Great Hungarian Plain. *Agrokémia és Talajtan*, **4**, 291. (In Hung.)
- Miháltz, I. (1967): The geology of superficial layers of the southern part of the Great Hungarian Plain. *Földtani Közlemények*, **97**, 294. (In Hung.)
- Molnár, B. (1979): The formation of lacustrine dolomite on the Great Hungarian Plain. *Földtani Közlemények*, **110**, 115. (In Hung.)
- Molnár, B. (1985): The Geological and hydrological features of the Madarász-lake at Mórahalom. *Alföldi Tanulmányok*. Békéscsaba, **9**, 17. (In Hung.)
- Morozova, O. (1979): The role of magnesium in the soil forming process and "magnesium soils". *Agrokémia és Talajtan*, **28**, 285. (In Hung.)
- Rónai, A. (1989): The chemical characteristics of ground waters on the basis of 1956–1985 data. In: Pécsi, M. (ed.): *The National Atlas of Hungary*. Kartográfia, Budapest. (In Hung.)
- Stefanovits, P. (1956, 1963): *Soils of Hungary* (First and second editions). Akadémiai Kiadó, Budapest. (In Hung.)
- Stefanovits, P. (1971): *Brown Forest Soils of Hungary*. Akadémiai Kiadó, Budapest, 261.
- Stefanovits, P., Dombóváriné, L. (1985): The Map of Clay Mineral Associations. *Agrokémia és Talajtan*, **34**, 317. (In Hung.)
- Stefanovits, P., Dombóváriné, L., Kónya K. (1989): The relationship between mineral composition and magnesium supply of Hungarian soils. *Növénytermelés* **38**, 417. (In Hung.)
- Szádeczky-Kardoss, E. (1975): *Geonomy*. Publication of MTA Research Lab., Budapest. (In Hung.)
- Szendrei, G. (1972): The role and the ways of determination of calcite and dolomite in soils. *Agrokémia és Talajtan*, **21**, 264. (In Hung.)
- Szendrei, G. (1977): Study of distribution of calcite and dolomite in soils of the Kiskunság area. *Agrokémia és Talajtan*, **26**. (In Hung.)
- Tóth, Gy. (1982): *The Hydrochemical Atlas of Hungary* (Manuscript). The Map Library of the Hungarian National Geology Institute, Budapest. (In Hung.)
- Zajkás, G. (1979): The medical effect of mineral and thermal water drinking treatments. In: Borszéki, B. (ed.): *Mineral and Thermal Waters*. Mezőgazdasági Kiadó, Budapest, 341. (In Hung.)

2. Magnesium forms present in the soil

The total magnesium content of soils varies in the interval 0.1–1.5%, depending on the mineral composition. In soils free from magnesium carbonate usually only 0.05–0.5% magnesium can be found. Jacob (1955) reported that in soils with a high magnesium deficiency, the total magnesium content ranges from 0.01 to 0.2%. The magnesium supply of plants depends primarily on the form in which magnesium is present in the soil. The total magnesium content does not permit a suitable estimate of this supply. In the present chapter, the comprehensive studies by Jacob (1955), Schilling (1957), Loch (1970), and Metson (1974) have been used as sources.

2.1. The significance of different magnesium forms in plant nutrition

The readily soluble and exchangeable soil nutrients are available to plants.

Readily soluble magnesium content includes water-soluble compounds such as magnesium chloride and magnesium sulphate, which abound primarily in saline soils. In carbonated soils, water-soluble magnesium hydrogencarbonate can be found.

Exchangeable magnesium is loosely attached (adsorbed) to the surface of soil colloids, in ionic form. Since the adsorbed ions and the ions in the soil solution are in chemical equilibrium, their quantity exerts a considerable influence on the supply of plants.

The magnesium concentration of the soil solution is influenced by the quantities of both magnesium and other adsorbed cations (Ca^{2+} , K^{+} and Na^{+}). In acid soils, not only metal cations but also H^{+} (H_3O^{+}) ions can be adsorbed on colloids.

In order to characterize the quantitative relations of the adsorbed cations, data concerning Hungarian soil types collected by Stefanovits (1975) are presented in *Table 2.1*, where T is the total adsorption capacity, and S is the quantity of adsorbed metal cations given in meq/100 g. The proportions of the different metal cations are expressed as percentages of the S value (S%). V% is the metal cation saturation of the total adsorption capacity.

The data in *Table 2.1* indicate that the quantity and proportion of the adsorbed cations vary in the different soil types, which means that they depend on the soil

Table 2.1. Average cation compositions and adsorption capacities of some Hungarian soils (Stefanovits, 1975)

Soil types	Ca ²⁺	Mg ²⁺	K ⁺	Na ⁺	S	T	V
	in S%				meq/100g		%
Calcareous chernozem	80	16	3	1	40	40	100
Solonetz-like meadow soil	57	25	3	25	52	52	100
Meadow soil	63	32	2	3	45	56	80
Brown forest soil	80	17	2	1	26	35	75
Acidic brown forest soil	61	36	2	1	14	40	35

formation conditions. The Table lists average values; in soils deficient in magnesium, the proportion of magnesium can be considerably smaller.

The sum quantity of the soluble and exchangeable magnesium available to plants is only a small fraction of the total magnesium content. In the studies by Michael and Schilling (1957), it was found to amount to 4–5%. The majority of the magnesium content is present in the form of minerals (soil reserves).

Studies written in English usually distinguish only exchangeable and non-exchangeable soil magnesium. However, differences between the availability of non-exchangeable reserves can also be found. It therefore seems reasonable to differentiate between non-exchangeable supplies according to their readiness to mobilize, i.e. between readily mobilizable ones and those which are difficult to mobilize.

Of the secondary soil formations, carbonates belong among the *readily mobilizable* reserves, e.g. magnesite (MgCO_3) and dolomite ($\text{CaCO}_3 \cdot \text{MgCO}_3$). In carbonic acid solution, such magnesium-containing carbonates dissolve to give water-soluble magnesium hydrogencarbonate.

Magnesium reserves which can be mobilized relatively easily include magnesium present in the soil in the form of stubble residues, other plant residues or organic manure. Magnesium in organic compounds is released only after decomposition of the organic matter.

The rest of the reserves become available to plants as a result of slow physical and chemical weathering processes, i.e. they are *difficult to mobilize*. Primary and secondary silicates belong to this group. Comprehensive studies on silicates have been published by Fieldes and Swindale (1954) and by Fieldes and Weatherhead (1968). As concerns Hungarian sources, the studies by Nemecz (1973) and Stefanovits (1975, 1985) may be referred to.

The most important primary silicates are those belonging in the ferromagnesian family and the micas. Members of the former include *olivines* (orthosilicates containing iron and magnesium), *pyroxenes* (metasilicates containing iron, magnesium, calcium and aluminium) and *amphiboles* (resembling the pyroxenes in chemical composition, with a layer-type structure). Augite and diopside contain magnesium.

The micas comprise two groups, both characterized by a 2:1 layer-type structure. *Muscovites* are potassium aluminium silicates in which magnesium can substitute aluminium only partially. In *biotites*, the aluminium ions can all be substituted by iron or magnesium.

Clay minerals are secondary silicates. The *chlorites* comprise a large family of aluminium, iron, and magnesium hydrous silicates, with a layered structure of 2:2 type, one of the layers being a *brucite* $[\text{Mg}(\text{OH})_2]$ layer. They weather fairly easily in an acidic environment (Read, 1968). In the 2:1-type *vermiculites*, the brucite layer is replaced by a water layer containing Ca^{2+} and Mg^{2+} ions. Stahlberg (1960) regards the chlorites and the vermiculites as important magnesium sources for Swedish soils.

Serpentine is a secondary hydrous silicate of the 1:1 layer lattice type, which can be a source of the exchangeable magnesium content of soils (Chittenden and Hodgson, 1953). *Talc* is a similar hydrous silicate.

Salmon (1963) reported that the magnesium content of clay minerals of the hydrous mica, illite, vermiculite and montmorillonite types amounts to about 1% of the mineral, which may contribute to an increase in the exchangeable magnesium level. Several authors including Christenson and Doll (1973), have suggested that magnesium can be released through decomposition of the clay mineral structure in strongly acidified clays. Thus, it can be concluded that clay colloids play an important role in the magnesium supply of soils.

2.2. Measurement of magnesium forms in the soil

Readily soluble and exchangeable magnesium contents are usually determined together. When soil is shaken with extractant solution, dissolution and ionic exchange take place, resulting in an equilibrium. In this way, the total exchangeable magnesium is exchanged only partially. In order to determine the total exchangeable magnesium content, the soil is taken in a glass tube and treated repeatedly with additional doses of fresh extractant until the ion exchange is completed.

It is not common to determine the water-soluble and total exchangeable magnesium contents separately. The magnesium content determined in extraction procedures is regarded as available to plants (pflanzenverfügbar).

A number of methods have been devised for examination of the magnesium content of soils. These differ from one another in the concentration of the extractant and in its pH (acid, neutral or alkaline; Table 2.2). Of the listed extractants, only the neutral salt solutions are suitable for determination of the readily soluble or exchangeable fraction.

When acids are used, the magnesium carbonates forming the reserve in calcareous soils are also dissolved. Comparative analyses (Loch, 1969) have demonstrated that the ammonium lactate-acetic acid extractant cannot be used for determination of the magnesium supply in calcareous soils, since both the readily soluble and mobilizable magnesium are dissolved.

The use of acids is proposed for the extraction of the reserves. Schachtschabel (1956) recommended 0.05 mol/dm^3 HCl to extract the difference between the total exchangeable and readily soluble magnesium. For the determination of soil reserves, Sestić (1965) employed 0.5 mol/dm^3 HCl, while Schroeder et al. (1963) used 2.0 mol/dm^3 HCl solution.

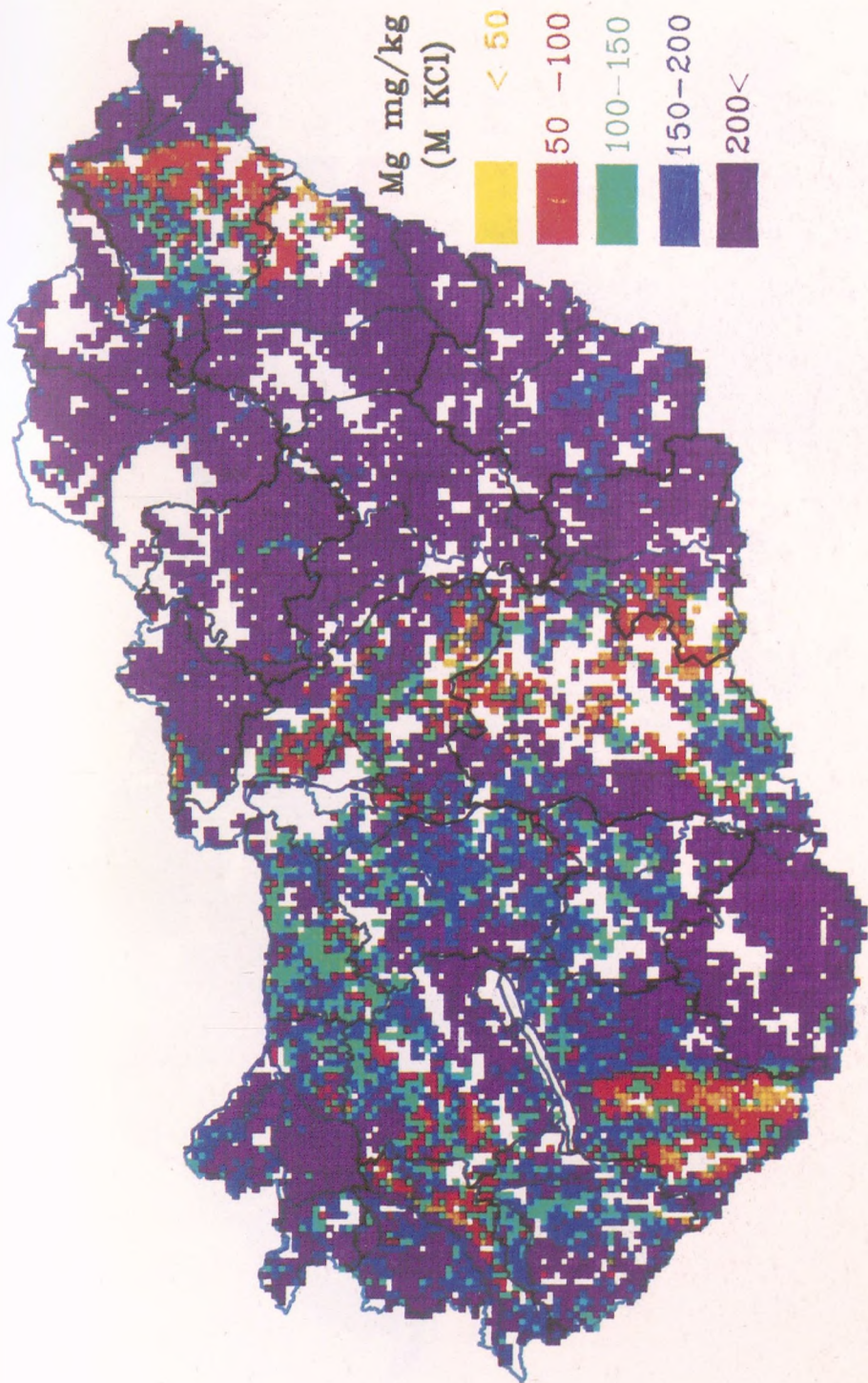


Fig. 2.1. Available magnesium contents of Hungarian soils

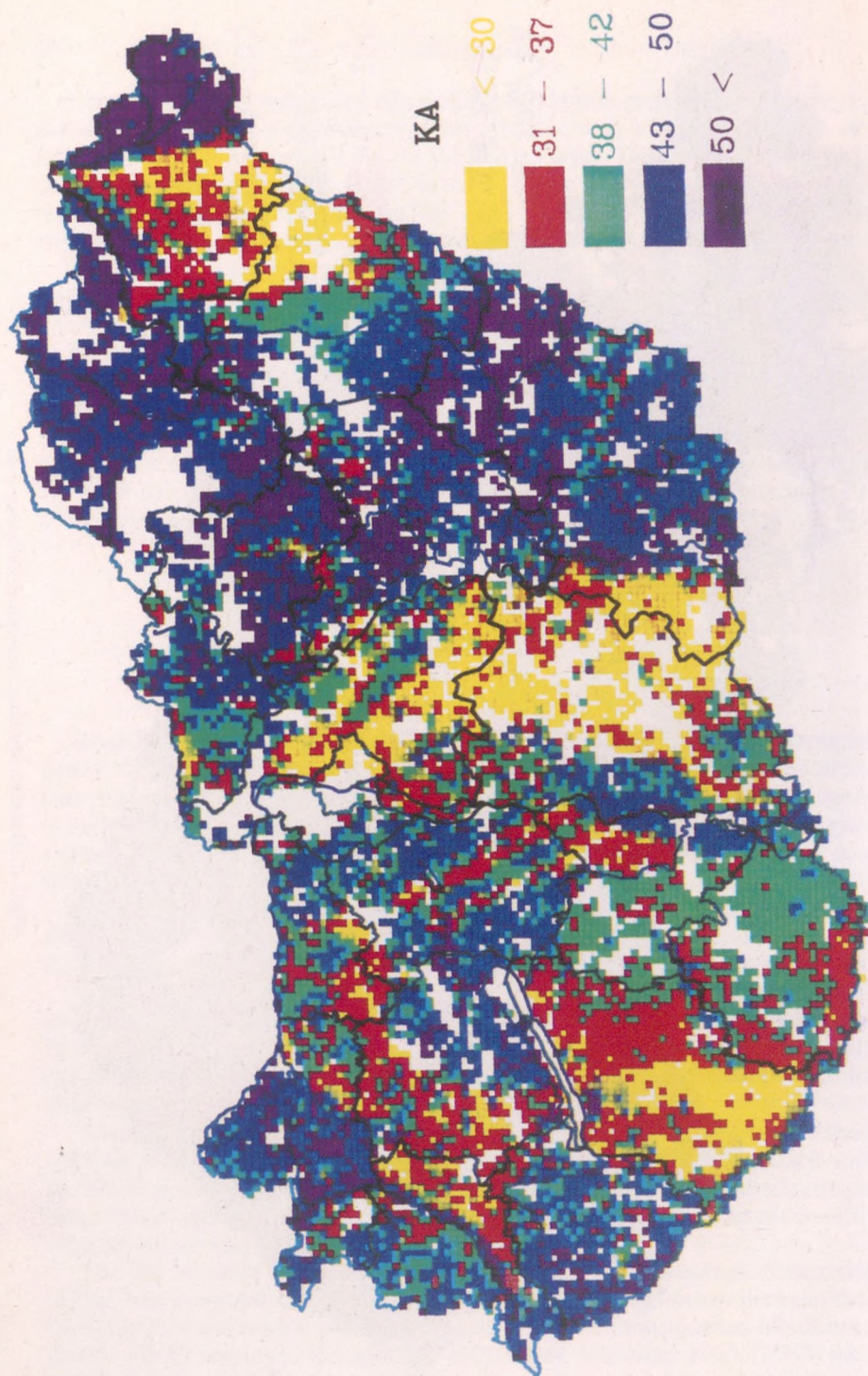


Fig. 2.2. Mechanical compositions of Hungarian soils (KA=Arany number)

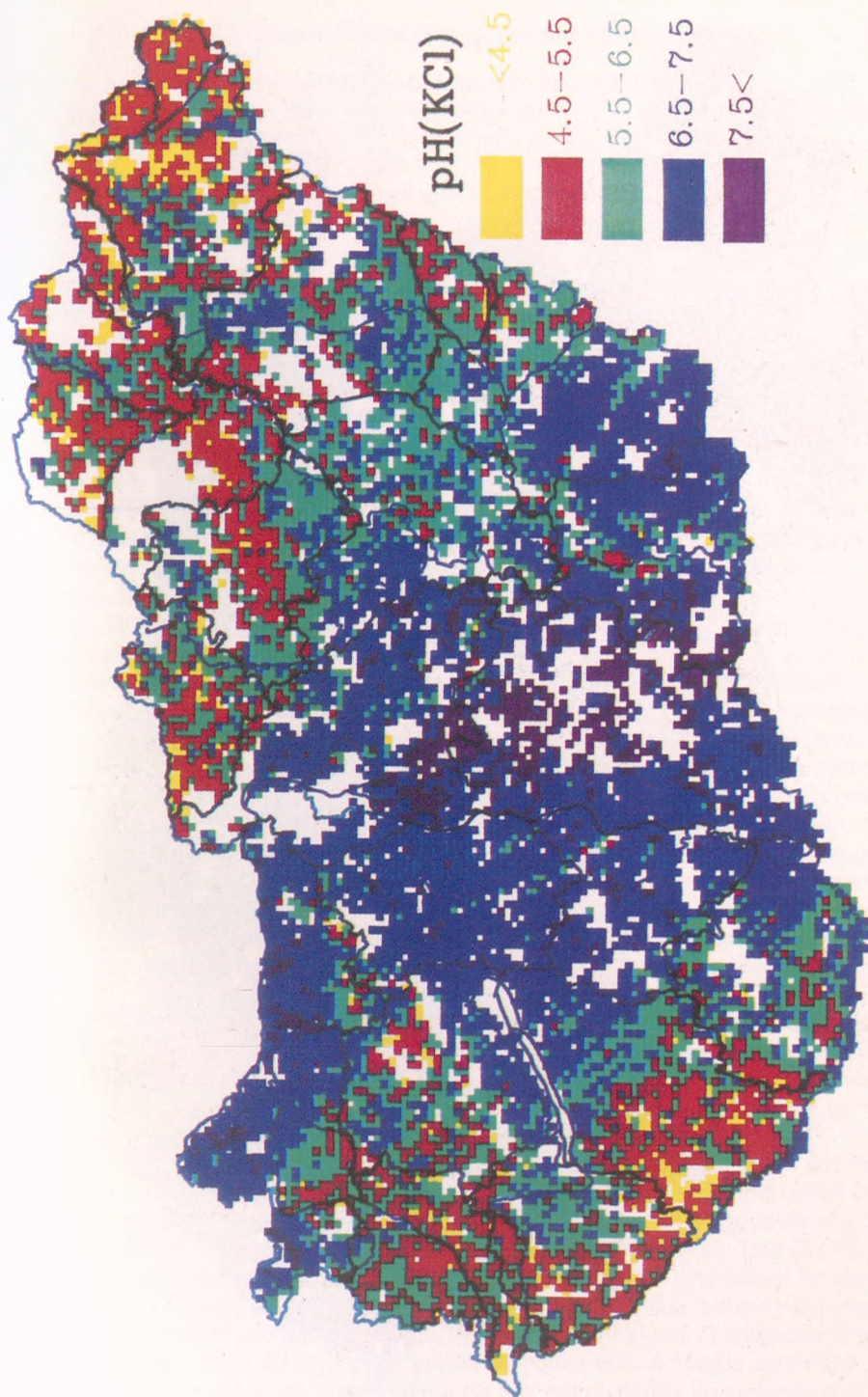


Fig. 2.3. Acidity and alkalinity in Hungarian soils

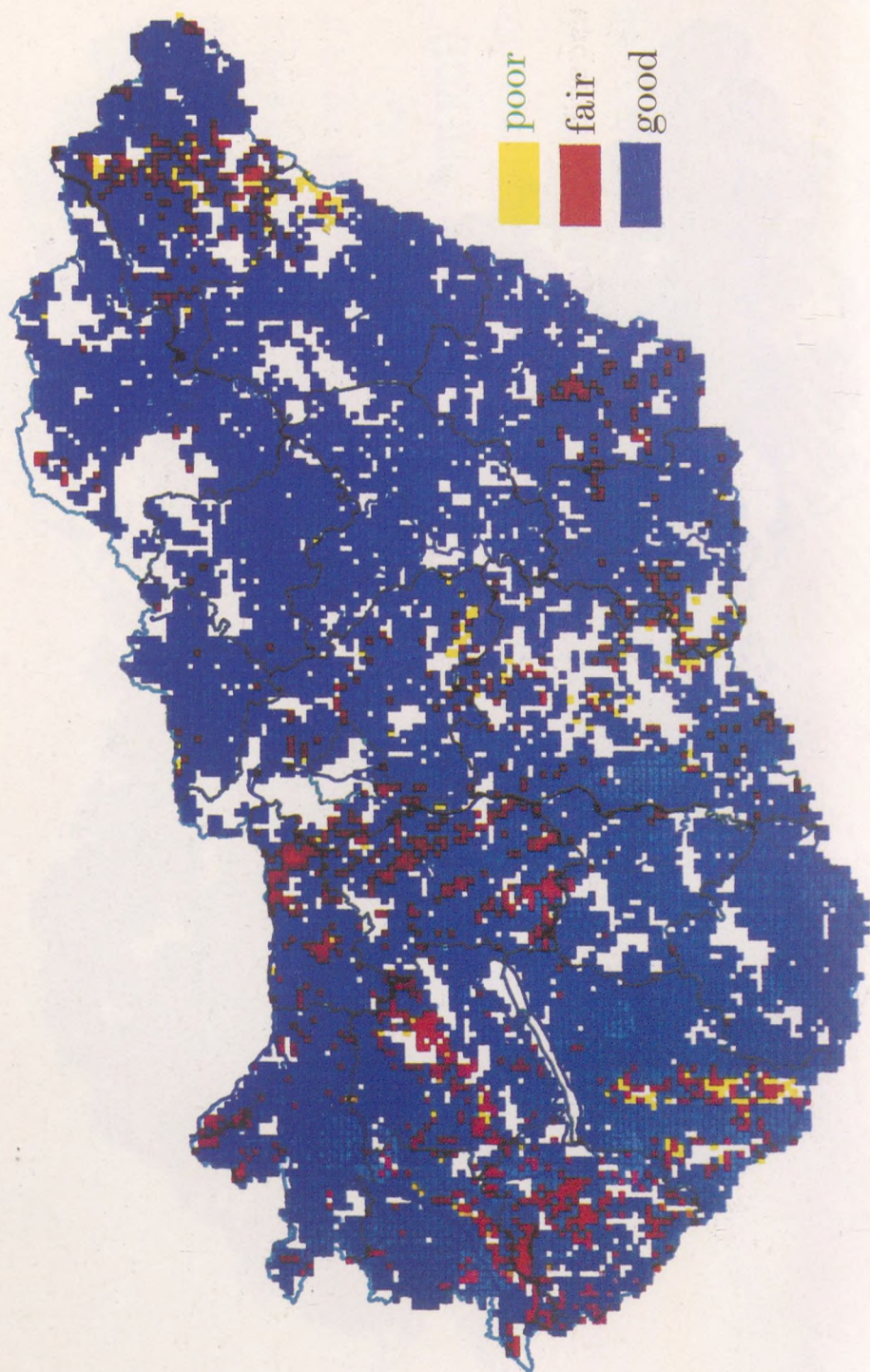


Fig. 2.4. Magnesium supply of Hungarian soils

Table 2.2. Extractants used for measuring the magnesium content of soils

Extractants			Authors
1.0	mol/dm ³ ammonium acetate	(pH = 7)	Schollenberger and Dreibebis (1930)
0.5	mol/dm ³ acetic acid		Castenmiller (1951)
1.0	mol/dm ³ sodium acetate		Peech (1940)
0.75	mol/dm ³ sodium acetate	(pH = 4.8)	Mulder (1950)
0.52	mol/dm ³ acetic acid		Stenuit (1954)
1.0	mol/dm ³ ammonium chloride	(pH = 4.8)	Kidson et al. (1940)
1.0	mol/dm ³ potassium chloride		Haddock (1933)
0.5	mol/dm ³ sodium chloride		Ferrari and Sluijsmans (1955)
1.0	mol/dm ³ sodium chloride		Mazaeva (1967)
0.125	mol/dm ³ calcium chloride		Schachtschabel (1954)
0.125	mol/dm ³ strontium chloride		Michael and Schilling (1957)

Jacob (1955) considered that neither the total magnesium content, nor the magnesium soluble in strong acid solution is suitable for a direct description of the supply in soils. However, attempts at such descriptions were present in further studies, too. Stahlberg (1960) examined the magnesium release from clay minerals in boiling 1 mol/dm³ HCl. Kaila and Rytö (1968) employed 1 mol/dm³ HCl to determine acid-soluble calcium and magnesium in soil fractions with different particle sizes. The magnesium content decreased in the following sequence: clay, silt, sand. Henriksen (1971) used nitric acid to determine the reserves in Danish soils, and establish significant correlations between the magnesium taken up by the plants and the reserves.

An electro-ultrafiltration (EUF) method was developed by Németh (1972) with the aim of determining actual and potential nutrient contents. This EUF method is based on repeated extraction of the nutrients with distilled water, between the poles of a D.C. power source. Ions released into the solution migrate to the opposite poles, and can thus be separated. The voltage can gradually be increased, which speeds up the ion migration, i.e. ion desorption from the soil is increased. In this way, the separation of differently bound fractions becomes possible. In the last phase of extraction, the separation cell can be heated, which also promotes the release of the reserves into the solution.

Németh (1976) developed this method in order to extract phosphorus and potassium, and later extended it to other elements. For the characterization of magnesium and heavy metal contents, he suggested utilization of the quantity precipitated on the electrode, since the bulk of these metals appears as insoluble hydroxides on the cathode.

Methodological studies (Loch, 1985a) have proved that magnesium is not fully precipitated on the cathode: it appears in measurable quantities in the individual fractions. The magnesium contents of the fractions are more suitable for characterizing the supply of soils than the magnesium precipitated on the electrodes. This EUF magnesium value is usually proportional to the magnesium content determined by means of traditional methods. The advantage of the EUF method is that it allows separation of the readily soluble nutrient content and the reserves in the case of magnesium, too.

EUF examinations require special, expensive equipment. A simple method therefore has been developed for determination of the water-soluble magnesium content

of soils. Extraction is carried out similarly as for water-soluble phosphorus (Loch, 1984).

The applicability of the method in comparison with others was tested experimentally. Correlations between the magnesium content of plants and the soil were examined. The correlation coefficients served as a basis for comparison.

It was found (Loch, 1988) that the magnesium taken up by plants displays the strongest correlation with the quantity of water-soluble magnesium (EUF, i.e. simple extraction), but its correlation with the calcium chloride-soluble Schachtschabel magnesium content is also strong and significant. There is a somewhat weaker correlation with the potassium chloride-soluble magnesium. In the case of acid soils, the magnesium measured in the ammonium lactate extraction solution is also suitable for characterizing the supply.

The quantity of magnesium which can be extracted from the soil by means of the different extraction media increases in the following sequence: water, CaCl_2 , KCl and ammonium lactate. The quantity of extracted, i.e. exchanged magnesium depends on the properties and concentration of the extractants, and also on the soil:extractant ratio. Simple water extraction combined with other methods (e.g. the ammonium lactate method) is of value not only for determining the available magnesium, but also for characterizing the reserves.

Gerzabek (1988) carried out comparative soil analyses with various known and new methods. On the basis of the measurement results, he classified the methods in three categories: methods suitable for measuring water-soluble forms, the exchangeable content, and the reserve nutrient content. He confirmed the findings of Christenson and Doll (1973) that the exchangeable magnesium concentration increases with decreasing particle size.

2.3. Regional distribution of the available magnesium content; the magnesium supply of Hungarian soils

Examination of the available magnesium content of soils was introduced on a regular basis in Hungary, in 1978, within the framework of a national unified nutrient examination system. Cation exchange had previously been studied primarily in the course of soil mapping and soil science consultancy work. In his comprehensive work entitled *Magyarország talajai* (Soils of Hungary), Stefanovits (1963) published a great number of examination data to characterize the individual soil types. Loch (1970) studied the different magnesium fractions in soils for purposes of agrochemical research.

The national unified nutrient examination system requires the obligatory examination of the physical and chemical properties of the soils and their macro- and micronutrient contents in all land under cultivation. Two parallel soil samples were earlier taken per 12 hectares every 3 years. At present, the time interval is 5 years. The available magnesium is extracted from the soil with 1 mol/dm^3 potassium chloride solution and is determined by atomic absorption analysis.

Table 2.3. Limiting values of the magnesium supply of soils
(measured in 1 mol/dm³ KCl extraction solution)

K _A *	Mechanical composition	Mg mg/kg		
		poor	fair	good
< 30	sand	< 40	40– 60	> 60
31–42	sandy loam, loam	< 60	60–100	>100
> 43	clayey loam, clay	<100	100–200	>200

* K_A = amount of water (ml) which can be taken up by 100 g soil until the plasticity level is attained (Arany number).

Limiting supply values (Table 2.3) were determined by means of comparative examinations involving a great number of samples, relying on the limiting calcium chloride values of Schachtschabel, the mechanical composition of the soils also being taken into consideration (*Guidelines for Fertilization...*, 1979).

Baranyai et al. (1987) characterized the magnesium supply of soils in each county in Hungary on the basis of nationwide examinations (Table 2.4). The magnesium supply in Hungary can in general be regarded as favourable, since almost 90% of the soils possess an adequate supply. However, special attention should be paid to the fact that there are many regions deficient in magnesium in certain counties, e.g. Szabolcs–Szatmár–Bereg and Somogy.

Table 2.4. Magnesium supply of soils in the counties of Hungary (Baranyai et al., 1987)

County	Magnesium supply expressed as percentage of total area		
	poor	fair	good
Baranya	0.1	0.2	99.7
Bács-Kiskun	8.0	11.5	80.5
Békés	0	0	100.0
Borsod-Abaúj-Zemplén	0.7	0.1	99.2
Csongrád	9.0	5.1	85.9
Fejér	1.0	0.2	98.8
Győr-Sopron	3.0	0.8	96.2
Hajdú-Bihar	4.4	1.8	93.8
Heves	0.4	0.8	99.3
Komárom	9.7	1.5	88.8
Nógrád	2.4	1.1	96.5
Pest	7.1	6.3	86.6
Somogy	13.2	6.7	80.1
Szabolcs-Szatmár	22.8	13.5	64.7
Szolnok	1.1	1.7	97.2
Tolna	4.9	0.6	94.5
Vas	10.1	2.9	87.0
Veszprém	12.2	2.8	85.0
Zala	10.6	1.6	87.8
Total	7.1	4.2	88.7

The magnesium deficiency is highest in the Nyírség region, where more than 50% of the areas are deficient in magnesium. The conditions are similar in the central parts of Somogy. Besides these, considerable magnesium-deficient areas can also be found in certain parts of the region between the River Danube and the River Tisza, and also in the counties of Pest, Bács-Kiskun and Csongrád.

The low magnesium content of a soil is usually related to the physical and chemical properties of the given soil, and also to the soil-forming processes (Loch, 1970). The majority of soils deficient in magnesium are acid soils containing little organic and inorganic colloid, with a low adsorption capacity. These soils usually belong in the categories of blownsand and weakly humous sands. Other soils with a low magnesium content include the strongly leached types of brown forest soils, such as the brown forest soils with alternating thin layers of clay substance ("kovárvány") that occur widely in the Nyírség region. Chernozem soils, meadow soils and bog soils are rich in magnesium (Loch, 1985b).

The magnesium contents and supplies of soils are presented here by means of the soil maps based on the data compiled by the NTSZ (Növény- és Talajvédelmi Szolgálat /Database of Plant and Soil Protection Service/) and processed by an NTSZ computer and a connected plotter.

The maps were drawn on a scale of 1:2,000,000. 1 pixel is equal to 1 mm² which is $2 \times 2 = 4$ km² in reality, i.e. 400 hectares. The database includes soil examination data on about 4 million hectares at present; 625,000 samples have been analyzed. The sizes of the fields are taken into consideration and the computer calculates the weighted means from the primary data; these appear on the maps in different colours. The white spots denote settlements, forests, national parks, or other areas from which no data are obtained.

The first map (Fig. 2.1) presents the available magnesium contents of the soils in mg/kg. The colouring makes it clear that considerable areas with a low magnesium content occur primarily in the county of Szabolcs-Szatmár-Bereg (north-eastern Hungary), between the River Danube and the River Tisza, and in Belső-Somogy (Southern Transdanubia), while scattered areas poor in magnesium are characteristic of the Kemeneshát ridges (north-western Transdanubia) and in the basin of the River Marcal (Southern Transdanubia). Thus, soil with a low magnesium content can be found in the Nyírség region (north-eastern Hungary) and on the sand ridges between the River Danube and the River Tisza on the Great Hungarian Plain, and on the sand ridges of Somogy in the southern Transdanubian region. The same was found by Elek and Patócs (1984) and Stefanovits et al. (1989).

The second map (Fig. 2.2) shows the mechanical compositions of soils (expressed by Arany number), while the third map (Fig. 2.3) presents the pH conditions of the soils. A comparison of the three maps reveals that soils with a low magnesium content are characteristic primarily of acid sandy regions, except for the carbonated sandy soils of the sand ridges between the River Danube and the River Tisza, which are also poor in magnesium.

The fourth map (Fig. 2.4) demonstrates the magnesium supply of soils on the basis of the limiting values given in Table 2.3. In order to determine the supply, the computer calculated the average magnesium content and the average Arany number characterizing the mechanical compositions of soils. The supplies shown on the map represent these mean values. Averaging the two parameters decreases the differences between the fields to a certain extent, on the given scale.

This map clearly illustrates that about 90% of the Hungarian soils have an adequate magnesium supply. Soils with a low magnesium supply on the map are the areas previously mentioned as soils with little available magnesium content, including the following regions: the Nyírség region (north-eastern Hungary), the area between the River Danube and the River Tisza, the central parts of Somogy, and the sandy soils occurring in a mosaic-like distribution on the Kemenshát ridges and in the basin of the River Marcal.

It is striking, however, that in the Mezőföld region (Transdanubia), where primarily almost neutral chernozem loams occur over a considerable area, a relatively high number of soils have only a fair supply of magnesium, although chernozem soils usually possess a high supply. In these areas magnesium deficiency symptoms have repeatedly been observed in winter wheat in early spring. Hence, it may be concluded that, as a consequence of leaching, soils with only a fair magnesium supply may occur in these areas.

2.4. Relations between the available magnesium and other soil properties

In the previous sections, it has been mentioned that the available magnesium content of a soil depends on the quantity of inorganic and organic colloids, i.e. on the clay and humus contents of the given soil. These relations are presented here in the light of a number of examination data.

Measurement of the clay content of a soil is a laborious task, which is not convenient for serial analysis. Instead of this, the Arany number is determined in Hungary. This number is used to express how much water can be taken up by 100 g soil during constant mixing, until the plasticity level is attained. Di Gleria et al. (1957) stated that the water saturation is parallel to the clay content. In Hungarian soil studies, this number has been used to characterize the mechanical composition.

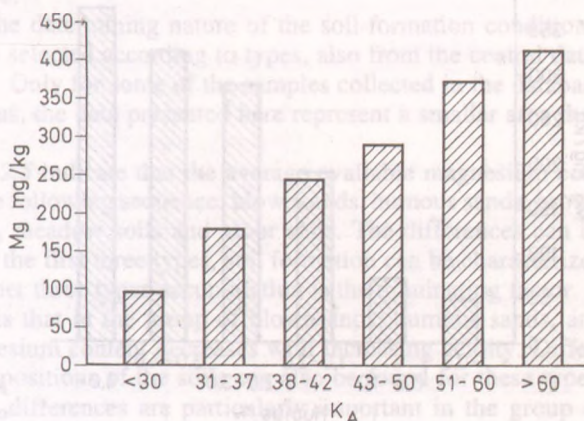


Fig. 2.5. Available magnesium contents of soils as a function of mechanical composition

Figure 2.5 shows the relations between the available magnesium content and the Arany number, based on the results of Hungarian soil examinations. The magnesium measurement data stored in the central database (NTSZ) were categorized and averaged by means of a computer, according to the Arany numbers of the soils, i.e. their mechanical compositions.

Mechanical compositions corresponding to the various Arany numbers (K_A) are as follows: $K_A < 30$: sand; 31–37: sandy loam; 38–42: loam; 43–50: clayey loam; 51–60: loam; over 60: heavy clay.

The several hundred thousand data processed clearly prove that the average available magnesium content increases with higher K_A value. This can be explained by the fact that in soils with a higher clay content the adsorption surface to which the exchangeable magnesium is bound is larger, and the magnesium reserves are higher too. The distribution of the different categories for the ca. 4 million hectares processed is as follows: sand 11.7, sandy loam 16.4, loam 21.4, clayey loam 28.5, clay 16.3, heavy clay 5.7%.

Figure 2.6 demonstrates the relation between the available magnesium content and the humus content of soils. A similar tendency can be observed here, too: in soils with a high humus content, where the adsorption surface is larger, more magnesium is adsorbed on the average and thus the available, i.e. exchangeable magnesium content is higher. The distribution of the sample groups in the sequence of increasing humus content to be seen in Fig. 2.6 is as follows: 0.33, 4.54, 30.8, 38.5, 20.4 and 5.4%.

This similar tendencies in the two Figures are related to the fact that sandy soils usually have a low humus content, whereas clay soils can be characterized by a high humus content. The two relations therefore mutually confirm each other. Regardless of this, it may be noted that low available magnesium contents can primarily be found in sandy soils with a low humus content. The low reserves in these soils also contribute to the fact that the majority of these soils are deficient in magnesium.

Figure 2.7 shows the relation between the available magnesium content and the pH (KCl) value of the soils.

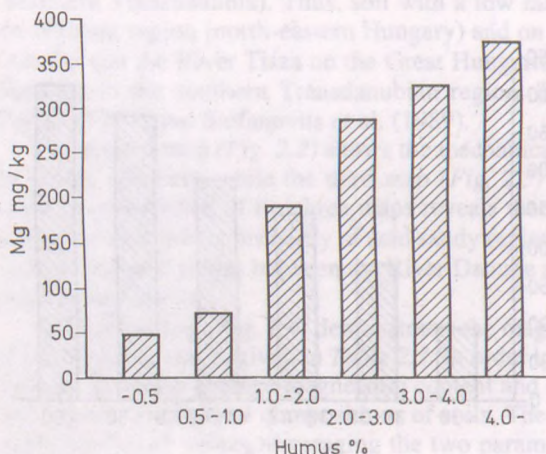
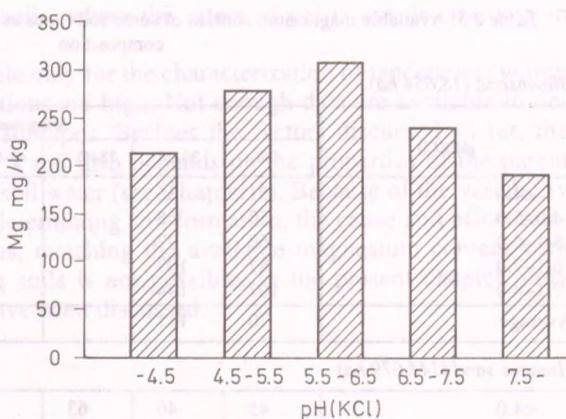


Fig. 2.6. Available magnesium contents of soils as a function of humus content

Fig. 2.7. Available magnesium contents of soils as a function of pH (KCl)



The specific maximum distribution describing the overall sample material does not reveal the relations that exist in different soil types, which are discussed separately. The low pH-low available magnesium content relation is characteristic only of soil types in the formation of which leaching processes play a dominant role. Acid meadow soils, however, can be characterized by a high available, i.e. exchangeable magnesium content, even if the pH values are low.

This explains the fact that the magnesium averages shown in the Figure are relatively high in the acid region, and lower in the pH(KCl) = 6.5-7.5 region regarded as neutral, to which mainly chernozem soils belong. The low average of the soils with a pH higher than 7.5 can be explained by the fact that this category contains the carbonated sands of the region between the River Danube and the River Tisza. Because of the above-mentioned overlap, no definite conclusions relevant to all soils of the country can be drawn as concerns the relation between the available magnesium content of the soils and the soil pH. The distribution of the individual categories in the overall sample material, in the increasing pH sequence to be seen in Fig. 2.7 is as follows: 5.8, 18.0, 24.9, 45.9 and 5.4%.

In order to demonstrate the determining nature of the soil-formation conditions, examination data on samples selected according to types, also from the central database, are shown in Table 2.5. Only for some of the samples collected in the database is the soil type indicated. Thus, the data presented here represent a smaller area than those discussed so far.

The data shown in Table 2.5 indicate that the average available magnesium content of the soil increases in the following sequence: blown sands, humous sands, brown forest soils, chernozem soils, meadow soils and moor soils. The differences can be explained by the fact that for the first three types, soil formation can be characterized by leaching, while for the other three types accumulation is the dominating factor. A further consequence of this is that in the group of blown sands, humous sands, and brown forest soils, the magnesium content decreases with increasing acidity. Differences in the mechanical compositions of the soils can also be found for these types, but mechanical composition differences are particularly important in the group of

Table 2.5. Available magnesium content of some soil types as functions of soil pH and mechanical composition

Blownsand (18,654 ha)

pH(KCl)	Arany number (K_A)						average
	<30	30-37	38-42	43-50	51-60	60	
<4.0	51	36					49
4.0-5.0	50	68					52
5.1-6.0	60	97					68
6.1-7.0	87	107					93
7.1-8.0	107	144					118
Average	70	111					78

Humous sand (144,079 ha)

<4.0	45	46	63				45
4.0-5.0	70	110	173				79
5.1-6.0	98	129	238				125
6.1-7.0	110	155	216				139
7.1-8.0	98	153	182				118
>8.0	172	172	155				171
Average	92	143	196				110

Brown forest soils (938,291 ha)

<4.0	55	131	209	230			139
4.0-5.0	74	145	226	267			172
5.1-6.0	96	170	251	265			209
6.1-7.0	116	184	256	246			222
7.1-8.0	104	157	184	188			174
Average	90	166	230	245			196

Chernozem soils (758,031 ha)

4.0-5.0	94	175	274	357			221
5.1-6.0	143	215	310	330			286
6.1-7.0	157	201	265	288			263
7.1-8.0	133	161	185	217			192
Average	137	177	220	246			220

Meadow soils (602,960 ha)

4.0	36	86	160	273	342	328	266
4.0-5.0	85	155	268	320	322	316	272
5.1-6.0	94	208	288	309	323	322	290
6.1-7.0	127	221	293	312	317	293	295
7.1-8.0	152	211	254	273	302	325	254
Average	124	210	273	297	317	312	277

Moor soils (193,691 ha)

4.1-5.0	86	179	215	254	283	325	260
5.1-6.0	129	201	232	293	309	325	291
6.1-7.0	111	208	272	286	309	308	287
7.1-8.0	108	189	235	252	282	315	244
Average	106	193	241	268	298	319	268

chernozem, meadow and moor soils, where the effect of pH is not determining in nature.

The data given here are suitable only for the characterization of tendencies: within the averages, the standard deviations are high. Not enough data are available to describe types not mentioned, or subtypes. Besides the factors discussed so far, the available magnesium content of a soil also depends on the properties of the parent rock and the composition of the soil water (see Chapter 1). Because of the variability and the high number of factors determining soil formation, the cause and effect relations are very complicated. Thus, matching the available magnesium content with only one property in describing soils is not possible. In the present chapter, only relations of major importance have been discussed.

References to Chapter 2

- Baranyai, F., Fekete, A., Kovács, I. (1987): *Results of Soil Nutrient Investigations in Hungary*. Mezőgazdasági Kiadó, Budapest. (In Hung.)
- Castenmiller, G.M.C. (1951): What is happening with regard to magnesium? *Maandblad voor de Landbouwworlichtingsdienst* **8**, 148.
- Chittenden, E.T., Hodgson, L. (1953): The influence of igneous intrusions on the magnesium content of the alluvial soils of the Waimea County. *N. Z. Journal of Science and Technology* **B 35**, 265.
- Christenson, D.R., Doll, E.C. (1973): Release of magnesium from soil clay and silt fractions during cropping. *Soil Science* **116**, 59.
- Di Gleria, J., Klimes-Szmik, A., Dvoracek, M. (1957): *Soil-physics and Soil-collodics*. Akadémiai Kiadó, Budapest. (In Hung.)
- Elek, É., Patócs, I. (1984): *Evaluation of the results of the first cycle of soil investigations in Hungary*. Edited by the Plant Protection and Agrochemical Centre by the Ministry of Agriculture, Hungary, 108. (In Hung.)
- Ferrari, Th.J., Sluijsmans, C.M.J. (1955): Mottling and magnesium deficiency in oats and their dependence on various factors. *Plant and Soil* **6**, 262.
- Fieldes, M., Swindale, L.D. (1954): Chemical weathering of silicates in soil formation. *N. Z. Journal of Science and Technology* **B 36**, 140.
- Fieldes, M., Weatherhead, A.V. (1968): Mineralogy of sand fractions. *N. Z. Soil Bureau Bulletin* **26**, 8.
- Gerzabek, M. (1988): Die Pflanzenverfügbarkeit von Magnesium. Teil I: Ein Vergleich verschiedener Mg-Extraktionsmethoden. *Bodenkultur* **39**, 117.
- Guidelines for fertilization and farm calculation method*. Plant Protection and Agrochemical Centre by the Ministry of Agriculture, Budapest, 1979. (In Hung.)
- Haddock, J. (1933): In: *Massachusetts Agricultural Experiment Station Annual Report* 305.
- Henriksen, A. (1971): On the availability of magnesium reserves in soil. *Tidsskrift for Planteavl* **75**, 647.
- Jacob, A. (1955): *Magnesium der fünfte Pflanzenhauptnährstoff*. Ferdinand Enke Verlag, Stuttgart.
- Kaila, A., Rytö R. (1968): Calcium, magnesium and potassium in clay, silt and fine sand fractions of some Finnish soils. *Maataloustieteellinen aikakauskirja* (Journal of the Scientific Agricultural Society of Finland) **40**, 1.

- Kidson, E.B., Askew, H.O., Chittenden, E.T. (1940): Magnesium deficiency of apples in the Nelson district of New Zealand. *N. Z. Journal of Science and Technology* **21**, 305.
- Loch, J. (1969): The AL-soluble magnesium content of soils and its relation to results of other methods. *DATE Tud. Közl.* **15**, 133. (In Hung.)
- Loch, J. (1970): *Relations between the magnesium content of soils and the magnesium taken up by plants*. C. Sc. Thesis, Debrecen. (In Hung.)
- Loch, J. (1984): Using the water-soluble K and Mg contents of soils to characterize their nutrition supply. *DATE Tud. Közl.* **24**, 247. (In Hung.)
- Loch, J. (1985a): Characterization of the magnesium status of soils by means of the EUF-Mg fractions. *Plant and Soil* **83**, 77.
- Loch, J. (1985b): State of magnesium supply of Hungarian soils. *C.I.E.C. Proc. of the 9th World Fertilizer Congress of the CIEC*, 11–16 June 1984, **3**, 46.
- Loch, J. (1988): Neuere Methoden zur Charakterisierung des pflanzenverfügbaren Mg im Boden. In: *Charakterisierung pflanzenverfügbarer Nährstoffe im Boden. Tagungsbericht* Nr. 267. Akademie der Landwirtschaftswissenschaften der DDR, Berlin, 109.
- Mazaeva, M.M. (1967): On the critical magnesium contents of soils. *Agrokhimiya*, **10**, 93.
- Metson, A.J. (1974): Magnesium in New Zealand soils. I. Some factors governing the availability of soil magnesium: a review. *N. Z. J. Exp. Agric.*, **2**, 277.
- Michael, G., Schilling, G. (1957): Magnesium in the arable soils of central Germany. *Z. Pfl.-ernähr. Düng. Bodenk.* **79**, 31. (In German.)
- Mulder, D. (1950): Magnesium deficiency in fruit trees on sandy soils and clay soils in Holland. *Plant and Soil* **2**, 145.
- Nemecz, E. (1973): *Clay Minerals*. Akadémiai Kiadó, Budapest. (In Hung.)
- Németh, K. (1972): Bodenuntersuchung mittels Elektro-Ultrafiltration (EUF) mit mehrfach variierter Spannung. *Landw. Forsch. Sonderh.* **27/II**, 184.
- Németh, K. (1976): Die effektive und potentielle Nährstoffverfügbarkeit im Boden und ihre Bestimmung mit Elektro-Ultrafiltration (EUF). *Habilitationsschrift*, Univ. Giessen.
- Peech, M. (1940): Determination of exchangeable magnesium in soils by titan yellow with reference to magnesium deficiency in citrus. *Proc. of the Soil Science Society of America* **4**, 189.
- Read, H.H. (1968): *Rutley's Elements of Mineralogy*. (24th ed.) Thomas Murry and Co., London.
- Salmon, R.C. (1963): Magnesium relationships in soils and plants. *Journal of the Science of Food and Agriculture* **14**, 605.
- Schachtschabel, P. (1954): Das pflanzenverfügbare Magnesium des Bodens und seine Bestimmung. *Z. Pfl.-ernähr. Düng. Bodenk.* **67**, 9.
- Schachtschabel, P. (1956): Der Magnesium-Versorgungsgrad nordwestdeutscher Böden und seine Beziehung zum Auftreten von Mangelsymptomen an Kartoffeln. *Z. Pfl.-ernähr. Düng. Bodenk.* **74**, 202.
- Schilling, G. (1957): *Magnesium ein universeller Pflanzennährstoff*. Bergbau-Handel, Berlin.
- Schollenberger, C.J., Dreibels, F.R. (1930): Analytical methods in base-exchange investigations on soils. *Soil Science* **30**, 161.
- Schroeder, D., Zahiroleslam, S., Hoffmann, W.E. (1963): Untersuchungen über die Verfügbarkeit der Magnesiumvorräte des Bodens. *Z. Pfl.-ernähr. Düng. Bodenk.* **100**, 215.
- Sestić, S. (1965): *Kolicina, pristupacnost i dinamika zamenljivog magnezijuma u glavijum tipovima zemljišta Srbije*. C. Sc. Thesis, Belgrade.
- Stahlberg, S. (1960): Studies on the release of bases from minerals and soils. IV. The release of calcium and magnesium by boiling normal hydrochloric acid. *Acta Agriculturae Scandinavica* **10**, 205.
- Stefanovits, P. (1963): *Soils of Hungary*. Akadémiai Kiadó, Budapest. (In Hung.)
- Stefanovits, P. (1975): *Soil Science*. Mezőgazdasági Kiadó, Budapest. (In Hung.)

- Stefanovits, P., Mrs Dombovári, L. (1985): The map of clay mineral associations in the soils of Hungary. *Agrokémia és Talajtan* **34**, 317. (In Hung.)
- Stefanovits, P., Mrs Dombovári, L., Kónya, K. (1989): Mineral composition and magnesium content of soils in Hungary. *Növénytermelés* **38**, 417. (In Hung.)
- Stenuit, D.F. (1954): The determination of magnesium deficiency in Belgian soils. *Transactions of the 5th Int. Cong. of Soil Science* **3**, 235.

3. The role of magnesium in the plant kingdom

Plants absorb the magnesium they need from primary sources and, after dying off, return part of it into the environment. This process is a very important step in the food chain since this is how magnesium is channelled from the inanimate to the living environment.

3.1. The relationship of magnesium with natural vegetation

The vegetation of soils rich in magnesium

Serpentine soils

In Europe, serpentine soils occur on the Balkan and Apennine peninsulae, in Lower Austria, Southern France, Switzerland and England.

They are generally characterized by the presence of more magnesium than calcium (cf. Babalonas et al., 1984). For example, in Northern Greece the magnesium content at a depth of 0–10 cm is 42.44–138.74 meq/100 g and the calcium content is 4.79–11.18 meq/100 g. The Ca:Mg ratio is lower than 1 (Karataglis et al., 1982). The total magnesium content of the serpentine soil in the Apennines is 5864–8436 µg/g and its total calcium content is 149–514 µg/g (Gambi et al., 1982).

The nutrients essential for plants (N, P and K) are present in only very low amounts. Considerable amounts of heavy metals (Co, Cr, Cu, Fe, Ni, Pb, Mn and Zn) are also detectable in serpentine soils. Of these, the amounts of nickel and chromium are significant. The barrenness of these soils is explained by the absence of nutrients and the presence of toxic heavy metals (Kinzel and Weber, 1982).

Some characteristics of serpentine soils may indirectly cause a nutrient deficiency. Chromium may precipitate phosphates; magnesium (at unfavourable concentrations) may interfere with the absorption of calcium and potassium.

Plants adapted to serpentine soils usually have low nutrient requirements. The heaviest load for the vegetation of such soils is the unbalanced ionic milieu.

Table 3.1. Calcium, magnesium and iron concentrations ($\mu\text{g/g}$ dry mass) in serpentine plants collected from Impruneta, M. Ferrato and Bobbio (Gambi et al., 1982)

Serpentine plants	Impruneta			M. Ferrato			Bobbio		
	Ca	Mg	Fe	Ca	Mg	Fe	Ca	Mg	Fe
<i>Cheilanthes marantae</i>	92.5	53.5	7.0	47.5	61.7	9.0			
<i>Asplenium cuneifolium</i>				104.8	164.5	2.2			
<i>Minuartia ophiolitica</i>				291.9	222.0	15.5	157.2	127.5	2.5
<i>Cerastium exile</i>	62.5	49.4	40.0	84.8	575.6	53.8	79.8	267.3	33.2
<i>Alyssum bertolonii</i>	858.3	283.7	8.4						
<i>Potentilla ophiolitica</i>				271.9	246.7	10.5			
<i>Euphorbia prostrata</i>	294.4	365.9	46.1	142.2	341.3	1.5			
<i>Armeria denticulata</i>	324.3	259.0	4.9	154.7	333.0	5.8	127.2	419.4	3.0
<i>Stachys serpentini</i>				107.3	127.5	2.9			
<i>Thymus ophioliticus</i>	291.9	234.4	9.0	207.1	230.3	6.1			
<i>Plantago holostium</i>	139.7	349.5	12.7						
<i>Scorzonera stenophylla</i>				142.2	427.6	6.3			
<i>Stipa pulcherrima</i>				12.5	69.9	1.8			
<i>Festuca glauca</i>				12.5	65.8	2.5			

Table 3.2. Calcium, magnesium and iron concentrations ($\mu\text{g/g}$ dry mass) in non-serpentine plants collected from Impruneta, M. Ferrato and Bobbio (Gambi et al., 1982)

Non-serpentine plants	Impruneta			M. Ferrato			Bobbio		
	Ca	Mg	Fe	Ca	Mg	Fe	Ca	Mg	Fe
<i>Ceterach officinarum</i>				89.8	168.6	14.8			
<i>Rumex scutatus</i>							296.9	1.152	10.3
<i>Herniaria glabra</i>				142.5	390.6	15.2			
<i>Silene italica</i>	194.6	172.7	18.9						
<i>Dianthus sylvestris</i>	254.5	185.0	4.3				588.8	127.5	3.9
<i>Sedum</i> sp.				386.7	263.1	3.4			
<i>Sanguisorba minor</i>				321.8	263.1	6.0			
<i>Linum tryginum</i>				57.4	349.5	3.4			
<i>Euphorbia exigua</i>				239.5	394.7	4.1			
<i>Euphorbia cyparissias</i>							386.7	349.5	5.6
<i>Cistus salvifolius</i>				214.6	328.9	14.2			
<i>Centaurium erythraea</i>				32.5	222.0	9.3			
<i>Galium lucidum</i>				249.5	222.0	10.5			
<i>Plantago lanceolata</i>				202.1	563.3	71.8			
<i>Jasione montana</i>				99.8	246.7	13.9			
<i>Ditrichia viscosa</i>				122.2	514.0	28.6			
<i>Senecio erucifolius</i>							192.1	452.3	11.4
<i>Centaurea rupestris</i>				137.2	139.8	2.4			
<i>Reichardia picroides</i>				184.6	752.5	7.7			
<i>Hieracium piloselloides</i>				389.2	111.0	9.1			
<i>Dactylis glomerata</i>	39.9	131.6	10.0						
<i>Scirpus holoschoenus</i>				7.5	102.8	2.5			

It has been proved in many experiments that nutrient solutions containing only or mostly magnesium as cation are toxic (cf. Kinzel and Weber, 1982). For example, the root formation of a serpentine-intolerant variety of *Agrostis* is highly inhibited by magnesium at a concentration of 10 ppm (0.4 mol/dm^3) whereas the serpentine tolerant clone is not affected.

A characteristic feature of plants living on serpentine soil is nanism (dwarfism). The leaves are small, yellow or bluish-green and thick, while the sclerenchyma is highly developed. The root system is large.

Both serpentine and non-serpentine plants contain appreciable amounts of magnesium (Tables 3.1 and 3.2). Of the characteristic serpentine plants, *Alyssum bertolonii* also contains a considerable amount of nitrogen (158–202 mg/g), which is probably related to the higher calcium content of this plant (cf. Table 3.1).

Members of the families *Caryophyllaceae* and *Violaceae* are frequent among serpentine tolerant species. Of the *Caryophyllaceae* genera, *Silene* species are noteworthy for their high magnesium content. Babalonas and Reeves (1988) measured 2.9–38.2 $\mu\text{g/g}$ magnesium in 13 *Silene* species growing on serpentine soil. The Ca:Mg ratio was 0.38–4.79.

The population of *Silene nutans* resident on Hungarian dolomite contained 2–3 times more magnesium than those plants living on limestone (Fekete et al., 1989).

Kinzel and Weber (1982) state that the tolerance of *Caryophyllaceae* living on serpentine is related to the oxalic acid content of their cells, which is neutralized by the plant as oxalate (oxalate type).

Dolomite

Of the Hungarian base rock types, dolomite has the highest magnesium content (nearly 20%).

Besides the features of the terrain and microclimatic factors, the physical and chemical characteristics of the base rock also play a role in the appearance of the particular vegetation living on dolomite (Zólyomi, 1942).

The chemical compositions of the plants in rock turfs evolved on dolomite-based soil in the Central Range of Hungary (*Festucetum pallentis hungaricum*) were studied by Láng-Kovács (1966). Calcium was found to be the dominant cation in the water and acid extracts of the dolomite soils studied (Sashegy /Budapest/ and Nagyszénás /Buda Mts/).

Within the same plant species, the magnesium content is higher in specimens growing on dolomite base rock than in those living on limestone. The calcium and magnesium contents and Ca:Mg ratios of the characteristic plant species of dolomite rock turfs are shown in Table 3.3.

The magnesium contents of certain plant species differ by a factor as high as 5.

As concerns identical species collected on limestone and dolomite habitats, the samples collected on dolomite contain more magnesium and copper, while those from limestone contain more calcium and sodium.

Table 3.3. Calcium and magnesium contents (mg/100 g) of the characteristic plants of dolomite rock turfs (Láng-Kovács, 1966)

Plants	Ca	Mg	Ca : Mg
<i>Seseli leucospermum</i>	1285	328	3.9
<i>Onosma visianii</i>	2862	1001	2.8
<i>Dianthus serotinus</i> var. <i>regis Stephani</i>	927	337	3.7
<i>Sesleria Sadleriana</i>	127	220	0.6

Table 3.4. Calcium and magnesium concentrations (g/kg) in "common" species collected in the spring (May 25, 1979) (Fekete et al., 1989)

Plants	Dolomite			Limestone		
	Ca	Mg	Ca:Mg	Ca	Mg	Ca:Mg
<i>Lithospermum purpureoeruleum</i>	19.0	3.00	6.33	18.8	1.60	11.75
<i>Cornus mas</i>	20.0	3.80	5.26	29.8	3.74	7.96
<i>Allium flavum</i>	13.6	3.84	3.54	20.0	2.24	8.92
<i>Helianthemum ovatum</i>	14.2	3.16	4.49	16.8	2.12	7.92
<i>Dictamnus albus</i>	18.0	4.00	4.50	21.6	3.12	6.92
<i>Lathyrus niger</i>	9.0	1.68	5.35	12.2	2.28	5.35
<i>Linaria genistifolia</i>	7.2	2.84	2.53	11.4	1.48	7.70
<i>Galium mollugo</i>	12.6	3.24	3.88	14.4	2.44	5.90
<i>Alliaria petiolata</i>	11.8	2.88	4.09	15.8	2.88	5.48
<i>Seseli osseum</i>	10.0	2.88	3.47	10.8	1.92	5.62
<i>Stachys recta</i>	9.4	3.36	2.79	13.4	2.24	5.98
<i>Polygonatum latifolium</i>	13.0	4.08	3.18	11.2	2.56	4.37
<i>Silene cucubalus</i>	8.4	3.88	2.16	15.2	4.24	3.58
<i>Chrysanthemum corymbosum</i>	8.0	3.16	2.53	8.4	2.92	2.87
<i>Geum urbanum</i>	13.0	4.32	3.00	15.0	6.80	2.20
<i>Melica uniflora</i>	5.2	2.28	2.28	4.2	1.56	2.69
<i>Melittis grandiflora</i>	8.8	4.20	2.09	9.4	3.28	2.86
<i>Cyanchum vincetoxicum</i>	6.4	3.48	1.83	8.4	3.00	2.80
<i>Viola cyanea</i>	8.2	3.96	2.07	10.4	4.24	2.45
<i>Poa nemoralis</i>	2.4	1.40	1.71	4.0	1.48	2.70
$\bar{x}$	10.9	3.27	3.35	13.6	2.80	5.30
s	4.6	0.80	1.31	6.0	1.26	2.63
cv	42.1	24.50	39.00	44.7	44.90	49.60

Table 3.5. Element contents of obligate dolomite plants (Fekete et al., 1989)

Dolomite plants	Ca	Mg	Ca : Mg	K	Na	P	S	Al	Fe	Mn	Zn	Cu
	(g/kg)						(mg/kg)					
<i>Dianthus serotinus</i>	12.6	2.92	4.3	13.8	0.024	1.37	1.32	54	117	21	38.8	2.6
ssp. <i>regis Stephani</i>	15.8	3.48	4.5	15.0	0.098	1.49	2.73	293	321	26	56.4	6.3
<i>Linum dolomiticum</i>												
<i>Thalictrum pseudo-</i> <i>minus</i>	7.8	2.60	3.0	17.7	0.024	1.18	4.05	54	67	25	41.2	7.2

Comparative studies of 20 plant species living on dolomite and limestone indicate that plants living on dolomite (17 species) contain more magnesium than do plants growing on limestone (Table 3.4; Fekete et al., 1989).

The element contents of certain obligate dolomite plants are listed in Table 3.5. No magnesium accumulation is observed in these plants.

The distribution of magnesium in forest components

Forest soils (depending on the base rock), and the plants in the different levels of the forest ecosystem that has evolved on these soils, contain varying amounts of magnesium.

The magnesium contents of the soil and the plants were determined in a *Quercetum petraeae-cerris* forest (Mátraháza) on lessivated brown forest soil and in a beech wood (*Luzulo-Fagetum*) on highly acidic, non-podsolic brown forest soil in the Mátra mountain (Northern Hungary) (Table 3.6).

The magnesium content of the lessivated brown forest soil at the 0–100 cm level varies between 1537 and 1980 $\mu\text{g/g}$, while the acidic soil contains considerably less magnesium (100–297 $\mu\text{g/g}$). The magnesium content of the leaves of sessile oak (*Quercus petraea*) is relatively high (1444–1813 $\mu\text{g/g}$).

In spite of growing on different soil types, the leaves of turkey oak (*Quercus cerris*) and beech (*Fagus sylvatica*) contain nearly identical amounts of magnesium.

Table 3.6. Distribution of magnesium in the components of *Quercetum petraeae-cerris* forest and an acidophilic beech wood ($\mu\text{g/g}$)

		<i>Quercus petraea</i>	<i>Quercus cerris</i>	<i>Fagus sylvatica</i>
Upper tree layer	leaf	1444	831	803
	twig	465	—	—
Middle tree layer	leaf	1699	895	848
	twig	372	—	—
Lower tree layer	leaf	1813	1025	863
	twig	513	—	—
Tree-trunk		199–333	—	—
Bark		208–374	278–378	—
Shrub stratum (leaves)		2886–4360		1288
Herb stratum (leaves)		595–7731		718–1271
Mushrooms (pileus)		356–5530		—
Moss stratum		1754–2713		567–779
Leaf-litter		1100–1300		—
Tree roots		784	—	—
Herb roots		1237–3238		413–742
Soil depth:	0– 10 cm	1537		100
	10– 30 cm	1654		111
	30– 50 cm	1787		155
	50– 70 cm	1756		187
	70– 90 cm	1866		297
	99–100 cm	1980		—

The magnesium content of the leaves is the highest in the leaves located at the lower foliage level.

The magnesium contents of the twigs (372–513 $\mu\text{g/g}$), tree-trunk (199–333 $\mu\text{g/g}$) and bark of the two oak species (208–378 $\mu\text{g/g}$) are relatively low. The components comprising the lower layers contain increased amounts of magnesium.

One of the points of accumulation of magnesium is the shrub layer, i.e. the leaves of the species that occur there. The leaves of the shrub species contain 2–4 times more magnesium than do oak leaves.

In the acidophilic beech wood, the shrub layer also consists of beech. The magnesium content of the leaves here is higher than that of the leaves of the trees that form the tree layer.

In the herb layer of the *Quercetum petraeae-cerris* forest ecosystem (second point of accumulation), the magnesium content of dicots is especially noteworthy. Large amounts of magnesium are present in the leaves of *Silene vulgaris* (7731 $\mu\text{g/g}$) and *Waldsteinia geoides* (7580 $\mu\text{g/g}$). In contrast, only small amounts of magnesium are found, for example, in the leaves of sedge (*Carex montana*: 1100 $\mu\text{g/g}$) and rush (*Luzula albida*: 1326 $\mu\text{g/g}$).

The magnesium content of mushrooms (pileus) varies within the range of 356–5530 $\mu\text{g/g}$.

There is an important difference between the two forest ecosystems in the order of magnitude of the magnesium content of the moss layer.

The roots of trees, shrubs and plants also play a role in the evolution of the magnesium content of the soil.

In the *Quercetum petraeae-cerris* forest, significant amounts of magnesium were measured in the roots of *Digitalis grandiflora* (2918 $\mu\text{g/g}$), *Potentilla alba* (2590 $\mu\text{g/g}$) and *Waldsteinia geoides* (3238 $\mu\text{g/g}$).

In the Sífkökút Project (in the eastern part of the Northern Central Range in the Bükk mountains), element contents relative to phytomass were determined (Papp, 1985). In 1 hectare of *Quercetum petraeae-cerris* forest, the amounts of magnesium (kg) in the individual components were as follows:

Trees: leaf	5.4	Shrubs: leaf	2.8
bough	20.0	twig-stem	1.6
trunk	51.2	root	2.5
root	22.1		

A magnesium amount of 7.5 kg/hectare passes into the soil with the leaves of the tree and shrub layer annually.

Magnesium in boughs and tree-trunks (73 kg/hectare) and in roots (25 kg/hectare) is excluded from the biogeochemical cycle for extended periods.

The amount of magnesium absorbed by tree and shrub species is estimated as 16 kg/hectare yearly.

The magnesium cycle in the ecosystem

Magnesium enters the ecosystem with floating dust and rainfall.

Larger amounts of magnesium may pass into the air with floating dust due to quarrying (dolomite powder) and weathering processes. The increasing CO₂ content* of the atmosphere and acidic rain both accelerate the weathering processes of rocks (especially limestone and dolomite).

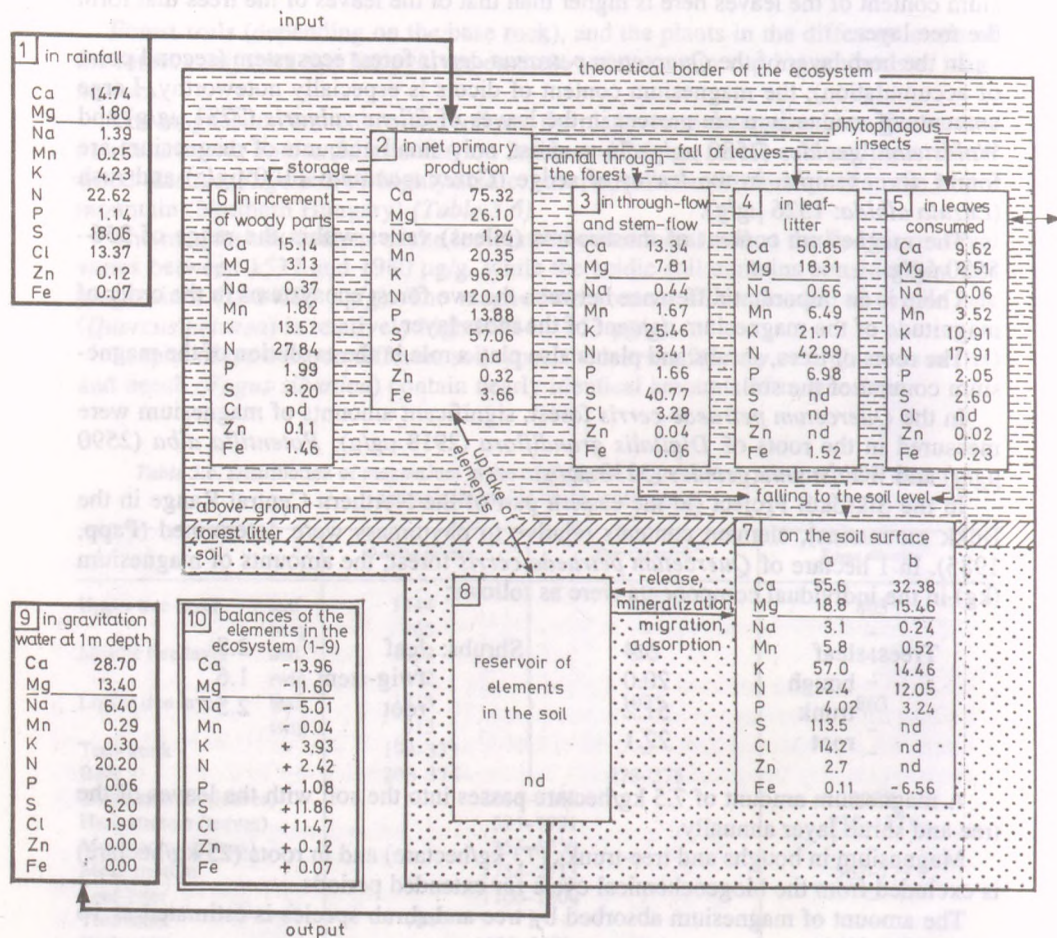


Fig. 3.1. Trends of element movements in the oak forest in the Síkőkut Project. The data in the individual blocks are average values of measurements over several years. Data are given as $\text{kg} \cdot \text{ha}^{-1} \cdot \text{year}^{-1}$; nd = not determined

* The rate of increase at present is 1.5 ppm/year (Ciborowski, 1989, cited by Faragó et al., 1990).

The magnesium content of the air may also be increased by power stations burning coal, by industrial activities (e.g. cement production) and by the application of salt: in some countries $MgCl_2$ is used to deice roads in the winter.

Rainfall contains varying amounts of magnesium. Kozák and Mészáros (1971) reported that in Europe 0.4–17 kg of magnesium is carried by rain to each hectare of soil annually.

Bublinec (1980) estimated that in the vicinity of Bratislava the annual amount of magnesium reaching each hectare was 22.3 kg.

In the Síkfőút Project, 1.8 kg of magnesium was found to fall per hectare of forest annually (Szabó, 1985).

The magnesium content of the precipitation falling through the foliage and flowing down the tree-trunks is increasing. As a yearly average (measurements carried out in 1974–76) 4.61 kg reaches the soil per hectare of forest (Szabó, 1985).

Part of the magnesium is excluded from the biogeochemical cycle for one year (leaves of annual plants or perennial trees and shrubs), several years (twigs and boughs of shrubs and trees, and roots of perennial plants) or decades (boughs and tree-trunks).

19 kg per hectare of magnesium reaches the soil surface with rainwater and leaf-litter.

Similarly to calcium, magnesium is relatively easily washed out of the soil and a yearly amount of 13.4 kg per hectare attains a depth of 100 cm with the gravitational water (output) (Kovács, 1985). When this amount is compared with that entering the ecosystem (input), i.e. 2 kg per hectare, it is evident that the annual magnesium loss of the *Quercetum petraeae-cerris* forest ecosystem is significant and the element balance is negative (Fig. 3.1, Jakucs et al., 1981; Jakucs, 1985).

These data support the impoverishment in magnesium and, at the same time, the acidification of soils evolved on basic rocks of low buffer capacity.

Magnesium deficiency and forest destruction

In Western Europe as in Hungary, one of the reasons for the decay of forests is identified as acidic precipitation and, as a consequence, the acidification of the soil and the outwash of magnesium.

In the *Quercetum petraeae-cerris* zone of the eastern part of the Northern Central Range in Hungary, the decay of sessile oak (*Quercus petraea*) has been observed since 1978. Comparative studies have been carried out in order to monitor the acidification of the soil and changes in its calcium and magnesium contents.

Detailed phytocenological and pedological surveys of various forest ecosystems have also been continued, among them *Quercetum petraeae-cerris* forests, started in the 1960s in the Mátra mountains (Kovács, 1975). The data obtained and our recent measurements reveal the extent of the changes in soil acidity.

Areas studied

Changes in acidity were studied on three sample locations where sessile oak was decayed to different extents. In all three cases the results of measurements carried out in 1966 were available (data were also recorded in 1986 in the same stage of the vegetation period, on the same soil profile).

1. Mátrafüred, Dobogó, height above sea level 310 m. The soil type is clay-bearing mull-ranker. The ecosystem is calciphilous oak forest (*Corno-Quercetum*) which, on the basis of its floristic composition, may be regarded as transitory to *Aceri tatarico-Quercetum*. *Quercus petraea* is represented in the stand with a coverage of 1–2. The decay of sessile oak is only sporadic.

2. Mátrafüred, Dobogó, height above sea level 340 m. A *Quercetum petraeae-cerris* forest has evolved on lessivated brown forest soil. The extent of oak decay is 10–20%.

3. Mátraháza, Nagylapát, *Quercetum petraeae-cerris* forest to the south from the resort-house of the Hungarian Academy of Sciences. The soil type is lessivated brown forest soil. This is where oak decay is most extensive (ca. 20–40%). The exposure (southern) and base rock (pyroxene-andesite) are identical in all three locations.

Survey data

At a depth of 5–40 cm in the clay-bearing mull-ranker soil at location #1, a decrease (by 0.7) in pH and an increase in hydrolytic acidity demonstrate the progress of soil acidification in 20 years (Table 3.7).

Maple (*Acer tataricum*) and cornel (*Cornus mas*) are represented in the tree and shrub strata with high coverage. The leaves of both species contain high levels of calcium. It is due to this that there is no change in the uppermost, litter layer of the soil.

In 1966, the soil profile at location #2 was the most acidic of the three. No further acidification occurred in the pale-grey, leached layer at a depth of 5–30 cm (Table 3.8). The pH of the uppermost, litter layer decreased by 1.6.

This phenomenon is similar to that described by Stefanovits (1986). The soil profile evolved on hydroandesite studied in the Mátra Hills was already so acidic to begin with that no further acidification could occur in the subsequent 25–30 years.

The decay of sessile oak and, consequently, the differences are largest on lessivated brown forest soil (Table 3.9).

The acidification of the soil has intensified up to a depth of 0–50 cm during the past 20 years.

Comparative studies in various periods in the eastern parts of the Northern Central Range (Stefanovits, 1986; Berki, 1987, cited by Berki and Holes, 1988) also prove that the acidity of soil has increased in recent decades.

The amount of absorbed calcium has changed primarily in lessivated brown forest soil. In soil profile #2, leaching into the lower layers is observed. In soil profile #3, a decreasing calcium content is measured down to a depth of 50 cm.

The amount of absorbed magnesium has decreased in both soil types and all three soil profiles within the 0–80 (100) cm layer studied.

Table 3.7. Changes in the characteristics of clay-bearing mull-ranker
in *Corno-Quercetum* and *Aceri tatarico-Quercetum* stands

Mátrafüred, Dobogó I., sample location #1.

Genetic levels Sampling (cm)		A ₁ 0-5	A 5-20	A 20-40	A 40-60	C 60-80
1966						
<i>Basic survey data</i>						
pH in water		5.8	5.4	5.4	5.5	6.3
in 1 mol/dm ³ KCl		5.4	4.3	4.3	4.5	4.9
hydrolytic acidity y ₁		17.5	22.5	19.0	13.0	4.5
<i>Exchangeable cations</i>						
Ca	mval/100 g	43.87	32.86	36.03	37.61	36.03
Mg	mval/100 g	8.56	7.25	8.68	7.79	8.56
K	mval/100 g	0.22	0.10	0.11	0.09	0.09
Na	mval/100 g	0.25	0.35	0.53	0.63	0.85
S	mval/100 g	57.76	40.56	43.35	46.12	45.53
T	mval/100 g	78.78	54.45	56.51	56.51	46.20
T-S	mval/100 g	21.02	13.89	11.16	10.39	0.67
V %		73.31	74.49	80.25	81.61	98.54
Ca	S %	84.36	81.01	79.44	81.54	79.13
Mg	S %	14.81	17.87	19.14	16.89	18.80
K	S %	0.38	0.26	0.26	0.21	0.21
Na	S %	0.45	0.86	1.16	1.36	1.86
1986						
<i>Basic survey data</i>						
pH in water		5.7	4.7	4.7	5.4	5.8
in 1 mol/dm ³		—	—	—	—	—
hydrolytic acidity y ₁		21.5	39.5	34.7	13.2	7.8
<i>Exchangeable cations</i>						
Ca	mval/100 g	56.40	25.50	34.00	40.60	40.60
Mg	mval/100 g	4.20	3.90	2.70	2.70	4.40
K	mval/100 g	1.27	0.43	0.35	0.16	0.12
Na	mval/100 g	0.60	0.49	0.60	0.95	1.12
S	mval/100 g	62.47	30.32	37.65	44.41	46.24
T	mval/100 g	67.43	53.40	49.15	47.02	46.18
T-S	mval/100 g	4.96	23.08	11.50	2.61	—
V %		92.64	56.74	76.60	94.44	100.06
Ca	S %	90.28	84.10	90.30	91.42	87.86
Mg	S %	6.72	12.86	7.17	6.07	9.51
K	S %	2.03	1.41	0.92	0.36	0.25
Na	S %	0.96	1.61	1.59	2.13	2.42

Description of the soil profile:

A₁: 0- 5 cm: deep black, loose, rich in organic material

A: 5-60 cm: deep black, upper layer slightly crumbly, lower layer compact, clayey

C: >60 cm: decayed andesite tuff

Table 3.8. Changes in the characteristics of lessivated brown forest soil in a *Quercetum petraeae-cerris* stand

Mátrafüred, Dobogó III., sample location #2.

Genetic levels . Sampling (cm)		A ₀ 0-5	A ₁ 5-30	B ₁ 30-60	B ₂ 60-80
1966					
<i>Basic survey data</i>					
pH in water		6.4	4.3	4.9	5.1
in 1 mol/dm ³ KCl		6.0	3.5	3.6	3.9
hydrolytic acidity y ₁			48.5	22.5	15.0
<i>Exchangeable cations</i>					
Ca	mval/100 g	53.49	8.49	23.80	28.09
Mg	mval/100 g	10.24	3.50	10.38	10.90
K	mval/100g	0.61	0.08	0.10	0.11
Na	mval/100 g	0.21	0.35	0.91	1.02
S	mval/100 g	64.55	12.42	35.19	40.12
T	mval/100 g	76.72	26.81	49.08	49.91
T-S	mval/100g	11.67	14.39	13.89	9.79
V %		84.13	46.32	71.69	80.38
Ca	S %	82.86	68.35	67.63	70.01
Mg	S %	15.86	28.18	29.49	27.16
K	S %	0.02	0.64	0.25	0.27
Na	S %	1.83	2.83	2.63	2.56
1986					
<i>Basic survey data</i>					
pH in water		4.8	4.4	4.6	5.9
in 1 mol/dm ³ KCl		—	—	—	—
hydrolytic acidity y ₁		49.6	—	28.0	6.2
<i>Exchangeable cations</i>					
Ca	mval/100 g	18.00	24.80	36.60	47.00
Mg	mval/100 g	3.70	2.70	3.80	5.00
K	mval/100 g	0.62	0.35	0.35	0.35
Na	mval/100 g	0.33	0.63	1.12	1.65
S	mval/100 g	22.65	28.48	41.87	54.00
T	mval/100 g	38.09	44.90	51.70	54.25
T-S	mval/100 g	15.44	16.42	9.83	0.25
V %		59.46	63.42	80.98	99.53
Ca	S %	79.47	87.07	87.41	87.03
Mg	S %	16.33	9.48	9.07	9.25
K	S %	2.73	1.22	0.83	0.64
Na	S %	1.45	2.21	2.67	3.05

Description of the soil profile:

A₀: 0- 5 cm: dark-brown, loose, rich in organic material

A₁: 5-30 cm: pale greyish-brown, dusty structure

B₁: 30-60 cm: yellowish-brown, compact, clayey

B₂: 60-80 cm: yellowish-brown, brown, compact, clayey

Table 3.9. Changes in the characteristics of lessivated brown forest soil in a *Quercetum petraeae-cerris* stand

Mátraháza I.

Genetic levels Sampling (cm)		A ₀ 0-10	A ₁ 10-30	A ₂ 30-50	B ₁ 50-70	B ₂ 70-90	C 90-100
1966							
Basic survey data							
pH in water		5.4	5.4	5.3	5.2	5.3	5.3
in 1 mol/dm ³ KCl		4.8	4.6	4.5	4.3	4.3	4.3
hydrolytic acidity y ₁		21.6	12.7	12.7	11.2	11.3	10.5
Exchangeable cations							
Ca	mval/100 g	18.98	11.83	10.40	12.85	13.06	17.55
Mg	mval/100 g	3.82	3.58	3.90	3.49	3.66	3.66
K	mval/100 g	0.65	0.44	0.42	0.46	0.45	0.35
Na	mval/100 g	0.18	0.11	0.15	0.28	0.29	0.45
S	mval/100 g	23.63	18.96	14.87	17.08	17.46	22.01
T	mval/100 g	38.77	24.75	23.10	20.62	21.45	23.10
T-S	mval/100 g	15.15	8.79	8.23	3.54	3.99	1.09
V %		60.94	64.48	64.37	82.83	81.39	95.25
Ca	S %	80.32	74.12	69.93	75.25	74.79	79.93
Mg	S %	16.16	22.43	26.22	20.43	20.96	16.62
K	S %	2.75	2.75	2.82	2.69	2.57	1.59
Na	S %	0.77	0.70	1.03	1.63	1.68	2.06
1986							
Basic survey data							
pH in water		4.9	4.6	4.9	5.2	5.3	5.3
in 1 mol/dm ³ KCl		—	—	—	—	—	—
hydrolytic acidity y ₁		36.2	32.2	17.7	13.2	12.2	11.5
Exchangeable cations							
Ca	mval/100 g	9.40	5.30	8.40	10.80	11.70	13.50
Mg	mval/100 g	1.10	1.80	0.0	1.10	2.40	2.60
K	mval/100 g	1.04	0.24	0.24	0.69	0.85	0.89
Na	mval/100 g	0.30	0.30	0.40	0.44	0.60	0.70
S	mval/100 g	11.84	7.74	9.04	13.03	15.55	17.69
T	mval/100 g	29.16	19.81	12.58	18.96	19.38	21.51
T-S	mval/100 g	17.32	12.07	3.54	5.93	3.83	3.82
V %		40.60	39.07	71.86	68.72	80.23	82.24
Ca	S %	79.39	69.76	92.92	82.88	75.24	76.31
Mg	S %	9.28	23.25	0.0	8.44	15.43	14.69
K	S %	8.78	3.10	2.65	5.29	5.46	5.03
Na	S %	2.53	3.87	4.42	3.37	3.85	3.95

Description of the soil profile:

A₀: 0- 10 cm: brownish-black, loosely structuredA₁: 10- 30 cm: brownish-black, dusty structure interwoven by roots, rock content 20-30%A₂: 30- 50 cm: dark brown, slightly clayey, polyhedralB₁: 50- 70 cm: light brown, compact, clayey, rock content over 60%B₂: 79- 90 cm: yellowish-brown, compact, polyhedral, with much andesite debris

C: 90- 100 cm: yellowish-brown, andesite debris

A number of authors (e.g. Bergseth, 1975; Matzner, 1983; Stumm et al., 1983; Ulrich, 1983; Johnson and Richter, 1984; Bredow et al., 1986) have reported that the decreasing magnesium content of the soil plays a role in forest decay.

Investigation of microhabitats around tree-trunks

Horváth and Mészáros (1984) found the pH of the rainfall over the area of the Northern Central Range of Hungary to be 5.3. In order to obtain evidence relating to the assumption that rain plays a role in the acidification of the soil, analysis of the zone around the tree-trunk may be performed (cf. Glavac et al., 1970, 1985; Glavac

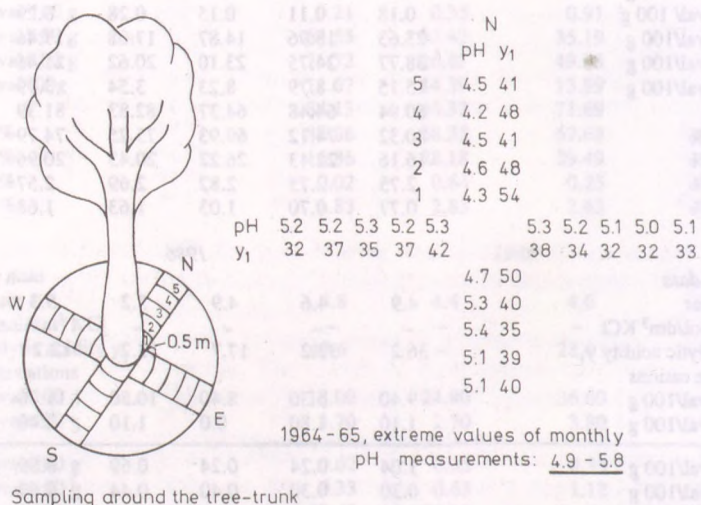


Fig. 3.2. pH and y_1 values around tree-trunks

pH and y_1 values of the 10-30 cm layer of the soil (average of measurements around the trunks of 5 *Quercus petraea* trees, carried out in 1987)

and Koenies, 1986; Glatzel et al., 1983; Wittig and Neite, 1983; Jochheim, 1985, 1986; Turcsányi and Fangmeier, 1990). The soil surrounding the tree-trunk is affected by rainfall: that falling through the foliage (throughfall) and that flowing down the tree-trunk (stemflow). Leaching and impoverishment in magnesium and calcium are more pronounced around tree-trunks (Jochheim and Schäfer, 1988).

In response to the stemflow on *Quercus petraea*, the soil (10-30 cm depth) in the immediate vicinity of the tree is acidified to a higher extent, as indicated primarily by the hydrolytic acidity values (Fig. 3.2).

Table 3.10. pH of the soil solution in an old beech forest
on a northern slope of the Mátra mountain
(Turcsányi et al., 1991)

Samples	Trunk, stemflow side	Trunk, rising side	Interstem area, stemflow side	Interstem area, rising side
tree 1	5.18	6.81	7.39	7.56
tree 2	4.48	5.16	6.51	6.15
tree 3	5.18	7.25	6.78	6.00
tree 4	3.70	6.89	5.86	6.76
Average	4.64	6.53	6.64	6.62

Table 3.11. Element contents ($\mu\text{g/g}$) of the soil solution in an old
beech forest on a northern slope
of the Mátra mountain (Turcsányi et al., 1991)

Elements	Trunk, stemflow side	Trunk, rising side	Interstem area, stemflow side	Interstem area, rising side
Al	3.009	1.055	0.865	0.514
Ca	15.720	13.860	55.270	43.050
Cd	<D.L.*	<D.L.*	<D.L.*	<D.L.*
Cu	0.019	0.010	0.013	0.010
Fe	1.251	0.297	0.276	0.259
K	40.740	30.220	25.260	19.830
Mg	4.464	9.736	7.533	6.342
Mn	3.116	1.666	1.423	0.466
P	1.987	2.653	2.817	1.835
Pb	0.049	D.L.	D.L.	0.073
V	0.010	0.008	0.008	0.007
Zn	0.233	0.097	0.164	0.079

* D.L. = detection limit.

Turcsányi and Fangmeier (1990) and Turcsányi et al. (1991) studied the effect of stemflow on the element content of the soil in beech forests in Germany and Hungary. The beech (*Fagus silvatica*) stands in the North-Eastern Central Range in Hungary have recently shown signs of forest decay.

On the stemflow area and on the stemflow side, the soil has become more acidified and its magnesium and calcium contents lower than in the rising areas around the tree. In contrast, the levels of aluminium, iron and manganese have increased (Tables 3.10 and 3.11).

The metal ion contents of beech roots also clearly reflect the downflow and element outwash processes around the tree-trunk (Table 3.12). On the stemflow side, the tree-roots have lower magnesium, calcium and phosphorus contents.

Table 3.12. Element contents of beech roots ($\mu\text{g/g}$ dry mass) in an old beech forest on a northern slope in the Mátra mountain (Turcsányi et al., 1991)

Samples	Trunk, stemflow side	Trunk, rising side	Interstem area, stemflow side	Interstem area, rising side
Al	2349	2934	3045	2452
Ca	3618	7580	7650	8229
Cd	0.653	0.707	0.916	0.794
Cu	14.99	8.297	10.24	6.478
Fe	1833	1755	1813	1388
K	2470	2692	3074	3083
Mg	672.4	925.1	952.7	997.3
Mn	268.6	218.7	282.5	250.5
P	777.1	891.8	1011	1123
Pb	55.37	7.731	4.437	4.147
V	4.588	4.704	5.076	4.177
Zn	56.16	65.93	75.27	54.84

Table 3.13. Magnesium content (mg/g dry mass) of 1–6-year-old pine needles collected in the 7th vertical of twigs of spruce (*Picea abies*) at different locations in different years

Experimental area	Year of collection	Vertical of twig/Age group					
		7/1	7/2	7/3	7/4	7/5	7/6
Sellhorn	1971	1.06	1.13	1.09	1.12	1.17	1.32
	1974	1.04	0.98	0.97	0.96	1.04	1.07
	1979	0.99	0.85	0.81	0.79	0.78	0.72
Oerrel	1964	1.36	1.02	1.10	1.27	1.25	1.05
	1971	0.97	0.81	0.66	0.71	0.81	0.99
	1976	1.13	0.84	0.90	0.85	0.84	0.94
	1981	1.00	0.79	0.67	0.76	0.93	0.82
Hardeggen	1974	0.82	0.69	0.62	0.64	0.63	0.64
	1981	0.62	0.55	0.54	0.55	0.62	0.64
Hardeggen	1975	0.68	0.55	0.55	0.61	0.64	0.77
	1981	0.53	0.33	0.34	0.30	0.39	0.46
Lauterbach	1965	0.87	0.85	0.72	0.83	0.81	0.91
Ziegenberg	1972	1.11	0.88	0.71	0.66	0.67	–
	1978	0.96	0.65	0.55	0.44	0.38	0.41
Neuenheerse	1968	0.63	0.46	0.37	0.30	0.29	0.33
	1975	0.50	0.28	0.26	0.23	0.25	0.25
Neuenheerse	1967	0.77	0.55	0.45	0.57	0.40	0.40
	1972	0.55	0.42	0.32	0.25	0.25	0.28
	1976	0.57	0.22	0.18	0.17	0.18	0.19

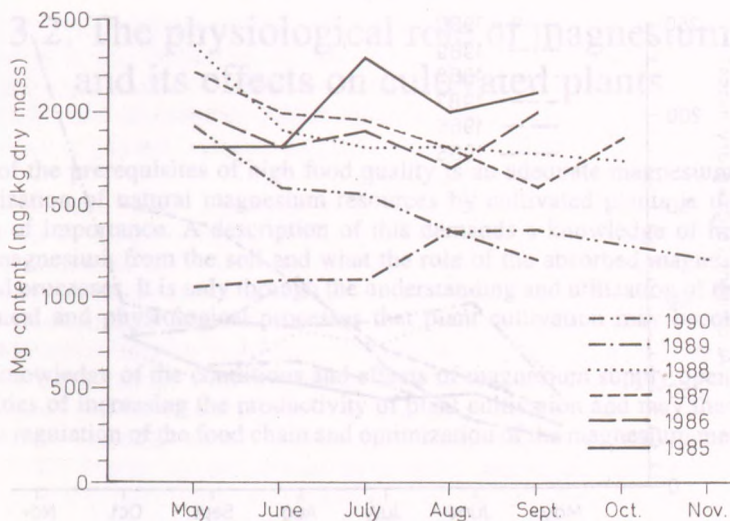


Fig. 3.3. Changes in magnesium content

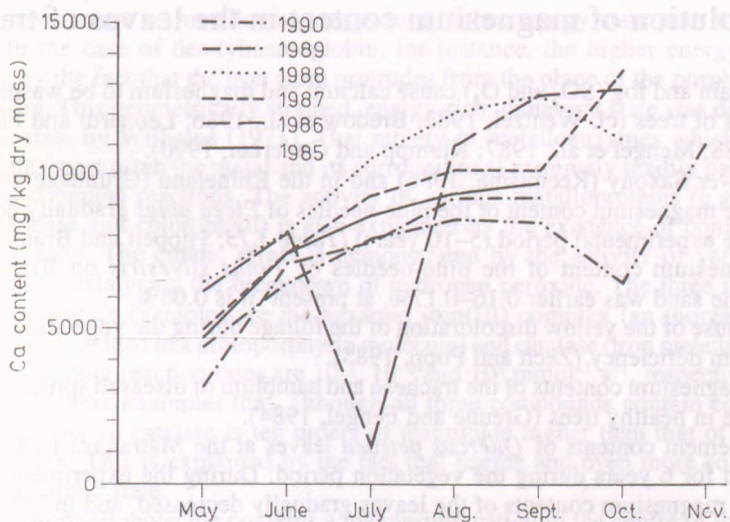


Fig. 3.4. Changes in calcium content

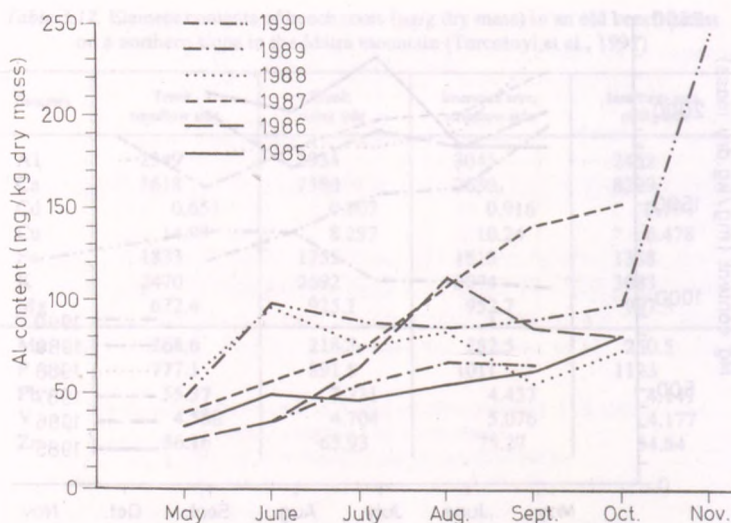


Fig. 3.5. Changes in aluminium content

Evolution of magnesium content in the leaves of trees

Acid rain and fog (SO_2 and O_3) cause calcium and magnesium to be washed out of the leaves of trees (cf. Wentzel, 1982; Bredow et al., 1986; Leonardi and Flückiger, 1986, 1988; Mengel et al., 1987; Klumpp and Guderian, 1990).

In Lower Saxony (Reemtsma, 1986) and in the Rhineland (Grünhage and Jäger, 1988), the magnesium content of the pine-needles of *Picea abies* gradually decreased during the experimental period (5–10 years) (Table 3.13; Hippeli and Branse, 1992). The magnesium content of the pine-needles of *Pinus silvestris* on Brandenburg Pleistocene sand was earlier 0.16–0.17%, at present it is 0.08%.

The cause of the yellow discoloration of the foliage during the vegetation period is magnesium deficiency (Zech and Popp, 1983).

The magnesium contents of the tracheae and cambium of diseased spruce are lower than those in healthy trees (Greune and Fengel, 1984).

The element contents of *Quercus petraea* leaves at the Mátraháza location were monitored for 6 years during the vegetation period. During the experiment, the calcium and magnesium contents of the leaves gradually decreased, and in 1989–90 the decrease accelerated (Figs 3.3 and 3.4). In contrast, the aluminium contents rose at an increased pace (Fig. 3.5). This phenomenon is related to the acidification of the soil and the increased mobilization of aluminium.

3.2. The physiological role of magnesium and its effects on cultivated plants

One of the prerequisites of high food quality is an adequate magnesium content. The utilization of natural magnesium resources by cultivated plants is therefore a question of importance. A description of this demands a knowledge of how plants absorb magnesium from the soil and what the role of the absorbed magnesium is in their vital processes. It is only through the understanding and utilization of these basic biochemical and physiological processes that plant cultivation may become really effective.

The knowledge of the conditions and effects of magnesium supply opens up new possibilities of increasing the productivity of plant cultivation and may thereby contribute to regulation of the food chain and optimization of the magnesium metabolism.

Magnesium and its complexes

Magnesium forms a divalent cation, Mg^{2+} . In biological systems, it usually forms complexes (e.g. chlorophyll), some involving nitrogen containing components (ammonia, pyridine, etc.).

The active centre of metalloenzymes is in a higher energy state than their other regions. In the case of deoxyhaemoglobin, for instance, the higher energy state is explained by the fact that the iron atom protrudes from the plane of the porphyrin ring by 0.075 nm. This geometrically strained, energy-rich, unnatural state was designated an entatic state by Williams (1971). That moiety of metalloenzymes which is in an entatic state (most often the metal and its surroundings) extremely readily participates in various chemical reactions. The activity of various metalloproteins (e.g. haemoglobin, catalase and chlorophyll) is also explained by the existence of complexes in the entatic state. The entatic effect is demonstrated by the activity of various iron compounds in catalysing the breakdown of hydrogen peroxide. The three iron compounds selected as examples are the hexaquo iron(III) complex (an inorganic salt), haeme (iron embedded in a protoporphyrin molecule) and catalase (iron metalloprotein). The corresponding reaction rates are 10^{-5} , 10^{-2} and $10^5 \text{ mmol}^{-1} \text{ s}^{-1}$, respectively. It is evident from these examples that, although all three compounds contain complexed iron, the activity of catalase is ten orders of magnitude higher than that of the inorganic complex. This is explained by the fact that haeme and even more so catalase, involve an entatic state.

The chlorophyll molecule contains a magnesium cation in the centre of the chlorin (porphin) ring. This central part with four ligands forms complexes with Zn, Cu and Fe ions, for example, the stabilities of which are much higher than that of the magnesium complex. Nevertheless, *in vivo*, only magnesium-chlorin is formed when magnesium is present. This is of importance because, if only one iron(II)-chlorin molecule were present among 4000 chlorophyll (magnesium-chlorin) molecules, the photosynthetic apparatus would be unable to function. The fact that only magnesium may be

incorporated into the chlorin ring is explained by kinetic considerations. Metal ions, including magnesium, are incorporated into the chlorin ring by way of enzyme-catalysed reactions. The enzyme is able to form a complex with each metal ion, but the stabilities of the complexes are not identical. It may be assumed that chlorin recognizes and reacts with only the magnesium-enzyme complex, leading to the formation of magnesium-chlorin (chlorophyll).

In Nature, chlorophyll molecules occur not as monomers, but as dimers or oligomers. Water is coordinated to the magnesium, and is hydrogen-bonded to the carbonyl group, as shown on Fig. 3.6 (Ballschmitter and Katz, 1969). The reason for this is that the magnesium present in chlorophyll, possessing a coordination number of 4, is coordinatively unsaturated and strives to become saturated with the help of some electron donor. In polar solvents, chlorophyll (Chl) binds solvent molecule(s) at one or both sites (Chl.L and Chl.L_2) and is in monomeric form. In non-polar solvents, it binds exogenous nucleophiles or another chlorophyll molecule and becomes saturated. In chlorophyll, the C=O (keto) group on ring 5 of the molecule serves as electron donor, whereby oligomeric chlorophyll may be formed in non-polar solvents. This phenomenon is termed an endogenous interaction, while binding to a nucleophile is considered exogenous. These interactions determine the aggregation state (monomer, dimer or oligomer) of chlorophyll. As described above, the donor-acceptor interactions of chlorophyll are dependent on the solvent (polar or apolar), which explains the solvent dependence of the absorption spectrum of the chlorophyll system.

Magnesium and adenosine triphosphate (ATP)

ATP is present in all cells of living organisms. Most of the processes accompanied by changes in free energy that take place in living organisms are coupled to the synthesis or breakdown of ATP. ATP is formed from ADP (adenosine diphosphate) in the chloroplasts with the help of energy absorbed from light (photophosphorylation),

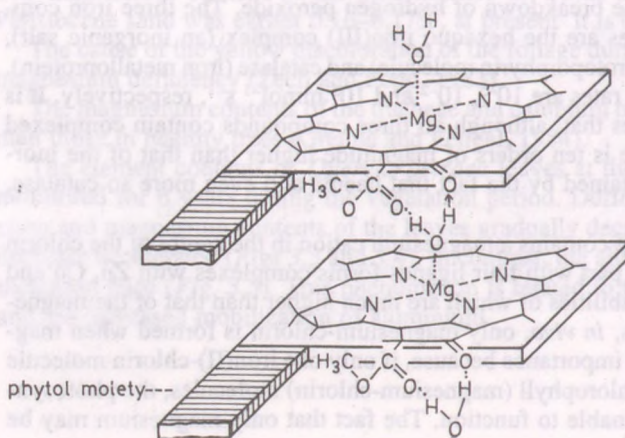
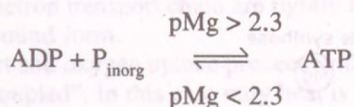


Fig. 3.6. Schematic structure of the chlorophyll-water complex (Ballschmitter et al., 1969)

in the mitochondria by the oxidation of carbohydrates, etc. (oxidative phosphorylation) and also in the course of glycolysis.

Magnesium plays an important role in all reactions involving ATP, as it forms a complex with ATP, thereby facilitating the course of the reaction and the transfer of energy:



It follows that at low magnesium concentrations ($\text{pMg} = 4-2.3$) increasing magnesium content enhances the formation of ATP (Lakatos, 1972; Kiss, 1973).

The results of reaction kinetic and structural studies have revealed that

- a) magnesium forms a complex with ATP;
- b) in solution, magnesium is in direct contact only with the phosphate moiety and is connected to the adenine ring via at most a water molecule, in the form of an outer sphere complex;
- c) ATP is bound to enzymes via the coordination sites of the magnesium ion which facilitates energy transfer (this is how magnesium plays the role of a coenzyme);
- d) magnesium inhibits the hydrolysis of ATP and thereby promotes the accumulation of ATP.

Magnesium and mitochondria

The primary function of all (plant and animal) mitochondria is to liberate the chemical energy stored in carbohydrates, fats, etc. by oxidation and to couple this process to phosphorylation (ATP synthesis). Thus, mitochondria, in addition to chloroplasts, are the most important sites of ATP synthesis.

Mitochondria are spherical or rod-shaped organelles a few micrometres in size and with a dry mass of 10^{-13} g. Their number per cell varies between 20 and 2500. They are able to change their volume in response to energy. The change in volume proceeds in parallel with the uptake or discharge of intracellular fluid, and may range from a few per cent to as high as 400%. Oxidative phosphorylation is closely related to the mitochondrial structure and occurs only in rod-shaped (not swollen) mitochondria. Swelling is an energy-consuming process, and swollen mitochondria therefore contain little ATP and much more ADP. Swelling is inhibited by the addition of ATP. Shrinking of swollen mitochondria is brought about by ATP only in the presence of magnesium. The lack of magnesium alone may cause swelling (Kiss and Mustárdy, 1985). It follows from the above data that the swelling of mitochondria is inversely proportional to the magnesium concentration.

Oxidative phosphorylation

Oxidative respiration and phosphorylation are typical energy-supplying processes, restricted to the mitochondrial structure. Oxidative or aerobic respiration involves the condensation of hydrogen from NADH and FADH reduced in the Szent-Györgyi-

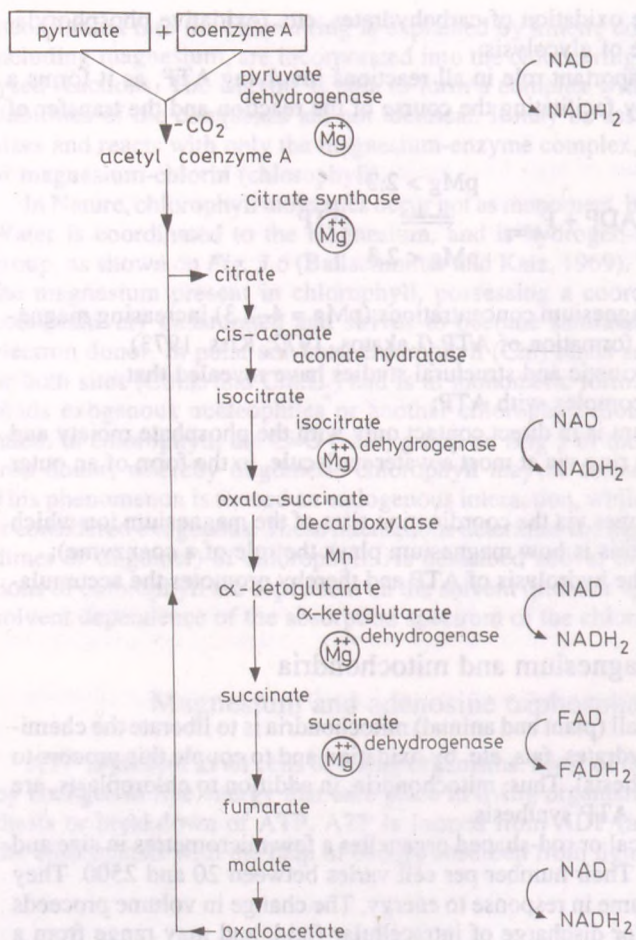
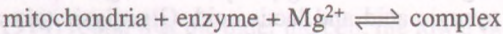


Fig. 3.7. The roles of enzymes utilizing magnesium as cofactor in the citric acid (Szent-Györgyi-Krebs cycle)

Krebs cycle and molecular oxygen to form water. The energy liberated thereby is utilized for ATP synthesis: this is oxidative phosphorylation. The diagram of the Szent-Györgyi-Krebs cycle (citric acid cycle) is shown in Fig. 3.7; enzymes whose cofactor is magnesium and the sites of NAD and FAD reduction are indicated.

NADH and FADH generated in the citric acid cycle are not able to react directly with molecular oxygen. They are oxidized by the cytochrome system in mitochondria. Electron migration between NAD and the cytochromes is stimulated by magnesium. The magnesium concentration optimal for this process is 10^{-4} – 10^{-5} mol/dm³. This amount of magnesium, however, is not present among the free cations of the intramitochondrial aqueous phase since two-thirds of all the magnesium is tightly bound to membranes. Magnesium ions increase the binding of ATPase to the mitochondrial membrane. The binding of the enzyme to the membrane occurs without any increase in the number of binding sites. This is possible only if a special, tertiary

complex is formed by the magnesium ion, the enzyme and the membrane. The process of binding is described by the following equation:



The members of the electron transport chain are tightly membrane-bound and may exert their effect only in bound form.

When electron transport and oxygen uptake proceed without the synthesis of ATP, the system is termed “uncoupled”. In this case only heat is generated instead of ATP. The presence of magnesium ions favours ATP synthesis, while lowered magnesium concentrations promote the uncoupled state.

Accordingly, magnesium plays a dual role, as a structural component and as an enzyme activator in oxidative phosphorylation.

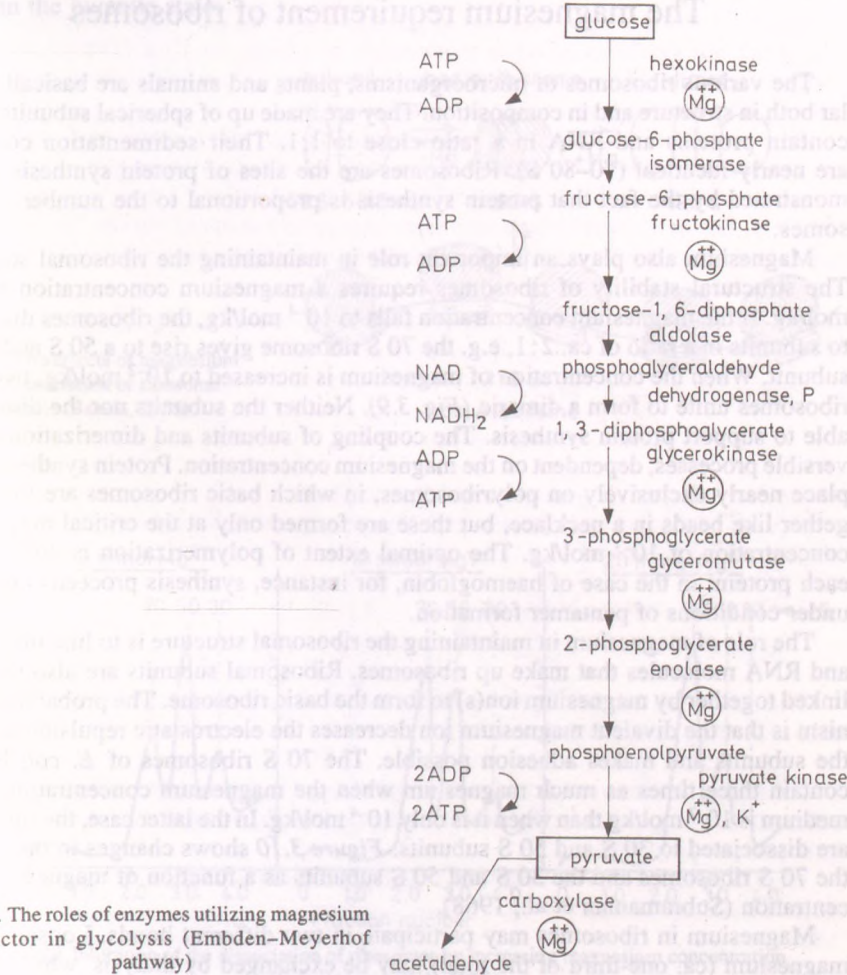


Fig. 3.8. The roles of enzymes utilizing magnesium as cofactor in glycolysis (Embden-Meyerhof pathway)

The role of magnesium in glycolysis

The literal meaning of the word "glycolysis" is sugar breakdown. The products of this process are pyruvic acid and lactic acid. Glycolysis takes place in the cytoplasm via enzyme reactions, the Embden–Meyerhof diagram of which is shown in Fig. 3.8. Steps in which magnesium is needed are indicated. It is evident that, just as in the citric acid cycle, magnesium plays an important role. The free magnesium concentration optimal for these processes is 0.5 mmol/kg. In all probability, magnesium exerts its effect by bringing the reaction partners spatially closer to each other by complexing, for example, thereby promoting favourable collisions and facilitating the onset of the reaction.

The magnesium requirement of ribosomes

The various ribosomes of microorganisms, plants and animals are basically similar both in structure and in composition. They are made up of spherical subunits which contain proteins and RNA in a ratio close to 1:1. Their sedimentation constants are nearly identical (70–80 S). Ribosomes are the sites of protein synthesis, as demonstrated by the fact that protein synthesis is proportional to the number of ribosomes.

Magnesium also plays an important role in maintaining the ribosomal structure. The structural stability of ribosomes requires a magnesium concentration of 10^{-3} mol/kg. If the magnesium concentration falls to 10^{-4} mol/kg, the ribosomes dissociate to subunits in a ratio of ca. 2:1, e.g. the 70 S ribosome gives rise to a 50 S and a 30 S subunit. When the concentration of magnesium is increased to 10^{-2} mol/kg, two basic ribosomes unite to form a dimeric (Fig. 3.9). Neither the subunits nor the dimers are able to support protein synthesis. The coupling of subunits and dimerization are reversible processes, dependent on the magnesium concentration. Protein synthesis takes place nearly exclusively on polyribosomes, in which basic ribosomes are linked together like beads in a necklace, but these are formed only at the critical magnesium concentration of 10^{-3} mol/kg. The optimal extent of polymerization is different for each protein: in the case of haemoglobin, for instance, synthesis proceeds optimally under conditions of pentamer formation.

The role of magnesium in maintaining the ribosomal structure is to link the protein and RNA molecules that make up ribosomes. Ribosomal subunits are also probably linked together by magnesium ion(s) to form the basic ribosome. The probable mechanism is that the divalent magnesium ion decreases the electrostatic repulsion between the subunits and makes adhesion possible. The 70 S ribosomes of *E. coli* bind or contain three times as much magnesium when the magnesium concentration of the medium is 10^{-2} mol/kg than when it is only 10^{-4} mol/kg. In the latter case, the ribosomes are dissociated to 30 S and 50 S subunits. Figure 3.10 shows changes in the ratio of the 70 S ribosomes and the 30 S and 50 S subunits as a function of magnesium concentration (Subramanian et al., 1968).

Magnesium in ribosomes may participate in two different bonds. Loosely bound magnesium (ca. one-third of the total) may be exchanged by dialysis, while the rest

may not. Non-dialysable, tightly bound magnesium is probably attached to RNA and links it to proteins, while dialysable magnesium is necessary for the adhesion of subunits.

Ricciardi et al. (1974) found that the older the cell, the lower the protein synthesis, even though the number of ribosomes was unchanged. However, while 80% of the ribosomes are polymerized in young cells, in older cells the corresponding value is only 10–15%. Kiss (1988) considers that the reason for this is that in old cells the magnesium level is lower, which may bring about depolymerization. He proved this assumption by treating (spraying) old cells (leaves) with magnesium, which restored protein synthesis. This was indicated by a larger increase in the amount of proteins of small molecular mass than in total protein content. Hence it may be supposed that magnesium treatment increased (restored) the polymerized state of the ribosomes. This result indirectly indicates the rejuvenating effect of magnesium and its power to maintain the juvenile state.

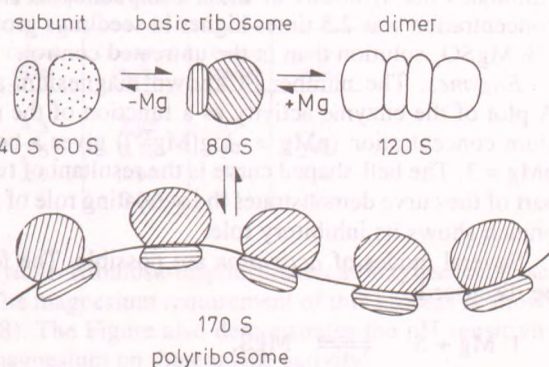


Fig. 3.9. The effects of magnesium on the association of ribosome subunits (Palade, 1955)

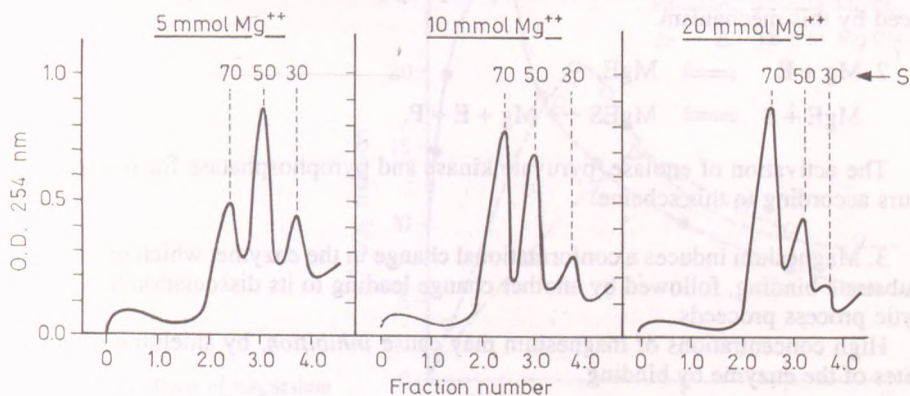


Fig. 3.10. Inhibition of the dissociation of ribosomes by increasing magnesium concentration (Subramanian et al., 1968)

The effects of magnesium on hormones and enzymes

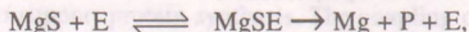
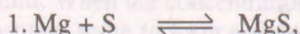
Magnesium exerts its effects on plant hormones and enzymes in two different ways: it stimulates their *de novo* synthesis and increases or inhibits their activity. In this section, some examples for such effects will be discussed.

Gibberellins. Magnesium stimulates the *de novo* synthesis of gibberellins. According to Lang (1970), the first steps of synthesis require magnesium and ATP. The process of ring closure is especially energy-intensive. This explains why more gibberellins were detected in wheat seedlings obtained from wheat seeds treated with magnesium than in the untreated control (Kiss, 1977). The effects of magnesium in bringing about elongation and inducing flowering of long-day plants under short-day conditions is explained at least partially by the stimulation of gibberellin synthesis (Kiss, 1977).

Auxins. Auxins are the other major group of growth hormones. Magnesium also stimulates the synthesis of these compounds as shown by Kiss (1980a): the auxin concentration was 2.5 times higher in seedlings grown from wheat seeds treated with 1% MgSO_4 solution than in the untreated control.

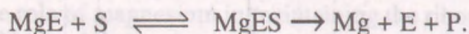
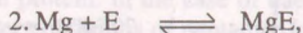
Enzymes. The number of known magnesium-activated enzymes is about 360. A plot of the enzyme activity as a function of the negative logarithm of the magnesium concentration ($\text{pMg} = -\log[\text{Mg}^{2+}]$) gives a bell-shaped curve with optimum at $\text{pMg} = 3$. The bell-shaped curve is the resultant of two sigmoid curves. The ascending part of the curve demonstrates the activating role of magnesium, while the descending branch shows its inhibitory role.

Several modes of *activation* are possible. The following most frequent ones will be discussed:



where S = substrate, E = enzyme and P = product.

The activation of hydrokinase and phosphoglycerate kinase is presumed to proceed by this mechanism.



The activation of enolase, pyruvate kinase and pyrophosphatase for instance, occurs according to this scheme.

3. Magnesium induces a conformational change in the enzyme, which gives rise to substrate binding, followed by another change leading to its dissociation as the catalytic process proceeds.

High concentrations of magnesium may cause *inhibition*, by shielding the active sites of the enzyme by binding.

The activation of certain enzymes by magnesium and the inhibitory effect of excess magnesium will next be considered.

Catalase. Catalase activity both in leaves and in wheat germs was stimulated by magnesium treatment (dressing, leaf spraying) by 10–70%, depending on the species and on the magnesium concentration (Kiss, 1980b). The significance of this result is that there is a positive correlation between catalase activity and ageing. The decrease in catalase activity triggered by a magnesium deficiency may be the other cause of ageing, in addition to the depolymerization of polyribosomes (Kiss, 1981a). During ageing, not only the catalase activity, but also the chlorophyll and protein contents decrease in leaves, while the peroxidase activity increases. This correlation is well demonstrated by the data shown in Table 3.14 for rice leaves.

Table 3.14. Changes in enzyme activity (catalase and peroxidase), and protein and chlorophyll contents in the course of the senescence of rice leaves, relative to dry mass (Sen et al., 1984)

Age (hour)	Catalase (IU/g)	Chlorophyll (mg/g)	Protein (mg/kg)	Peroxidase (IU/g)
0	4.5	2.95	47	210
48	3.6	2.70	39	290
96	2.0	1.00	32	310
144	1.1	0.30	27	350

Ribulose-bisphosphate-carboxylase. Ribulose-bisphosphate-carboxylase catalyses the first step of sugar synthesis. The magnesium requirement of this process is shown in Fig. 3.11 (Bassham et al., 1968). The Figure also demonstrates the pH sensitivity of the enzyme and the effect of magnesium on the enzyme activity.

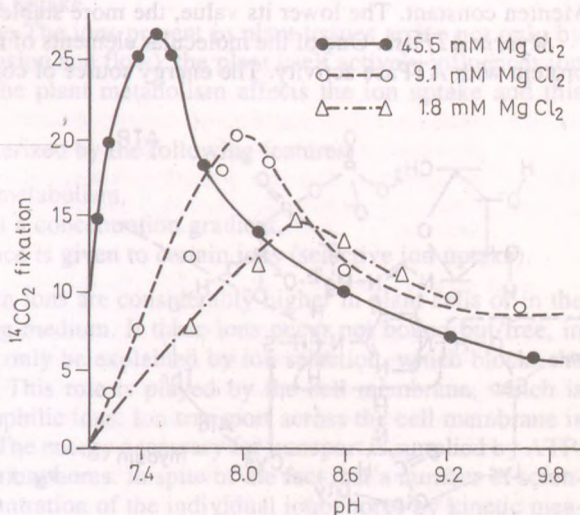


Fig. 3.11. The effects of magnesium supply and pH on the rate of CO₂ fixation (Bassham et al., 1968)

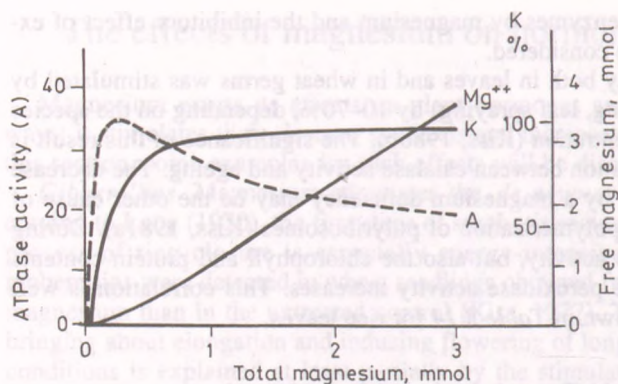


Fig. 3.12. Correlations between ATPase activity (A) and the concentrations of Mg^{2+} and $MgATP^{2-}$ (Fleury et al., 1980) (K = percentage of ATP present in the complex $MgATP^{2-}$)

ATPases. ATP is hydrolysed by various ATPases bound to the surface of the cell membrane. In the absence of magnesium, ATPase does not hydrolyse ATP, since its activity is low. Even small amounts of magnesium (0.1 mmol/dm^3) increase ATPase activity to near maximum, but at higher concentrations magnesium may be inhibitory (Fig. 3.12). Whereas the ATPase activity of the wheat microsome fraction is close to zero in the absence of magnesium, its activity in 0.06 mmol/dm^3 magnesium solution is 70% and at 0.12 mmol/dm^3 it is 83%. The activation of ATPase occurs according to scheme no.1 described under Enzymes, with formation of the complex $MgATP^{2-}$. The increase in activity is related to the formation of this complex (Fig. 3.12, curve K), since the substrate of the enzyme is the complex $MgATP^{2-}$. As the magnesium concentration is increased, besides the complex $MgATP^{2-}$ more and more free magnesium ions are present, which may bind to the active sites of the ATPase and act as a competitive inhibitor. Inhibition (within a certain range) is incomplete, because the magnesium ion has a lower affinity ($K_m = 2.5$) for the active sites of ATPase than does the complex $MgATP^{2-}$ ($K_m = 0.14$) (Fleury et al., 1980). K_m is the Michaelis-Menten constant. The lower its value, the more stable the complex characterized.

Myosin ATPase. One of the molecular elements of muscle contraction is myosin, a protein with ATPase activity. The energy source of contraction is ATP. Although the

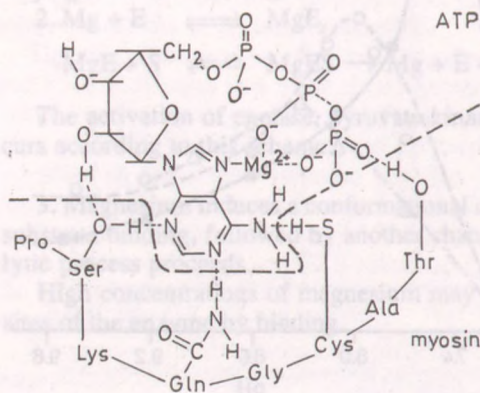


Fig. 3.13. Schematic structure of the complex myosin-Mg-ATP (Elődi, 1983)

mechanism of energy transfer has not been fully elucidated, it has been assumed to proceed via a magnesium complex (*Fig. 3.13*) (Elődi, 1983). It is through the complex interaction of ATP, myosin and magnesium that myosin acquires the extra energy required for muscle contraction. It may be interesting to mention that, although the ATPase activity of myosin is inhibited by magnesium, after combination with actin, resulting in the formation of actomyosin, magnesium increases the ATPase activity of myosin about 200-fold (Elődi, 1983). This phenomenon, just like those mentioned in connection with ribosomes, again points to the intimate relation of structure and function (activity).

Acetylcholinesterase is active only in the presence of magnesium. Its role is to break down acetylcholine continuously to produce choline and acetic acid. If this breakdown is not intensive enough, acetylcholine is accumulated, ultimately leading to serious spasms, cardiac necrosis, etc. Pesticides containing phosphoric acid esters or barium compounds block acetylcholinesterase; their poisoning effect is therefore mostly due to the accumulation of acetylcholine. In the event of such poisoning, it is desirable to include magnesium in the detoxication therapy applied, with the aim of breaking down acetylcholine and reactivating acetylcholinesterase.

The mechanism of magnesium uptake in plants

The uptake of minerals by plants is a much debated problem. It should be noted in advance that the ion uptake mechanism described here is only one of the possible modes of uptake.

The cation absorption theory. Magnesium reaching the surface of the roots is absorbed by ion exchange. The cell walls of the root cortical parenchyma do not present a significant resistance and ions pass into the "free space" or "free cavities" by diffusion. Diffusion is permitted only up to the endoderm; from this point on, ion transport may proceed only by active ion uptake.

The active ion uptake theory. The ions present in plant tissues arrive not only by purely physical processes (diffusion and flow): the plant itself actively influences ion uptake. "Active" means that the plant metabolism affects the ion uptake and this consumes energy.

Active ion uptake is characterized by the following features:

- it is related to the plant metabolism,
- it is also possible against a concentration gradient,
- in ion mixtures, preference is given to certain ions (selective ion uptake).

The concentrations of certain ions are considerably higher in plant cells or in the cell sap than in the surrounding medium. If these ions occur not bound but free, in solution, this phenomenon can only be explained by ion selection, which blocks the outflow of ions from the cell. This role is played by the cell membrane, which is impermeable to inorganic hydrophilic ions. Ion transport across the cell membrane is an energy-consuming process. The energy necessary for transport is supplied by ATP. Ion transport is carried out by ionophores. In spite of the fact that a number of scientists have determined the concentration of the individual ionophores by kinetic mea-

surements, the ionophore itself has not been isolated yet. The reason for this is that only membrane-bound ionophores function normally. No consensus has been reached as to the mechanism of ionophore transport (whether their movement is rotational or hinge-like). There is agreement that ionophores belong among the integrant proteins of the membrane and are ion specific, even though several types of ionophores exist. As an example, the distribution of ionophores in the potassium and magnesium uptake systems of oats is presented as reported by Schuffelen (1974):

- 3% for special uptake of magnesium,
- 30% for special uptake of potassium,
- 67% for common uptake of potassium and magnesium.

The existence of this common ionophore offers an explanation for the antagonism of the potassium and magnesium uptakes. As demonstrated by the data shown, the majority of ionophores (67%) are shared for the transport of the two ions, which means that potassium and magnesium compete for uptake.

The ionophore concentrations of individual plant species or even varieties differ from each other. This is indicated by an observation made on plants propagated by grafting (e.g. grape-vines) at the site between the stock and the graft: the stock is able to take up less magnesium than the amount needed by the graft, which means a magnesium deficiency in spite of a satisfactory supply of magnesium in the soil. The data of Couvillon (1982) demonstrate that trees grafted on their own stock are better supplied by magnesium than are those grafted on a different variety as stock. The magnesium uptake of peach grafts as a function of stock is shown in Table 3.15. Bergmann (1979) obtained similar results when observing symptoms of magnesium deficiency on Jonathan apple grafted on M-IV stock, while Jonathan apple trees on other high-boled stocks did not exhibit such symptoms. As concerns grape-vines, the Chasselas variety is very sensitive to a magnesium deficiency. When grafted on '5-99', '5-C' or 'CO-4' stock, magnesium deficiency symptoms (fruit-stalk necrosis) and consequently reduced yields are to be expected.

Table 3.15. Magnesium content of peach grafts as a function of understock, based on leaf analysis (Couvillon, 1982)

Understock	Graft	Mg (%)	Understock	Graft	Mg (%)
Springold	Springold	0.52	Loring	Loring	0.65
Lovel	Springold	0.46	Siberian	Loring	0.39
Redhaven	Redhaven	0.49	Nemaguard	Loring	0.37
Bailey	Redhaven	0.41	Lovel	Loring	0.34

The differences in the magnesium uptakes of plants as described by Madhok and Walker (1969) are shown in Table 3.16. The Table contains magnesium uptake data for two sunflower species (*Helianthus annuus* and *Helianthus bolanderi* ssp. *exilis*) grown in nutritive solution, at increasing magnesium concentrations. The difference in magnesium uptake is manifested in an increased growth rate (dry mass of shoots). There is a significant difference between the magnesium contents of the individual plants, as revealed in Table 3.28.

Table 3.16. Magnesium uptake of sunflower (*Helianthus*) species as a function of the magnesium concentration of the nutrient medium (Madhok and Walker, 1969)

Mg in medium (mmol)	<i>H. annuus</i>	<i>H. exilis</i>
	Mg (mg/100 g dry mass)	
0.02	83	78
0.05	100	72
0.20	180	106
0.40	250	207
2.00	522	250

The dynamics of magnesium uptake by plants

Besides the quantitation of all nutrient elements in plants, it is also important to know the dynamics of nutrient uptake during the breeding season, since the demands of plants on the nutrient supply of the soil differ in the various phenophases. Knowledge of the dynamics of nutrient uptake opens up the possibility of supplementing nutrient deficiencies (detected, for example, by leaf analysis) at the most appropriate time, in the necessary quantity, by means of foliage spraying, for instance. The first two rows in Table 3.17 show the percentage changes in the magnesium contents of rye and wheat in different phenophases. The magnesium concentrations in wheat and rye are highest at the time of stooling and gradually decrease in the course of the breeding season. This "dilution" is also observed in the ash content. The third and fourth rows in the Table illustrate the seasonal magnesium uptakes of blue-grass and shamrock. It is evident that the magnesium contents of both blue-grass and shamrock increase in the course of the breeding season, in contrast with the decreasing tendency of the magnesium contents of wheat and rye. Since the magnesium content of the studied grass species in early spring is approximately half of the autumn value, it is understandable why grass tetany due to magnesium deficiency occurs mostly in the spring.

In radish and bean the magnesium content describes a maximum curve with increasing age, while in lettuce, rape and maize it is inversely related to age.

The dynamics of the magnesium uptake of grape-vines is illustrated on Fig. 3.14 (Jakab, 1976). It is clearly seen that 34% of the total amount of magnesium is taken up

Table 3.17. Changes in the magnesium content (%) of rye, wheat, blue-grass and white clover in the course of the breeding season

Plant	28 Oct.	17 April	8 May	30 May	16 June	15 July	9 Sept.
Rye 0.28	0.15	0.11	0.08	—	—	—	—
Wheat —	0.28	0.20	0.18	0.16	0.12	—	—
Blue-grass	0.27	0.12	—	0.15	0.21	0.18	0.25
White clover	—	—	—	—	0.23	0.23	0.26

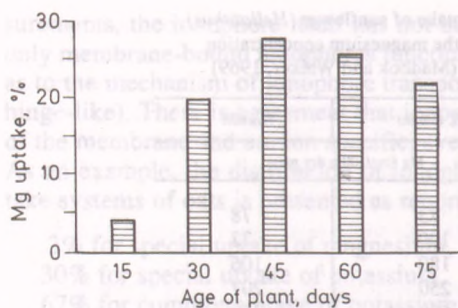


Fig. 3.14. The dynamics of magnesium uptake by grape as a percentage of the total magnesium content (Jakab, 1976)

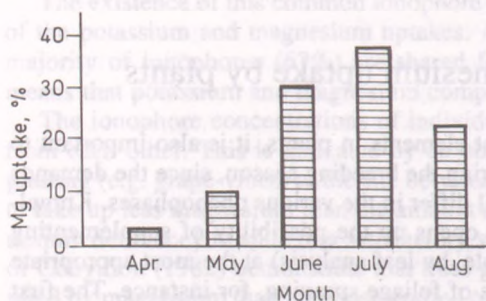


Fig. 3.15. The dynamics of magnesium uptake by cucumber as a percentage of the total magnesium content (Jakab, 1976)

in the month of July and 75% in July and August, during the time of grape development and sugar production. Grape-vines are therefore not characterized by a decreasing magnesium requirement (content).

The dynamics of magnesium uptake by cucumber is shown in Fig. 3.15 (Jakab, 1976). With the exception of the first 2 weeks, cucumber takes up magnesium at a nearly constant rate.

As demonstrated by the above data, the dynamics of the magnesium uptake by plants differs from species to species. Some plants take up more magnesium at the beginning and at the end of the breeding season, while others require a uniform magnesium supply throughout the whole breeding period. The optimal time and amount of magnesium supplementation or foliage spraying should therefore be determined individually for each plant species.

The transport of magnesium in plants

Ion transport takes place in plant tissues specialized for this task: the vascular tissue system. Ions are displaced from the cortical tissue (cortical parenchyma) to the xylem by active transport, for in general the concentrations are considerably higher in the xylem sap than in the solution. After entering the xylem, magnesium is carried to the organs above ground by the transpirational flow. Transport in the xylem is exclu-

sively acropetal. This vertical transport is much faster than transversal transport. The basipetal mobility of magnesium directed towards the roots is considerably less than its acropetal movement towards the apex. The probable reason for this is that magnesium hardly enters the phloem. In this way, magnesium sprayed on the leaves is primarily transported towards the leaf apex, i.e. by the transpirational flow. The basipetal transportation of magnesium or, in the case of a magnesium deficiency, its movement from older parts (leaves) to younger ones is still possible, as demonstrated by the observation that a magnesium deficiency is first manifested in the older, lower leaves. This means that basipetal magnesium flow is also influenced by the magnesium supply.

Schimansky (1973) grew sunflower plants for 14 days in Hoagland solution, and then from day 14 to day 36 in 1/2 Hoagland solution without magnesium. He found that, as compared with the 22-day-old plants, the magnesium content decreased in the older parts, while it increased in the young shoots (Fig. 3.16). These results are direct proof of a basipetal magnesium flow and of a flow from older to younger parts of the plant under conditions of magnesium deficiency. The age dependence of magnesium uptake by sunflower was also studied by Schimansky, whose measurements of radioactive magnesium uptake showed that the degree of magnesium uptake depends on both age and organ. 23, 34 and 40-day-old plants exhibited uptakes of 48.11, 50.74 and 30.51×10^4 cpm/10 g fresh mass, respectively, indicating a higher ^{28}Mg uptake by 23 and 34-day-old plants, which were in a phase of more intensive growth. In all cases, the magnesium uptake was higher in young shoots. These measurements confirm that at times of intensive growth, when protein synthesis is enhanced, the magnesium requirement increases.

During the discussion of the theory of ion uptake, it was mentioned that all processes have an optimal temperature. It is understandable, therefore, that ion uptake also depends on temperature. Experiments in this respect showed that higher temperatures are more disadvantageous than lower ones for the development and cation content of plants. The decrease in cation content affected plant growth and decreased the gain in mass.

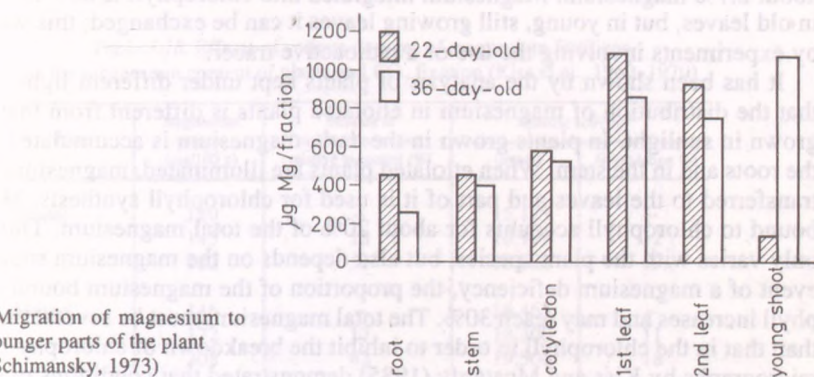


Fig. 3.16. Migration of magnesium to the younger parts of the plant (Schimansky, 1973)

The outwash of magnesium from plants

The process opposite to uptake is outwash. Rainwater is able to wash out a certain amount of magnesium from leaves and fruits. The extent of such outwash depends on the solubility of the magnesium compounds in the plants and on the duration of the outwash.

Some of the magnesium in plants is in a bound form (bound to proteins, pectin, phytin, etc.) while another part is soluble in water. As compared with other ions present in plants, magnesium exhibits intermediate solubility (Fe, Ca, Mg, P and K). Since magnesium is one of the moderately outwashed elements (i.e. it is more difficult to wash out than potassium), its outwash is less significant than that of potassium.

The experiments of Kiss (1984a) showed that MgSO_4 sprayed on sorrel plants is absorbed within a short period of time (5–7 hours) and most of it gets bound to proteins. This is supported by the observation that exogenous magnesium taken up in this way is washed out at the same rate as original (endogenous) magnesium. Rousselet and Durlach (1971) suggest that this occurs because magnesium forms complexes with proteins in reactions leading to equilibrium. The equilibrium is shifted towards the complexes, as indicated by the equilibrium constant of $K = 33.77$ (Copeland and Sunderman, 1952).

The role of magnesium in photosynthesis

Magnesium plays two different roles in photosynthesis. One of these is generally known: magnesium is an essential structural part of the chlorophyll molecule. The functional importance of magnesium is proved by the observation that, if it is exchanged for another atom, e.g. copper, the resulting molecule is inactive; to put it another way: only magnesium porphyrin is active. The other, non-structural role of magnesium is independent of chlorophyll: magnesium is a cofactor of enzymes. These two functions do not exclude each other, but are complementary.

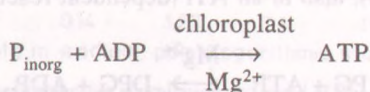
There are several types of chlorophyll molecules (a, b and c) and they contain about 2.7% magnesium. Magnesium integrated into chlorophyll is non-exchangeable in old leaves, but in young, still growing leaves it can be exchanged; this was verified by experiments involving the use of a radioactive tracer.

It has been shown by the analysis of plants kept under different light conditions that the distribution of magnesium in etiolated plants is different from that in plants grown in sunlight. In plants grown in the dark, magnesium is accumulated mostly in the roots and in the stem. When etiolated plants are illuminated, magnesium is rapidly transferred to the leaves and part of it is used for chlorophyll synthesis. Magnesium bound to chlorophyll accounts for about 20% of the total magnesium. This ratio not only varies with the plant species, but also depends on the magnesium supply. In the event of a magnesium deficiency, the proportion of the magnesium bound in chlorophyll increases and may reach 30%. The total magnesium must be several times higher than that in the chlorophyll in order to inhibit the breakdown of chlorophyll. Electron micrographs by Kiss and Mustárdy (1985) demonstrated that conditions of decreased magnesium supply lead to a gradual deterioration of the plastid structure, and conse-

quently CO_2 fixation and O_2 production are impaired. Chlorophyll molecules readily dimerize to form aggregates when the magnesium concentration of the medium is appropriate. The carbonyl group in one molecule is hydrogen-bounded to the water molecule coordinated to the magnesium in a second chlorophyll molecule thereby contributing to membrane coherence (cf. complexes).

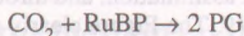
After the role of magnesium integrated in chlorophyll, let us now examine how "free" magnesium ions affect photosynthesis. It has been proved by means of CO_2 -fixation experiments (Kiss et al., 1960–1970) that magnesium enhances photosynthesis apart from increasing the chlorophyll content. Table 3.18 shows the effect on CO_2 fixation if the magnesium content of plants is increased by magnesium fertilization. These data unambiguously demonstrate that magnesium enhances CO_2 fixation.

The effect of magnesium on CO_2 fixation is explained by magnesium stimulating the incorporation of inorganic phosphorus into ADP in such a way that ATP is formed at the expense of the light energy absorbed by chlorophyll:



The amount of ATP formed is strongly dependent on the magnesium concentration, as illustrated in Fig. 3.17.

Carbon dioxide is fixed with the help of ribulose biphosphate (RuBP) and two molecules of phosphoglycerate are formed:



RuBP is generated in the reductive pentose cycle (Calvin cycle), in a reaction in which the terminal phosphate of ATP is transferred to ribulose monophosphate (RuMP) with the help of magnesium:

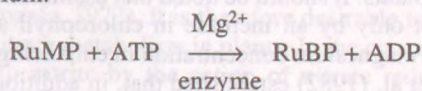


Table 3.18. Effects of various dosages of magnesium fertilizer on the magnesium content of plants and CO_2 fixation (Kiss et al., 1960–1970)

Plant	Magnesium content (mg/100 g)	Increase in magnesium content relative to control (%)	Specific activity*	
			(imp/s)	(stimulation %)
Wheat	120	—	15,129	—
	143	18	16,999	12
	182	51	18,022	19
Maize	146	—	16,463	—
	172	17	18,300	11
	208	42	19,500	18

* Value proportional to $^{14}\text{CO}_2$ fixed by 1 g of chlorophyll.

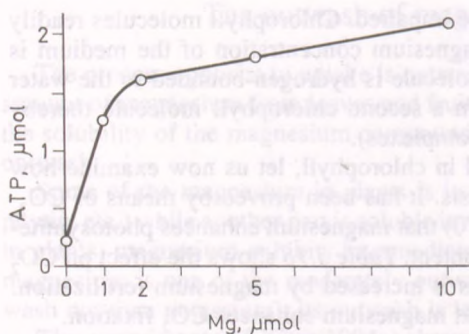
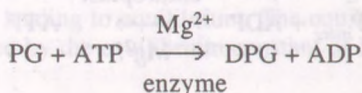


Fig. 3.17. The effects of magnesium on ATP synthesis (Mudd, 1959)

In a later stage of the Calvin cycle, 3-phosphoglycerate (PG) is turned into 1,3-diphosphoglycerate (DPG), also in an ATP-dependent reaction and with the help of magnesium:



The dependence of the above CO_2 assimilation on magnesium is depicted in Fig. 3.18. This activity curve virtually coincides with the curve relating to the stimulation of ATP formation, suggesting a correlation between the two.

The effects of magnesium on assimilation, and through assimilation on the yield of dry mass, are shown in Fig. 3.19. The Figure clearly reveals that, as the magnesium content of barley leaves increases, the net assimilation and the accumulation of dry mass also increase (within certain limits). This Figure summarizes the effect of magnesium on chlorophyll, on assimilation and (through the latter) on the overall organic matter production by plants. It should be noted that assimilation and dry mass production are promoted not only by an increase in chlorophyll activity, but also by the action of an increased magnesium concentration in enhancing the chlorophyll content (Kiss, 1983). Stanev et al. (1982) established that, in addition to its effect in increas-

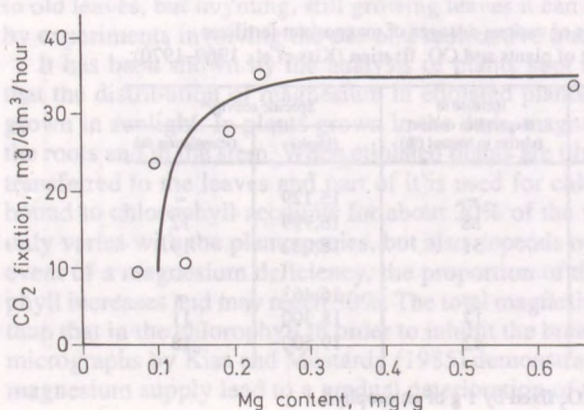


Fig. 3.18. Correlation between the magnesium content of maize leaves and CO_2 assimilation (Kirkby and Mengel, 1976)

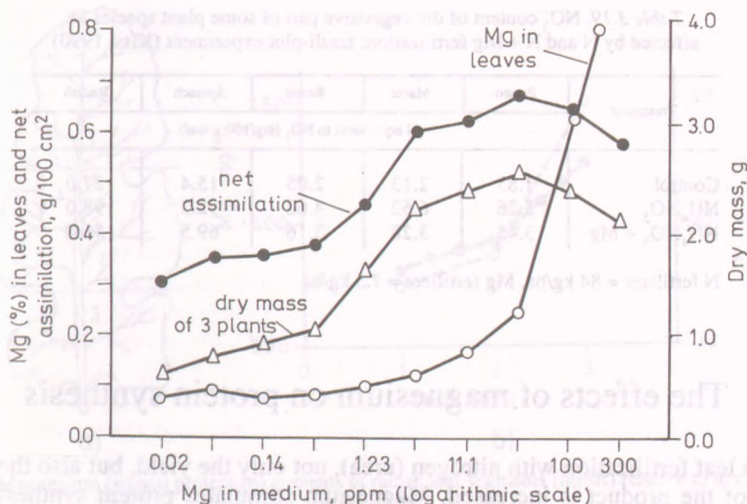


Fig. 3.19. The effects of magnesium on net assimilation and yield of dry mass by barley (Neales, 1955)

ing CO_2 fixation, magnesium also decreased the intensity of respiration, and offered this phenomenon as an explanation for the increase in organic matter production by magnesium.

The effects of magnesium on the nitrate level

Relatively high nitrate and nitrite contents in human food and animal fodder are deleterious because of the danger they present as methaemoglobinaemic and carcinogenic agents (Kiss and Pozsár, 1977). It is therefore desirable to decrease nitrate levels and to stimulate the nitrate metabolism in plants. In the course of the latter process nitrate is first reduced to nitrite by the action of nitrate reductase, with reduced coenzymes NADH and NADPH as H^+ -donors. Nitrite is further reduced by nitrite reductase in an energy-consuming process.

In the studies of Kiss (1973), the nitrate content of plants was increased by N-fertilization, whereas magnesium supplementation decreased the nitrate content at an identical dose of nitrogen (Table 3.19). With increasing age, the nitrate content increases due to the natural decay of nitrate reductase activity, but even then the favourable effect of magnesium prevails (Kiss, 1990).

The decrease of nitrate level by magnesium indicates that magnesium exerts some kind of influence on the nitrate metabolism. Magnesium has no direct effect on the activity of nitrate reductase; it affects nitrate reduction only indirectly. Some of the indirect pathways are as follows: a) stimulation of photosynthesis (ATP and NADPH), b) via the ribosomes (enzyme synthesis), c) stimulation of gibberellin synthesis. All these effects increase the *de novo* synthesis and therefore the activity of nitrate reductase. In these ways magnesium indirectly decreases deleterious nitrate levels.

Table 3.19. NO_3^- content of the vegetative part of some plant species as affected by N and N + Mg fertilization; small-plot experiment (Kiss, 1990)

Treatment	Potato	Maize	Beans	Spinach	Radish
	N equivalent to NO_3^- (mg/100 g leaf)				
Control	1.83	2.13	2.05	15.4	27.0
NH_4NO_3	5.26	6.62	4.62	92.3	98.0
$\text{NH}_4\text{NO}_3 + \text{Mg}$	3.45	3.28	3.16	69.5	56.0

N fertilizer = 84 kg/ha, Mg fertilizer = 7.5 kg/ha

The effects of magnesium on protein synthesis

Upon leaf fertilization with nitrogen (urea), not only the yield, but also the protein content of the product is increased. Magnesium stimulates protein synthesis by its action on ribosomes and enzymes. It was therefore supposed that leaf fertilization combining urea and magnesium should produce an even more intensive increase in protein synthesis. The joint effect of nitrogen and magnesium in increasing protein content was studied in millet and peas (Kiss and Pozsár, 1975). Plants from two very different families were chosen because different species react to leaf fertilization in very dissimilar ways. The results of these experiments unambiguously confirmed the effect of magnesium in stimulating protein synthesis: the actual protein content of peas was increased 5-fold, and that of millet 2-fold by treatment with magnesium, as compared with the effect of the control treatment with nitrogen (urea) only. Kirkby and Mengel (1976) observed an unambiguous correlation between protein synthesis and magnesium supply both in the stem and in the roots.

The studies of Kiss (1975) disclosed that the magnesium contents of the various parts of plants differ even within relatively short distances, as demonstrated by leaf sections excised from the leaf blades of various vegetable plants. The results of mag-

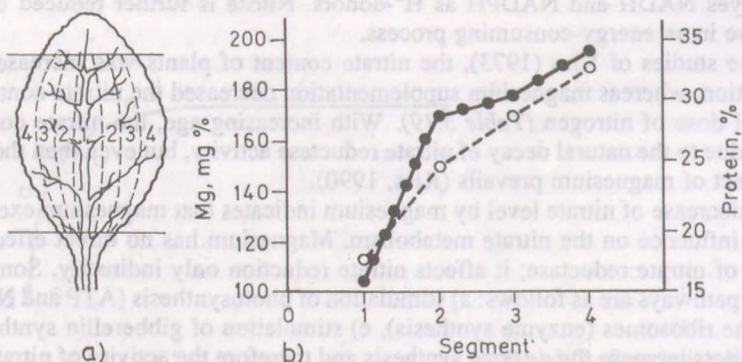


Fig. 3.20. Magnesium (●) and protein (○) contents of Brussels sprouts leaf segments relative to dry material (Kiss, 1975)

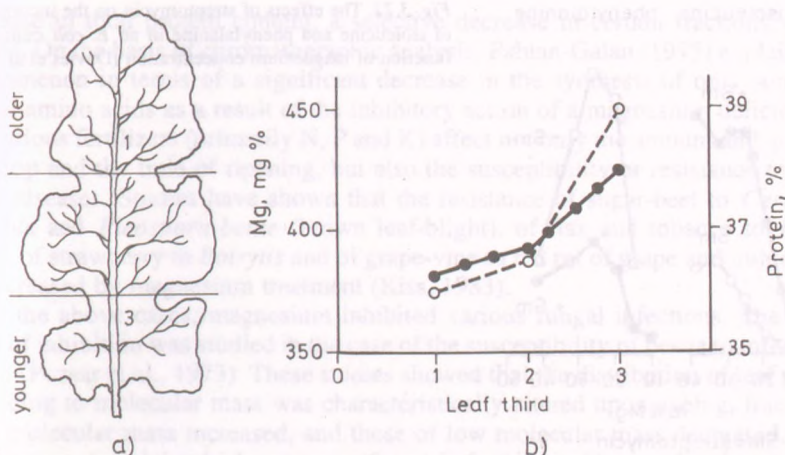


Fig. 3.21. Magnesium (●) and protein (○) contents of radish leaf segments (thirds) relative to dry material (Kiss, 1975)

nesium and protein analyses of Brussels sprouts leaf sections are shown in Fig. 3.20, and those of radish leaf segments on Fig. 3.21. These data draw attention to the fact that, at a location of higher protein concentration, the magnesium content is also higher. Similar results were reported by Repka and Jurenková (1981) for maize leaves.

Magnesium-dependent misincorporation of amino acids

The magnesium induced incorrect incorporation of amino acids was investigated by Szer and Ochoa (1964) in a cell-free system, using a synthetic polynucleotide (UUU) containing only uridylic acid (U). When solutions containing identical concentrations of phenylalanine, isoleucine and tyrosine were mixed, an increased magnesium concentration led to all three amino acids being incorporated into the polypeptide synthesized, though in different ratios (Table 3.20). Albeit poly-U (UUU) encodes phenylalanine, the incorporation of leucine encoded by codons UUA and UUG

Table 3.20. The effect of the magnesium concentration on the incorporation of some amino acids into polypeptides in the presence of poly-U (UUU) (Szer and Ochoa, 1964)

Magnesium concentration (mmol/dm ³)	Phenylalanine	Isoleucine	Tyrosine
14	23.5	0.002	0
28	15.3	0.505	0.028

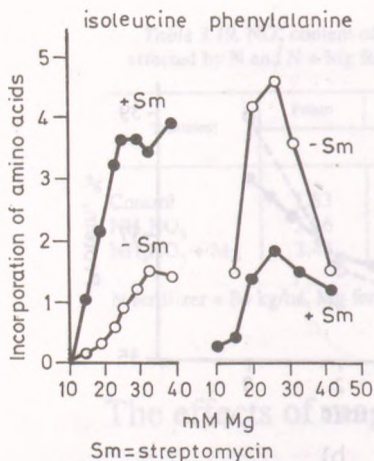


Fig. 3.22. The effects of streptomycin on the incorporation of isoleucine and phenylalanine in an *E. coli* culture as a function of magnesium concentration (Davies et al., 1964)

of isoleucine encoded by AUU, AUC and AUA, and of tyrosine encoded by UAU and UAC is also possible at higher magnesium concentrations. It seems that at higher concentrations of magnesium rRNAs read UUU as UUA, AUU or UAU, i.e. they misread. This reading error, due to higher-than-optimal magnesium concentrations, will result in faulty polypeptide (protein) synthesis. Depending on the importance of its function, the imperfect protein generated may cause the disease or the death of the organism, e.g. in the case of haemoglobin S (Hb-S), where the disease (sickle-cell anaemia) is caused by the incorrect incorporation of a single amino acid (Durlach, 1985).

Protein synthesis is also strongly influenced by temperature. In general, at identical magnesium concentrations, the incorrect incorporation of amino acids occurs more often as the temperature rises (Szer and Ochoa, 1964).

It should be noted that the experiments described above, demonstrating the ability of magnesium to cause misreading were performed *in vitro*, in a cell-free medium. An enrichment of magnesium such as to present a source of error does not occur *in vivo* under normal conditions; however, it may be brought about in plants by intensive foliage spraying with magnesium or in humans or animals by renal failure.

The studies of Davies et al. (1964) on the action of streptomycin are very instructive. Using ribosome fractions of *E. coli*, these authors established that magnesium and streptomycin had a joint effect on the incorporation of amino acids. As the magnesium concentration was increased, streptomycin increased the incorporation of isoleucine several-fold, while it decreased the incorporation of phenylalanine (Fig. 3.22). In this way, very many errors could occur, which might kill the host (bacterium). Since the antibiotic effect of streptomycin is exactly this, i.e. the synthesis of proteins with erroneous amino acid composition, the presence of magnesium will even enhance this effect. It may therefore be concluded that a magnesium deficiency decreases the effectivity of certain antibiotics.

Kuderev and Babulka (1975) studied the soluble proteins of maize poorly supplied with magnesium and found that not all the protein fractions decreased: within the

decrease in total protein content, a selective decrease in certain fractions was observed. On the basis of chromatographic analysis, Fabian-Galau (1975) explained this phenomenon in terms of a significant decrease in the synthesis of only some individual amino acids as a result of the inhibitory action of a magnesium deficiency.

Various fertilizers (primarily N, P and K) affect not only the amount and quality of the crop and the time of ripening, but also the susceptibility or resistance to certain plant diseases. Studies have shown that the resistance of sugar-beet to *Cercospora beticola* and *Pleospora betae* (brown leaf-blight), of flax and tobacco to *Phytophthora* fungi, of strawberry to *Botrytis* and of grape-vine to red rot of grape and mildew were all increased by magnesium treatment (Kiss, 1983).

In the above cases, magnesium inhibited various fungal infections. The mechanism of inhibition was studied in the case of the susceptibility of beans to infection by blight (Pozsár et al., 1973). These studies showed that the distribution of leaf proteins according to molecular mass was characteristically altered upon ageing: fractions of high molecular mass increased, and those of low molecular mass decreased. Young bean leaves containing high amounts of protein fractions of low molecular mass were less susceptible to infections than older leaves with large amounts of high molecular mass proteins. It may be supposed that the amount of low molecular mass (soluble) protein fractions is positively correlated with the active fractions identified by immunological techniques.

The protein content of plants always increases upon magnesium treatment (fertilization), but this fact alone is not sufficient proof of an increased resistance. The changes in protein fractions were therefore measured in lettuce leaves 24 hours after spraying with magnesium sulphate. The results are shown in Table 3.21 (Kiss and

Table 3.21. Changes in the protein and magnesium contents of lettuce leaves in response to magnesium fertilization, relative to dry mass (Kiss and Pozsár, 1977)

Treatment	Magnesium content (mg/100 g)	Total protein		Soluble protein	
		(%)	(stimulation %)	(%)	(stimulation %)
Control	490	34.4	—	12.9	—
MgSO ₄	530	36.2	6.5	14.3	11.6

Table 3.22. Percentage infectability of tobacco by *Peronospora tabac* as a function of tobacco variety and foliage spraying with Mg(NO₃)₂ (Schiltz and Coussairat, 1978)

Variety	Control	Spraying with Mg(NO ₃) ₂ (mg/dm ²)			
		750	1000	1500	2000
P 48	98	97	76	81	71
Florida 513	95	79	58	22	6
Bel 61-70	90	59	32	11	2

Pozsár, 1977). The level of low molecular mass (soluble) fractions increased to a much higher extent than did the total protein content. Leaf fertilization with magnesium resulted in similar increases in protein synthesis in peas and millet (Kiss and Pozsár, 1975).

These experimental results unambiguously proved the rejuvenating effect of magnesium through the stimulation of protein synthesis, this resulting in an increase in resistance. This is in accord with the observation of Gilly and Király (1980), i.e. that juvenility induced by plant hormones increased resistance to facultative parasites causing leaf necrosis in plants, while induced senescence had the opposite effect.

Schiltz and Coussairat (1978) studied the changes in the resistance of tobacco to *Peronospora tabacina* in response to leaf fertilization with magnesium. They used three varieties with different genetic resistances as plant indicators: P 48 (sensitive), Florida 513 (moderately resistant) and Bel 61-70 (highly resistant). The experimental results are shown in Table 3.22. It is clear that the infectability is negatively correlated with both resistance and magnesium concentration. These results are in agreement with the above-mentioned hypothesis by Kiss and Pozsár (1977) on *de novo* protein synthesis and juvenility.

Magnesium and nucleic acid synthesis

The N-bases present in the building blocks of nucleic acids, i.e. in nucleotides, are purine and pyrimidine derivatives. The biosynthesis of the two most important purine bases (adenine and guanine) starts out from ribose-5-phosphate and proceeds through about 14 enzyme reactions. Nearly half of these reactions require magnesium. Pyrimidine bases (thymine, cytosine and uracil) are synthesized in 7 steps, starting from guanine and asparagine. The synthesis of pyrimidine bases, although requiring less magnesium than purine synthesis, does not proceed in the absence of magnesium.

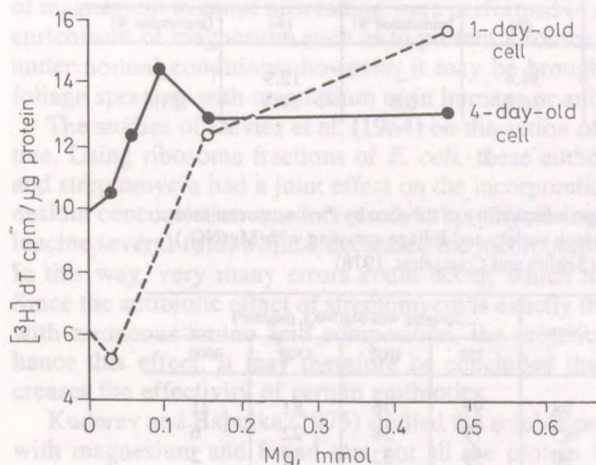


Fig. 3.23. The effect of magnesium on the incorporation of thymidine (dT) into DNA (Rubin, 1975)

Table 3.23. The effects of gibberellins (GS) and auxins on RNA synthesis in coconut milk (Roychondhury et al., 1969)

Location of RNA	Treatment		
	0	GS	Auxin
Nucleus (cpm)	15,800	32,400	30,100
Cytoplasm (cpm)	91,000	145,000	141,000

The dependence of DNA synthesis on the magnesium concentration is illustrated by Fig. 3.23 (Rubin, 1975), which shows the incorporation of tritiated thymidine into DNA in two cells of different ages. The stimulatory effect of magnesium is evident.

In addition to its direct effect on the synthesis of RNA in plants, magnesium also has an indirect effect by stimulating gibberellin and auxin synthesis. Table 3.23 exemplifies the effects of gibberellins and auxin (as indirect magnesium effect) on RNA synthesis, measured by ^{32}P incorporation in coconut milk substrate (Roychondhury et al., 1969).

Nucleotide synthesis may proceed not only with magnesium, but also with other divalent cations, e.g. Be^{2+} , Cd^{2+} , Co^{2+} or Ni^{2+} , but in these cases the resulting structure is different: incorrect RNA is obtained. This is one of the reasons why heavy metals have mutagenic and carcinogenic effects.

Magnesium is necessary not only for nucleotide synthesis, but also for the stability and therefore the function of nucleic acids. Under natural conditions, DNA assumes the double helix structure. If the two strands of the helix are separated by heat treatment, reannealing is possible only in a medium containing cations. The stabilizing effect of divalent cations is considerably higher than that of monovalent ones. The fact that copper ions decrease the stability of the double helix suggests that magnesium and copper bind to different sites. It is supposed that magnesium binds to the phosphate groups of DNA and thereby stabilizes its structure. Copper, however, binds to the N-bases via hydrogen-bonding and in this way causes destabilization. The sequence of divalent cations with respect to their influence on DNA stability is as follows: $\text{Mg}^{2+} > \text{Co}^{2+} > \text{Ni}^{2+} > \text{Mn}^{2+} > \text{Zn}^{2+} > \text{Cd}^{2+} > \text{Cu}^{2+}$. Whereas magnesium is an excellent stabilizer, copper already has a destabilizing effect (Eichorn, 1962).

Magnesium also has a favourable effect on the structure of RNA. Various cations influence the stability of the RNA structure in different ways. Here too, magnesium and copper represent the two extremes of stabilization.

Appropriate concentrations of magnesium are therefore indispensable for the synthesis and structural stability of both DNA and RNA.

Nucleotides are not only the building blocks of nucleic acids (DNA and RNA), they also make up the mono- (ATP, ADP, etc.) and dinucleotides (NAD and NADP) present in all living cells in "free" form. Magnesium therefore plays a further role in the synthesis of these compounds, as described above.

NAD (nicotinamide-adenine-dinucleotide) and NADP (nicotinamide-adenine-dinucleotide phosphate) are two important coenzymes of oxidative phosphorylation. Both are pyridine nucleotides. They are found in cells in both their reduced (NADH and NADPH) and oxidized (NAD) forms. There are more dinucleotides in animal cells than in plant cells, which may be related to the relative "slowness" of the plant

metabolism. The combined amount of NAD+NADH in all cells exceeds that of NADP+NADPH several-fold.

The oxidation of NADH and NADPH requires magnesium. This was proved by Moller et al. (1982) in mitochondria from *Neurospora crassa*. Besides the magnesium sensitivity, they also studied the pH dependence (Fig. 3.24).

Figure 3.24 (part A) shows that the pH optimum of NADH oxidation under conditions of good magnesium supply is 7.0; this changes to 6.5 in a magnesium deficiency, while at the same time the activity decreases by ca. 40%. Maximal inhibition by pH (65%) occurred at pH 7.2 (Fig. 3.24, part C). Similar values were measured in mitochondria of higher plants (Moller et al., 1982).

Part B of Fig. 3.24 depicts the oxidation of NADPH. The pH optimum of this process at a good magnesium supply is 7.75, which changes to 7.0 at a magnesium deficiency, with a concomitant loss in activity by ca. 35%. The oxidation of NADPH ceases at pH=8 (cf. Fig. 3.24, part C). The pH optima for NADPH are one unit higher than those measured for the mitochondria of higher plants.

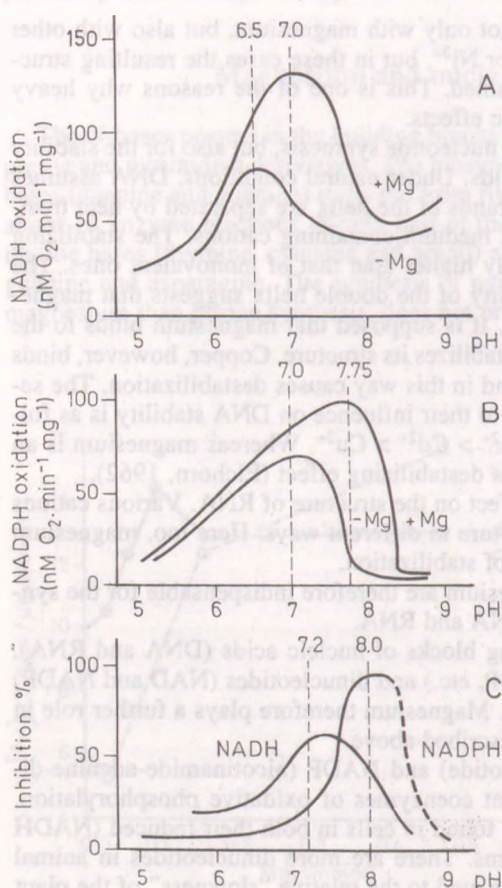


Fig. 3.24. pH and magnesium dependence of the oxidation of NAD(P)H (Moller et al., 1982)

The absence of calcium ions also inhibits the oxidation of NADPH, but this effect can be countered by increasing the concentration of magnesium ions.

It is clear from what was said above that the rates of oxidation of NADH and NADPH are dependent upon pH and magnesium concentration. In a magnesium deficiency, the rates of oxidation of these compounds decrease by nearly 50% and the pH optimum shifts towards the acidic region.

The effects of magnesium on membranes

In living cells, the fundamental processes of life take place in spaces bordered by membranes. Cell membranes vary widely in composition; in general, they contain 40–60% of lipids, 30–50% of proteins and about 10% of carbohydrates. Although chemical composition plays a role in membrane function, it is the linkage of the molecules, i.e. the membrane structure, that is most important.

The basic membrane structure is a lipid bilayer, in which the lipid molecules rotate along their own longitudinal axis; on the other hand, the fatty acid moieties of lipid molecules carry out a “meandering” motion; the integrant proteins are able to diffuse laterally (Ligeti, 1980). The state (fluidity) of the membrane depends on the composition of the lipid bilayer, and in general on the phospholipid:cholesterol ratio. If the ratio of cholesterol and its derivatives is increased, the membrane fluidity decreases. As the fluidity is reduced, the membrane becomes more and more rigid. The rigidity of membranes is increased if the proportion of saturated fatty acids is increased or if the protein:lipid ratio is shifted towards the proteins, since proteins are known to increase the ordered state of the lipid layer in membranes.

The direct effect of magnesium in stabilizing membranes is manifested in an increase in membrane permeability for K^+ , Na^+ and Ca^{2+} as the magnesium content is decreased. Conversely, upon increase of the magnesium concentration, the calcium uptake of the mitochondria decreases.

Studies on mitochondria have shown that magnesium ions are bound on the membrane surface, on phospholipids, and the binding is saturated at a magnesium concentration of 5 mmol/kg. The distribution of magnesium within the mitochondria is not

Table 3.24. The effects of magnesium treatment on the uptakes of NO_3^- and PO_4^{3-} as measured on the basis of the nitrogen and phosphorus contents of plants* (Kiss, 1989a)

Plant and treatment	Magnesium content		Nitrogen content		Phosphorus content	
	(%)	(Δ%)	(%)	(Δ%)	(%)	(Δ%)
Lettuce						
Control	0.23	—	3.23	—	—	—
Mg through root	0.26	13	4.12	28	—	—
Mg through leaves	0.28	22	4.28	32	—	—
Potato						
Control	0.18	—	—	—	0.42	—
Mg-fertilizer	0.22	21	—	—	0.52	42

* Nitrate and phosphate fertilizers were used.

Table 3.25. The effect of magnesium fertilization on the yield as a function of species and variety (Kiss, 1983)

Plant	Yield (pc)			Yield (mass, g)		
	control	magnesium-treated	Δ%	control	magnesium-treated	Δ%
<i>Wheat</i> (grains/ear)						
Fertődi	22.5	25.6	13.7	0.92	1.17	27.1
Kavkaz	30.6	31.4	2.6	1.32	1.62	25.0
Mv1	23.7	30.0	26.6	1.04	1.35	30.1
<i>Peas</i> (pods/plant)						
Budai	4.9	5.9	20.4	7.3	9.3	27.4
Express	4.1	4.6	12.2	4.8	5.5	14.6
<i>Beans</i> (pods/plant)	54.4	69.7	28.1	14.7	18.7	27.2
<i>Flax</i> (capsule/plant)	37.3	41.7	11.8	—	—	—
<i>Paprika</i> (fruits/plant)						
Cecei	12.2	13.1	6.7	226	232	26.0
Apple-shaped	10.2	14.1	36.3	184	265	44.4
PCR	15.3	16.9	14.4	370	424	10.8
Rekord	24.4	32.2	31.6	276	337	22.1
<i>Tomato</i> (berries/plant)						
Harow	24.3	24.9	2.4	1526	1746	14.5
K-stiff stem	13.1	17.9	36.1	637	859	34.9
Heterosis	23.8	27.6	15.7	1271	1289	1.4

The effects of magnesium on crop quantity and quality

Besides the genotype, the crop quantity and quality are strongly affected by the nutrition. It therefore follows that an increasing magnesium supply should lead to an increase in the quantity of the crop. Table 3.25 illustrates the effects of magnesium on the crop elements of several plant species (Kiss, 1983). For some species, several varieties were tested in order to demonstrate the wide range of the effect of magne-

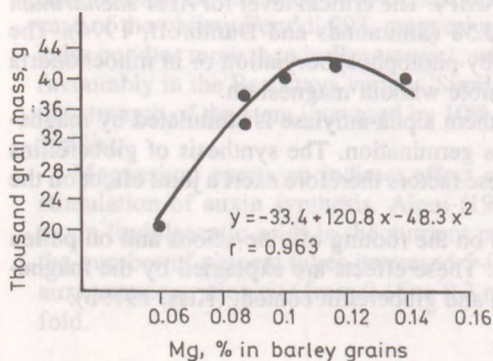


Fig. 3.25. Correlation of the magnesium content of barley and the thousand grain mass (Beringer and Forster, 1981)

Table 3.26. The effects of magnesium fertilization on the contents of various compounds in plants (Jacob, 1955)

Plant and compound studied	Untreated	Treated with magnesium
<i>Potato</i>		
Starch (% dry mass)	13.5	14.0
Citric acid (% dry mass)	1.6	2.1
Vitamin C (IU)	21.0	23.0
<i>Spinach</i>		
Vitamin C (mg/100 g)	190.0	510.0
Carotene (mg/100 g)	15.0	58.0
<i>Sugar beet</i>		
Sugar (%)	14.2	16.6

sium and its dependence on the variety. In the Table, yields are given per ear of wheat. The difference between the yields of control and magnesium-treated plants was manifested not in the length of the ears but in the number of grains per ear.

Beringer and Forster (1981) carried out a fertilization experiment with magnesium on barley and found that the numbers of ears and grains and also the grain mass increased in parallel with the magnesium content (Fig. 3.25).

Table 3.25 lists the numbers and masses of pods per plant for beans and peas. The increase in the mass of pods per plant in response to magnesium treatment is related not only to the higher pod number, but also to the development of more seeds per pod. For one tomato variety, the increase in yield was mostly due to the increase in fruit size, while in another variety the number of berries increased more than did their mass.

Besides influencing yields, magnesium also has a considerable effect on crop quality (content), as may be seen in Table 3.26 (Jacob, 1955). Pfützer et al. (1952) established that a magnesium deficiency inhibited vitamin synthesis. The results published by Fecencko and Francaková (1979) demonstrated that magnesium fertilization increased the starch content and decreased the protein content of malting barley. Both changes resulted in improved quality.

Experience relating to *sugar beet* production revealed that increasing fertilization with nitrogen improved the yield, but the sugar content of the root decreased. The accumulating nitrate stimulated the metabolism and drew off more energy (ATP) from sugar synthesis. However, when nitrogen was administered together with magnesium, both the yield and the sugar content of sugar beet increased. The studies of Ebert (1967) verified the favourable effects of magnesium on the harvest result and on the sugar content (Fig. 3.26) and the decrease in the negative effect of nitrogen.

Magnesium increases sugar content not only by enhancing the amounts of chlorophyll and ATP, but also by stimulating the transport of sugar from the leaves to the root. This is important, because the accumulation of sugar in the leaves slows down sugar synthesis.

In *grapes*, a magnesium deficiency not only lowers the yield, but may also bring about necrosis of the fruit stalk. Grapes formed under such conditions remain sour, their sugar content is low and some of them may fall in rainy weather. Necrosis of the

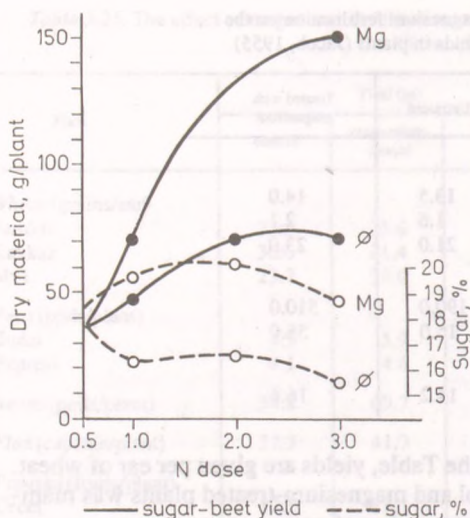


Fig. 3.26. The effects of nitrogen and magnesium fertilization on the yield and sugar content of sugar beet (Ebert, 1967)

fruit stalk occurs mostly on vines whose leaves exhibit the symptoms of magnesium deficiency. In the leaves of plants with diseased grapes, high potassium and low magnesium levels were measured. At K:Mg ratios around 5–6, there is no necrosis of the fruit stalk, but at higher values the disease will appear.

In *apple*, a magnesium deficiency may develop even when there is enough absorbable magnesium in the soil, but the understock is unable to supply the graft with sufficient amounts of magnesium. In such a case, only foliage spraying helps. Schumacher and Frankhauser (1974) established that the potassium and magnesium contents of fruits and the K:(Ca+Mg) ratio increase from the inner parts of the foliage outwards. Overdoses of magnesium enhance the tinder spot of apple; magnesium should therefore be administered strictly in accordance with the data of leaf analysis, in cases when the result relative to the fresh leaf mass is below the normal value (MgO=2.4%).

The symptoms of magnesium deficiency

The threshold of magnesium deficiency in leaf tissue is about 2 mg/g dry mass, although several factors influence this value. On tomato leaves, symptoms of deficiency were already observed when the magnesium level was as high as 3 mg/g dry mass (Ward and Miller, 1969).

A magnesium deficiency results in a very characteristic leaf necrosis pattern. Symptoms usually appear first on old leaves, since magnesium is transferred from old to younger leaves. This magnesium transfer begins in the leaf blade and proceeds towards the veins; a wider or narrower green border will therefore persist for a longer time along the veins. Chlorotic leaves develop brown necrotic spots and slowly die and fall. In some plants, necrosis is preceded by the appearance of an orange, reddish or purple discoloration, due to anthocyanin pigments in the leaves.

The identification of a magnesium deficiency from the symptoms necessitates great experience and caution. For example, the viral yellowness of carrot caused by the Yellow virus can easily be mistaken for a magnesium deficiency. In the latter case, a yellow discoloration begins in the intervenous area and spreads inwards from the edges of the leaf, with a green border along the veins, and the borderlines of the chlorotic areas are indistinct. In the case of the viral disease, the discoloration spreads from the leaf tip towards the edges, covers a larger contiguous area, and has a well-defined borderline, and the spot appears on only one side of the leaf. This asymmetric character quite definitely excludes a deficiency disease, the appearance of which is symmetric. All that has been said applies to dicotyledonous plants. In monocots, the chlorophyll accumulation is local in character; in a magnesium deficiency, therefore the leaves assume a mottled (tiger-striped) appearance (Bergmann, 1979, 1986).

The sensitivity of plants to a magnesium deficiency; the magnesium coefficient

Mándy and Kiss (1976) found that the efficiency of magnesium treatment depends most of all on the plant species and variety. Some plants are especially sensitive to a magnesium deficiency: these are employed as indicator or test plants (e.g. spinach and tobacco). The magnesium contents of plants and plant parts do not always express their sensitivity to a magnesium deficiency. The magnesium concentration itself does not give sufficient information about the magnesium sensitivity of the plant since together with magnesium, other cations are also accumulated, and the sensitivity to depletion must therefore be examined in relation to these. Kiss (1972) established such a relation in the ratio of the magnesium content expressed in ion equivalents and total cation content. He gave the name magnesium coefficient (z) to this ratio. Its mathematical formulation is as follows:

$$z = \frac{0.5 \text{ Mg}^{2+}}{\text{K}^+ + 0.5 \text{ Ca}^{2+} + \text{Na}^+ + 0.5 \text{ Mg}^{2+}}$$

Kiss sought a correlation between the magnesium coefficient (z) and the ion equilibrium constant (i). He computed the ion equilibrium constant from the ion equivalent values calculated from the determination of 8 macroelements (N, P, S, Cl, K, Ca, Mg and Na in mol/kg) in the plant studied, in the following way:

$$i = \frac{\Sigma^- - \Sigma^+}{2(\Sigma^- + \Sigma^+)}$$

where

$$\begin{aligned}\Sigma^- &= \text{NO}_3^- + \text{H}_2\text{PO}_4^- + 0.5 \text{SO}_4^{2-} + \text{Cl}^- \\ \Sigma^+ &= \text{K}^+ + 0.5 \text{Ca}^{2+} + 0.5 \text{Mg}^{2+} + \text{Na}^+\end{aligned}$$

On plotting the magnesium coefficient against the ion equilibrium constant, Kiss (1972) found that the calculated values describe three curves (Fig. 3.27). He assumed that this grouping is explained by the connection between the sulphur and magnesium

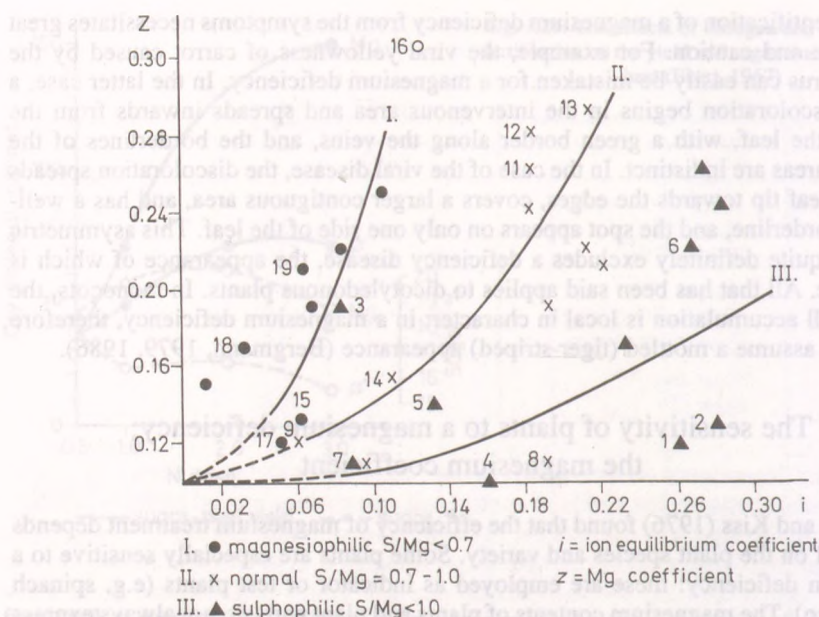


Fig. 3.27. Correlations of the magnesium coefficient with the ion equilibrium constant and the sulphur/magnesium ratio (Kiss, 1972)

contents of plants, which can be expressed by the ratio of these two elements. On the basis of the value of the ratio, plants can be classified into three groups: plants with a high (sulphophilic), normal or low (magnesiophilic) sulphur content. The correlation between z and i as a function of sulphur content can also be formulated in an equation. The equations determining the individual curves and the corresponding S:Mg values are listed in Table 3.27, and the magnesium coefficients, ion equilibrium constants and S:Mg ratios of a number of plants in Table 3.28. Figure 3.27, constructed partly on the basis of this Table, demonstrates that the magnesium sensitivity depends not only on the total magnesium content, but also on the ratio of magnesium to total cation content (i.e. the magnesium coefficient) and on the S:Mg ratio. These assumptions were verified at identical magnesium levels in sand culture experiments (Table 3.29) (Kiss, 1972). Three plants with different sulphur and magnesium requirements

Table 3.27. The classification of plants on the basis of the sulphur/magnesium (S:Mg) ratio (Kiss, 1972)

S:Mg	Plant type	Equation of curve	Serial number of curve
Below 0.7	magnesiophil	$17 \cdot i^2 + 0.1$	I.
0.7-1.0	normal	$4 \cdot i^2 + 0.1$	II.
Above 1	sulphofil	$i^2 + 0.1$	III.

i = ion equilibrium coefficient

Table 3.28. Magnesium coefficient (z), ion equilibrium constant (i) and sulphur/magnesium ratio (S:Mg) of plants (Kiss, 1972)

Serial no.	Plant	Σ^*	Mg	z	i	S	S:Mg
1.	Garden cabbage	1.54	0.18	0.12	0.26	1.01	5.60
2.	Broccoli	3.84	0.50	0.13	0.28	1.95	3.90
3.	Celery	3.52	0.67	0.19	0.08	1.75	2.60
4.	Kohlrabi	3.68	0.46	0.10	0.16	1.11	2.40
5.	Savoy	2.09	0.30	0.14	0.13	0.65	2.20
6.	Radish	1.40	0.30	0.23	0.28	0.50	1.50
7.	Turnip	12.63	1.50	0.11	0.19	1.87	1.20
8.	Head lettuce	1.48	0.16	0.11	0.19	0.14	0.87
9.	Parsley	1.62	0.19	0.12	0.06	0.16	0.89
10.	Potato	9.19	1.04	0.11	0.08	0.91	0.87
11.	Barley	2.73	0.72	0.26	0.18	0.59	0.82
12.	Rye	2.97	0.85	0.28	0.18	0.67	0.78
13.	Wheat	2.75	0.80	0.29	0.21	0.62	0.77
14.	Timothy grass	2.85	0.43	0.15	0.11	0.30	0.70
15.	Tomato	15.02	1.92	0.13	0.06	1.25	0.65
16.	Spinach	2.60	0.80	0.30	0.12	0.50	0.62
17.	Alfalfa	12.70	1.53	0.12	0.05	0.70	0.45
18.	Sugar beet	13.80	2.37	0.17	0.03	1.00	0.40
19.	Red clover	7.30	1.42	0.19	0.06	0.70	0.31

$\Sigma^* = K + 0.5 \text{ Ca} + 0.5 \text{ Mg} + \text{Na}$

The serial numbers in the Table are at the same time the identification numbers of the points in Fig. 3.27.

Table 3.29. The effects of magnesium fertilization on plants with various magnesium coefficients (z), grown in vegetation pots (Kiss, 1972)

Plant	z	S:Mg	% increase by magnesium treatment	
			yield	CO ₂ fixation
Radish	0.22	1.50	17	—
Wheat	0.29	0.77	12	9
Spinach	0.30	0.62	80	11

were chosen for these studies. The magnesium coefficients might suggest that magnesium fertilization would have the highest effect on wheat. The measurements, showed, however, that radish benefited most. Kiss (1972) explained this phenomenon in that the magnesium coefficient of radish is situated above the sulphophile curve, while that of wheat is on the normal curve characteristic of this species. For this reason, he suggested that the farther away the magnesium coefficient of a plant is from the corresponding z - i curve, and at the same time from the x -axis, the more sensitively that plant reacts to a magnesium deficiency. Spinach, for example, is not only a member of the magnesiophile group, but is also very far from the x -axis, i.e. its magnesium

Table 3.30. The extent of magnesium accumulation and the yield as a function of maize varieties, on soil poor in magnesium (Gallaher and Jellum, 1976)

Variety	Magnesium content of the husk leaves (meq/100 g)	Grain yield (t/ha)	Magnesium content of soil (ppm)
Dekalb XL 12	10.7	5.55	15
Pioneer 3956	10.2	5.79	17
Cargill 830	9.6	5.86	19
Pioneer 3975	8.8	4.98	20
Dekalb 045	8.8	4.49	20
Dekalb XL 10	8.1	5.39	19
Funks G-4180	7.6	4.30	19
Dekalb XL 19	7.3	4.42	19

coefficient is high. As seen in Table 3.25, in connection with the effects on crop elements, the sensitivity of plants to a magnesium deficiency varies not only with the species, but also with the variety. For this reason, the data listed in Table 3.30, measured in plants grown in soils with approximately identical magnesium contents, are also of interest. The Table reveals that the maize variety Dekalb XL 12 took up the most magnesium (10.7 meq/100 g) from the soil poorest in this element (15 ppm) and the yield was also high. This means that the magnesium accumulation in plants is dependent not only on the magnesium content of the soil, but also on the genotype of the plant, which justifies the introduction of the magnesium coefficient (Gallaher and Jellum, 1976).

The interactions of magnesium with other elements

The magnesium uptake by plants is affected by the other nutrient elements, and especially by K^+ , Ca^{2+} , H^+ and NH_4^+ , which are antagonists of Mg^{2+} .

The acidity of the medium (soil solution) strongly inhibits magnesium uptake. On acid soils, the root system of plants is weaker (Saigusa et al., 1980) and it is partly for

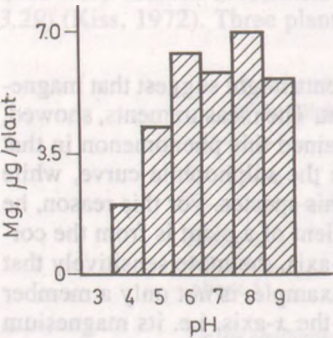


Fig. 3.28. The effect of the soil pH on magnesium uptake by tomato (Arnon et al., 1942)

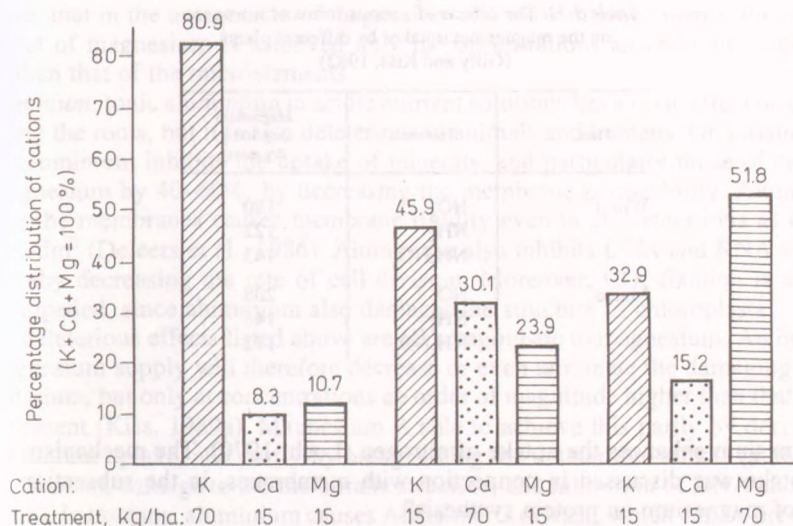


Fig. 3.29. Effects of fertilization with various macroelements (K, Ca and Mg) on the cation content of oats (Bodrawy and Bussler, 1968)

this reason and partly because of the antagonizing effect of H^+ that the magnesium uptake is decreased. This explains why plants tolerate acid soils better when the soil is rich in magnesium. The effect of the soil pH on the uptake of magnesium ions according to Arnon et al. (1942) is shown in Fig. 3.28.

Figure 3.29 illustrates the effects of potassium, calcium and magnesium fertilization on the potassium, calcium and magnesium contents of oats (Bodrawy and Bussler, 1968). The Figure at the same time illustrates the antagonism. In the experiments of Grimme and Braunschweig (1974) on oats, when the potassium content of the medium was increased, the uptakes of magnesium and calcium decreased, but they did not fall below a certain limit: 0.16% for magnesium and 0.50% for calcium. From this, it follows, that if sufficient amounts of magnesium and calcium are available, the plant is able to take up the necessary amounts of magnesium and calcium even when treated with high doses of potassium fertilizers.

The magnesium uptake is also affected by the extent and form of the nitrogen supply. Ammonium ions decrease the magnesium content of plants, while nitrate ions increase it. Table 3.31 shows the separate and joint effects of NO_3^- and NH_4^+ (Gilly and Kiss, 1982). These results prove that nitrate strongly stimulates magnesium uptake. When the two forms of nitrogen were applied together, the magnesium contents of plants assumed intermediate values. Even though the $NO_3^- : NH_4^+$ ratio was 1:1, the magnesium content did not correspond to half of the difference, but was lower than that, which means that the inhibitory effect of the ammonium ion on magnesium uptake is stronger than the stimulation by nitrate.

Table 3.31. The effects of various forms of nitrogen on the magnesium uptakes by different plants (Gilly and Kiss, 1982)

Plant	Treatment	Magnesium (mg/100 g dry mass)
Wheat	NO_3^-	180
	NH_4^+	122
	NH_4NO_3	143
Maize	NO_3^-	208
	NH_4^+	146
	NH_4NO_3	172

Magnesium enhances the uptake of nitrogen (Loch, 1970). The mechanism of nitrate uptake was discussed in connection with membranes, in the subsection "The effects of magnesium on protein synthesis".

Magnesium stimulates the utilization (uptake) of phosphorus to an extent which may even be comparable to the effect of phosphate fertilizers. Lityinski (1973) established that the administration of magnesium increased the phosphorus uptake about 2-fold and enhanced the phosphorus flux to the seeds at the expense of the straw. Loch (1990) reported similar results from an analysis of the interconnections of nitrogen, phosphorus, potassium and magnesium uptakes. The mechanism of the stimulation of phosphorus uptake was discussed in the section on membranes.

Rainy weather may also bring about a magnesium deficiency, the magnesium level then possibly decreasing by 20–40% as compared with dry years. A magnesium deficiency is caused not only by outwash from the plants, but also by the fact that in rainy summers monovalent cations (K^+ and Na^+) are more motile than the divalent Mg^{2+} and they thereby slow down magnesium uptake. A magnesium deficiency is therefore observed more markedly in plants in rainy summers than in dry weather. A factor enhancing this effect is that warm, rainy weather stimulates plant growth and hence increases their magnesium requirements.

The interactions of magnesium with toxic microelements

The uptake and biological effect of magnesium are influenced not only by the macroelements, but also by microelements. It has been established (Kiss, 1990) that some microelements are antagonists of magnesium. Toxic microelements harm not only plants, but also animals and humans, as they reach them from plants along the food chain. This is why magnesium treatment (fertilization), which inhibits the uptake of toxic microelements, is of great significance. These microelements are accumulated in poisonous concentrations primarily in acidic soils, since acidification of the environment favours their dissolution.

The effectivity of magnesium was found to be 5 times higher, while that of microelements proved to be 10–20 times higher than that of potassium. It is understandable,

therefore, that in the antagonism of magnesium and toxic microelements, the tolerating effect of magnesium is achieved only in concentrations an order of magnitude higher than that of the microelements.

Aluminium. Ionic aluminium in acidic nutrient solutions has a toxic effect on plants, poisoning the roots, but it is also deleterious to animals and humans. On passing into plants, aluminium inhibits the uptake of minerals, and particularly those of calcium and magnesium by 40–60%, by decreasing the membrane permeability. Aluminium entering the membranes causes membrane rigidity even in concentrations as low as $25 \mu\text{mol/dm}^3$ (Deleers et al., 1986). Aluminium also inhibits DNA and RNA synthesis, thereby decreasing the rate of cell division. Moreover, CO_2 fixation is significantly impeded, since aluminium also damages the structure of chloroplasts.

The deleterious effects listed above are all antagonistic to magnesium. An increasing magnesium supply will therefore decrease or even terminate the damaging effect of aluminium, but only at concentrations an order of magnitude higher than that of the toxic element (Kiss, 1989a). Magnesium is able to achieve this partly by decreasing the aluminium uptake, and partly by antagonizing the deleterious effects (a decrease in CO_2 fixation, damage to the membrane structure, and inhibition of DNA and RNA synthesis). In humans, aluminium causes Alzheimer's disease, which can be prevented primarily by the administration of magnesium (Leszek and del Campo, 1985).

Cadmium. Cadmium is a microelement poisonous to plants, and to animal and human organisms. It enters the human body via the food chain and is accumulated; hence, even low concentrations are dangerous (Rigby et al., 1983). Cadmium may cause sterility and cancer of the kidney and the prostate. It passes into the soil mostly with phosphate fertilizers, sewage and sewage-sludge. Cadmium inhibits the growth of the roots and shoots of plants; this can be counterbalanced by magnesium treatment (Kiss et al., 1991) via the competitive inhibition of uptake. Here too, toleration results only if the magnesium concentration is an order of magnitude higher than cadmium concentration. Guet-Bara et al. (1990) observed a similar antagonism between magnesium and cadmium in human placental villi.

Arsenic. It is commonly known that arsenic is poisonous to animals and humans. Its damaging effect on plants is less well known. Arsenic inhibits plant growth because it decreases magnesium uptake and also inhibits several physiological processes. Kiss et al. (1990) established that arsenic in the soil, and especially in irrigating water sprayed on the leaves, poisons plants; this can be reversed by magnesium treatment (fertilization). This antagonism is explained by the competitive inhibition of uptake and, in the case of physiological processes, by counterbalancing of the toxicity, but in this case a 10-fold magnesium excess is necessary.

Decreasing the arsenic content of vegetal foodstuffs is significant mainly in areas where the drinking water also contains arsenic, since the arsenic entering the human body from these two sources decreases the effectivity of the immune system (macrophages) by inhibiting active oxygen formation and thereby promotes the development of cancer (Fisher et al., 1986).

Zinc is another antagonist of magnesium. Kumar et al. (1981) carried out experiments on wheat in vegetation pots and found that an increasing magnesium supply decreased the uptake of zinc; this could be compensated by fertilization with zinc.

Lead. Water containing lead acetate decreases the germinative ability of seeds (beans, maize and rice). The effect of lead in inhibiting germination was antagonized

Table 3.32. Ranges of magnesium content satisfactory for the most important crop plants (Bergmann, 1986)

Plant	Time of sampling	Satisfactory magnesium content (% dry mass)		Plant part studied
		lower limit	upper limit	
Autumn wheat (<i>Triticum aestivum</i>)	onset of spearing, Feekes scale 5/6	0.15	0.30	whole shoot about 5 cm from surface
	middle of spearing Feekes scale 7/8	0.12	0.25	
Autumn barley (<i>Hordeum vulgare</i>)	onset of spearing, Feekes scale 5/6	0.15	0.30	whole shoot about 5 cm from surface
	middle of spearing, Feekes scale 7/8	0.12	0.30	
Maize (<i>Zea mays</i>)	40–60 cm tall	0.25	0.60	fully developed leaves
Potato (<i>Solanum tuberosum</i>)	onset of flowering	0.25	0.80	just developed leaves
Cauliflower (<i>Brassica oleracea botrytis</i>)	flower formation	0.25	0.50	middle leaves
White and red cabbage (<i>Brassica oleracea capitata</i>)	hearting up	0.25	0.50	developed leaves
Lettuce (<i>Lactuca sativa capitata</i>)	hearting up	0.35	0.60	middle leaves, developed

by magnesium (Kiss, 1991). To explain the inhibitory effect on germination, Maitra and Mukherji (1979) suggested that RNA and DNA synthesis in the embryo is inhibited. Kiss (1991) considered that the favourable effect of magnesium is realized via an increase in the level of gibberellins, since the administration of gibberellins alone was sufficient to eliminate the effect of lead in inhibiting germination.

Lead absorbed by plants is deleterious to humans consuming those plants, since it causes lung tumours and other diseases. Poirier et al. (1984) reported that magnesium prevented the lung-tumour inducing effect of lead acetate by antagonism.

The indication of magnesium supply by plant analysis

A knowledge of the magnesium content of the soil allows an estimate as to the potential magnesium supply of plants. Just as in the case of other elements, however, the amount of magnesium absorbed by plants is influenced by other factors as well. For this reason, quantitative determination of the amount of nutrient elements in the soil is not itself sufficient for an evaluation of the nutrient supply of plants.

There are two possibilities for characterizing the nutrient supply of plants: one is visual diagnostics (Bergmann, 1986), and the other is analytical determination (Patócs, 1989).

As has been described earlier, a magnesium deficiency is to be seen first on older, i.e. basal leaves. The strongest symptoms are usually localized chlorotic spottiness, with or without necrosis.

Although visual diagnostics provides fast information on the symptoms, this method is still not sufficient itself for a clear-cut answer, since a hidden nutrient deficiency cannot be revealed in this way. However, analytical diagnosis based on plant or leaf analysis yields reliable information on the nutrient supply or deficiency. The principle underlying plant analysis to monitor the nourishment status is that, in the developmental periods of importance for optimal growth and yield, different plant parts (leaf, leaf stalk, apical meristem, etc.) are characterized by well-defined nutrient contents and nutrient ratios. The determination of nutrient concentrations necessary for a harmonious nutrient supply is possible only via analytical measurements. The characteristic magnesium contents of some important crop plants are listed in *Table 3.32*. Of these data, the results of the analysis of winter wheat are emphasized. The magnesium supply of winter wheat (plant analysis on ca. 56,000 hectares) at the time of stooling reveals that on more than 40% of the area the magnesium supply of winter wheat was inadequate. For 21% of the plants, the magnesium deficiency could be explained by the inadequate magnesium supply of the soil. Winter wheat deficient in magnesium could be found even on soil very well supplied with magnesium. In order to ensure the optimal magnesium supply, it is essential that, in addition to soil analyses, plant analyses also be carried out in the course of the vegetative period and that, when necessary, magnesium be supplemented by foliar spraying.

3.3. The effects of magnesium on biomass formation and special metabolism in plant tissue culture

It is evident from the preceding section that magnesium is indispensable for plant development. In connection with the utilization of natural magnesium sources in crop plants, it was pointed out there that a deeper knowledge of the effect of the magnesium supply provides an opportunity for enhancement of the effectivity of agricultural production. In order to achieve this goal, it is first absolutely necessary to know how plants absorb magnesium from the soil and what role this element plays in their life processes (Kiss, 1983).

In this section, the results of experiments with plant tissue cultures will be utilized to demonstrate, that in addition to influence primary metabolic processes, magnesium also has effects on the secondary or special metabolism.

The effects of magnesium on the growth and essential oil content of organized camomile cultures

Since camomile is at present one of the best-known and most sought-for herbs in Hungary and is nowadays cultivated rather than collected in Nature, it appears of interest to demonstrate how magnesium affects the growth of organized camomile

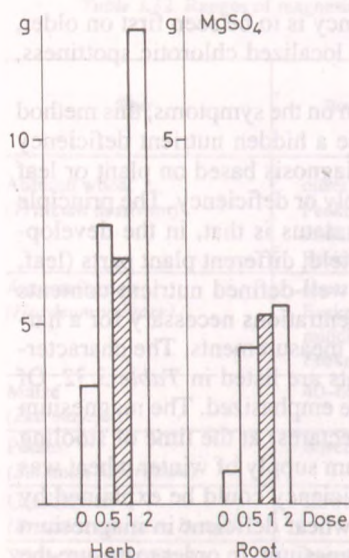


Fig. 3.30. Effects of MgSO_4 on the fresh weight of the herb and root from organized camomile cultures
(1 dose $\text{MgSO}_4 = 370 \text{ mg/dm}^3$)

cultures and the synthesis of essential oils, with especial regard to components of therapeutic importance (Cartoni et al., 1990; Gilbertson and Koenig, 1981).

A considerable proportion of camomile is now extracted from cultivated plants. Accordingly, the possibility arises that perhaps magnesium might be used to increase yields, in so far as it does not decrease the biosynthesis of essential oil. In this way, in addition to the achievement of higher yields of drug and essential oil, the magnesium content of the drug would also hopefully increase. Herbs with a high magnesium content and the infusions or therapeutic products made from them, have recently acquired increasing significance, as the drinking water in many areas is poor in magnesium, and this deficiency may lead to the development of numerous ailments (cf. Section 8.2).

A better understanding of the physiological role of magnesium is promoted by experiments on organized camomile cultures, primarily with respect to biomass formation and essential oil production (Szőke et al., 1979, 1989, 1992b).

Organized cultures obtained from floral callus tissue of camomile (*Matricaria recutita* L., syn.: *Matricaria chamomilla* L., Asteraceae) grow and develop well on Murashige-Skoog (1962) [MS] medium (containing $370 \text{ mg/dm}^3 \text{ MgSO}_4$), and their root formation is also intensive (Fig. 3.30). Of the essential oil components synthesized in the herb, α -farnesene, β -farnesene and cis- and trans-spiroethers (en-indicycloethers) are produced in significant amounts.

Cultures kept on medium without MgSO_4 hardly grow and their rooting is also seriously impaired (Fig. 3.30, Table 3.33).

In the herb of cultures grown on a medium poor in magnesium (185 mg/dm^3) or entirely lacking this element, destruction of the chloroplasts is observed. The gradual disintegration of the thylakoid membrane system of chloroplasts is probably related to the fact that the stabilizing role of the Mg^{2+} ions is inoperative in cells deficient in magnesium (Kiss, 1989).

Table 3.33. Effect of magnesium on the biomass production and the essential oil content of the herb from organized camomile culture

Culture medium (MgSO ₄ mg/dm ³)	Fresh weight (g)	Dry weight (g)	Dry matter content %	Growth value (GV)		Growth rate mg/day	Essential oil content g/g %	Essential oil production mg/culture
				by fresh mass	by dry mass			
0 MgSO ₄ 0	3.297	0.258	7.830	1.53	2.62	40	0.055	0.141
1/2 MgSO ₄ 185	7.648	0.642	8.400	7.65	8.02	112	0.063	0.403
1 MgSO ₄ 370	6.800	0.737	10.840	6.69	9.35	98	0.100	0.736
2 MgSO ₄ 740	12.994	0.842	6.480	13.70	10.82	201	0.096	0.804

When the concentration of MgSO₄ in the medium is doubled (740 mg/dm³), the fresh mass of the herb is approximately doubled, i.e. it increases from 6.80 g to 12.99 g (as compared with cultures on MS medium). This tendency is also shown by the growth values, relative to both fresh and dry mass (Fig. 3.31, Table 3.33). The leaves are bright green.

Root formation is already significant at 185 mg/dm³ MgSO₄ (1/2 dose), but is most intensive in response to the double MgSO₄ concentration. It should be noted, however, that when the concentration is raised (from 185 to 740 mg/dm³), the mass of the roots is increased only slightly (Fig. 3.30).

Analysis of the essential oil content (w/w%) and essential oil production of the herb from the cultures reveals that, on a medium lacking magnesium or containing only 185 mg/dm³ MgSO₄, the biosynthesis of essential oils is inhibited. Since biomass formation by the cultures is intensified by increase of the MgSO₄ concentration to 185 mg/dm³, the essential oil production exhibits an increasing tendency in response (Table 3.33). On further increase of the concentration of MgSO₄ (to 370 or 740 mg/dm³), however, the essential oil content is nearly doubled. The essential oil pro-

The effects of magnesium on changes in growth intensity of hairy root cultures of the *Datura candida* × *D. aurea* hybrid

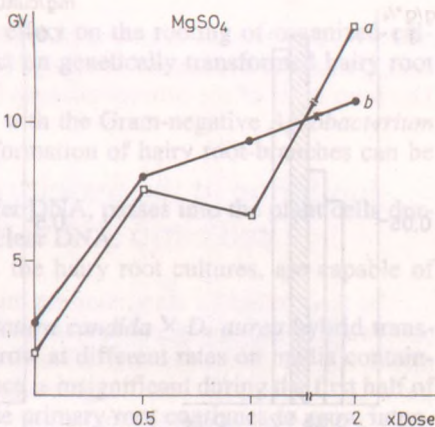


Fig. 3.31. Effects of MgSO₄ on the growth value (GV) of the herb from organized camomile culture. (a = by fresh mass; b = by dry mass (1 dose MgSO₄ = 370 mg/dm³))

duction is most significant on the medium with the double MgSO_4 concentration: it is about 6 times higher than that of the control culture, since the magnesium causes both the fresh mass and the essential oil content of the herb to increase significantly (Figs 3.30 and 3.32).

Analysis of the composition of the essential oils reveals that the administration of magnesium significantly increases the amounts of the components as compared with the cultures grown on the medium without magnesium. It is noteworthy, however, that at 185 mg/dm^3 MgSO_4 proportions of α -farnesene, α -farnesene and *cis*- and *trans*-spiroethers within the total essential oil are the highest (Fig. 3.33).

The amounts of sesquiterpenes and polyene compounds relative to the total amount of essential oil varies according to a maximum curve. However, it must be taken into consideration that higher magnesium concentrations increase the essential oil production of the cultures several-fold; thus, the ratios of the antiphlogistic α -farnesene (Janku and Zita, 1954) and the strongly spasmolytic *en-in*-dicycloethers (Breinlich and Scharnagel, 1968) relative to the biomass are increased. The proportion within the essential oil of spatulenol (Schmialek, 1961; Motl et al., 1978; Motl and Repčák, 1979), a compound with a juvenile hormone-like effect, reaches its maximum in response to the highest MgSO_4 concentration (740 mg/dm^3). Its amount is further increased by intensified essential oil production. Since there is very little spatulenol in intact plants, the administration of magnesium (e.g. fertilization) may be of special importance in field cultivation. From the components of therapeutic importance, ever more attention is currently being given to spatulenol and polyene compounds. It is very noteworthy that the amounts of these compounds are significantly increased by magnesium treatment.

It can therefore be stated that addition of MgSO_4 to the medium favourably effects the development of organized camomile cultures, significantly increases the biomass formation of both the herb and the root, and strongly influences the production and composition of essential oils.

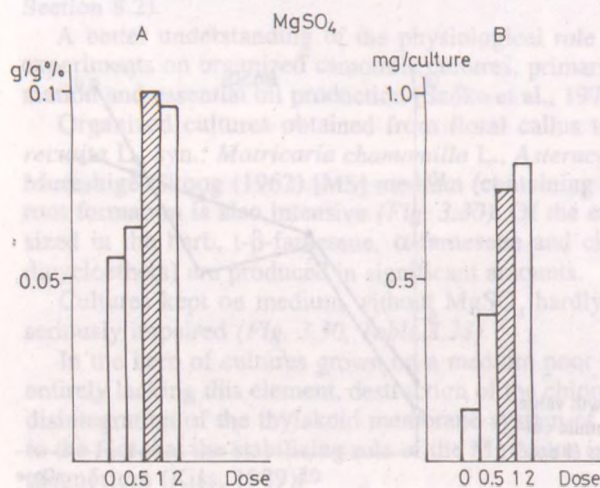


Fig. 3.32. Effects of MgSO_4 on the essential oil content (A) and essential oil production (B) from organized camomile cultures (herb) (1 dose $\text{MgSO}_4 = 370 \text{ mg/dm}^3$)

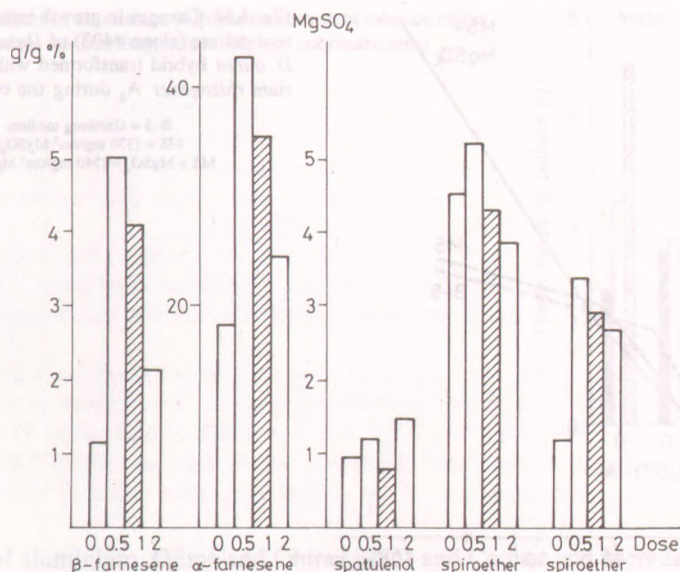


Fig. 3.33. Effects of MgSO_4 on essential oil components from organized camomile cultures (herb)
(1 dose $\text{MgSO}_4 = 370 \text{ mg/dm}^3$)

The effects of magnesium on changes in growth intensity of hairy root cultures of the *Datura candida* × *D. aurea* hybrid

As MgSO_4 has an exceptionally positive effect on the rooting of organized cultures, it is of interest to demonstrate its effect on genetically transformed hairy root cultures.

On the wound surfaces of plants infected with the Gram-negative *Agrobacterium rhizogenes* of the family *Rhizobiaceae*, the formation of hairy root-branches can be observed.

Part of the bacterial Ri plasmid, the transfer DNA, passes into the plant cells during infection and is stably integrated into nuclear DNA.

The secondary root-branches formed, i.e. the hairy root cultures, are capable of unlimited growth on hormone-free medium.

Hairy root cultures (clone #403) of the *Datura candida* × *D. aurea* hybrid transformed with *Agrobacterium rhizogenes* A₄ grow at different rates on media containing different amounts of MgSO_4 . The difference is insignificant during the first half of the culture period, but after the day 20–22 the primary root continues to grow inten-

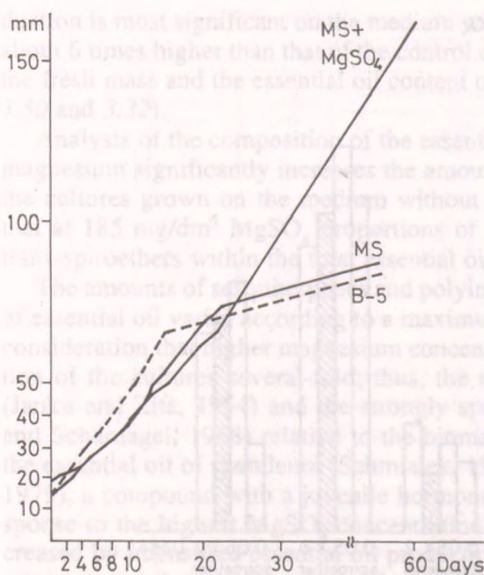


Table 3.34. Growth of hairy root culture (clone #403) of *Datura candida* x *D. aurea* hybrid transformed with *Agrobacterium rhizogenes* A₄ on media with different MgSO₄ concentrations

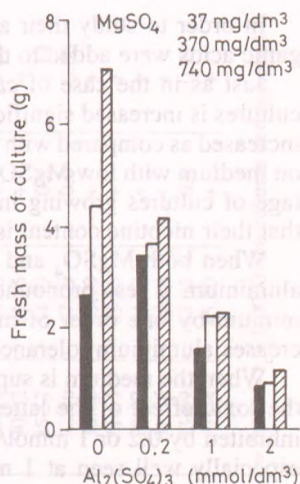
Medium		Length of primary root (mm)		Length of secondary root (mm)		Fresh mass of culture (g)	
type	MgSO ₄ mg/dm ³	$\bar{x}$	s	$\bar{x}$	s	$\bar{x}$	s
MS	185	41.80	7.330	34.20	3.826	0.184	0.0121
MS	370	81.60	10.647	51.50	8.115	0.798	0.0333
MS	740	157.25	11.145	52.40	7.272	1.231	0.1127

sively on the medium with double MgSO₄ concentration, while on the medium containing a normal concentration of MgSO₄ its growth abruptly slows down (Fig. 3.34). The fresh mass of the cultures changes in a similar way (Table 3.34).

Inhibition of the toxicity of aluminium by magnesium and citric acid in tobacco tissue cultures

The toxic effect of aluminium on intact plants was described in the previous section, which also mentioned the interactions of magnesium with some toxic microelements, among them aluminium (Guerrier, 1979; Wallace and Anderson, 1984; Matsumoto and Morimura, 1980; Wagatsuma, 1983; Allen, 1987). Ahmad and Tan (1986), and Cambraia et al. (1983) studied the effects of organic and inorganic acids on the

Fig. 3.35. Effects of aluminium sulphate on growth of tobacco callus tissues (at various magnesium sulphate concentrations)



toxicity of aluminium. Ojima and Ohira (1985) and Conner and Meredith (1985a, b) likewise demonstrated the toxic effect of aluminium in plant tissue cultures. Further, they succeeded in selecting an aluminium-resistant cell line.

The antagonism of magnesium and aluminium has been demonstrated in tobacco (*Nicotiana tabacum* L., Hevesi-276) tissue cultures, as has the inhibition of aluminium toxicity by magnesium and citric acid, as manifested in growth and alkaloid content (Szöke et al., 1992a).

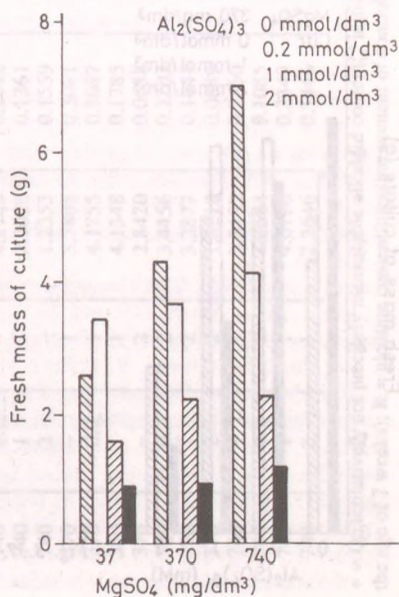


Fig. 3.36. Effects of magnesium sulphate on growth of tobacco callus tissues (at varying aluminium sulphate concentrations)

In order to study their aluminium toxicity-tolerating effects, magnesium and organic acids were added to the medium in 24 variations (Table 3.35).

Just as in the case of camomile cultures, the growth intensity of tobacco callus cultures is increased significantly when the concentration of MgSO_4 in the medium is increased as compared with the basic MS medium (370 mg/dm^3). Tissues grow slowly on medium with low MgSO_4 concentration (37 mg/dm^3) (Fig. 3.35). A special advantage of cultures growing intensively on medium with a high magnesium content is that their nicotine content is reduced by half (Table 3.35).

When both MgSO_4 and $\text{Al}_2(\text{SO}_4)_3$ are present in the medium, the toxic effect of aluminium is less pronounced if the magnesium concentration exceeds that of aluminium by one order of magnitude (antagonism). This means that magnesium increases aluminium tolerance.

When the medium is supplemented with citric acid, which complexes aluminium, the toxic effect of the latter is hardly observed, if at all. The culture growth is not inhibited by 0.2 or 1 mmol/dm^3 $\text{Al}_2(\text{SO}_4)_3$ in the presence of citric acid. The effect is especially well seen at 1 mmol/dm^3 $\text{Al}_2(\text{SO}_4)_3$ where the intensity of biomass formation is essentially similar to that of the control and about twice as high as in the absence of citric acid (Fig. 3.36, Table 3.35).

These experimental results conclusively prove that citric acid antagonizes the toxic effect of aluminium by complexing it. However, citric acid cannot complex aluminium present at higher concentrations, e.g. 2 mmol/dm^3 . At this aluminium concentration, therefore, the culture growth decreases to half of the control value, but is still twice as high as that without citric acid (Fig. 3.37).

It must be noted for the sake of completeness that, when the medium contains no aluminium sulphate, but only MgSO_4 , the biomass production of the cultures is de-

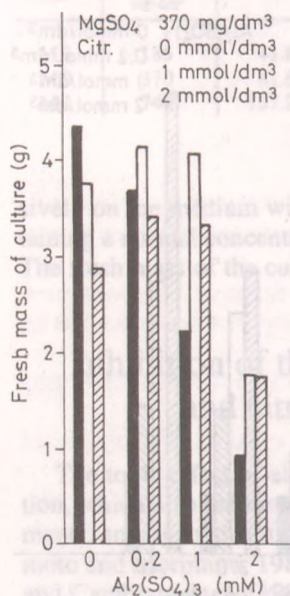


Fig. 3.37. Effects of citric acid on growth of tobacco callus tissues (at varying aluminium concentrations)

Table 3.35. Tolerance to aluminium toxicity caused by magnesium and citric acid in tobacco tissue cultures

Culture medium (AMS-2)		Fresh mass (g/culture) ^a		Dry mass (g)	Dry matter content %	Growth value (GV)		Daily increase in fresh mass (mg/day)	Nicotine content % 10 ⁻⁴	R
MgSO ₄ (mg/dm ³)	Al ₂ (SO ₄) ₃ mmol/dm ³	Citric acid mmol/dm ³	$\bar{x}$	s_k		by fresh mass	by dry mass			
37	—	—	2.6513	0.2389	0.1193	4.50	15.74	50.87	1.2	1.71
37	0.2	—	3.4742	0.1354	0.1598	4.61	20.93	67.67	1.9	2.71
37	1	—	1.6297	0.1176	0.1010	6.20	9.29	30.03	1.0	1.43
37	2	—	0.9211	0.0643	0.0694	7.53	4.82	15.57	1.2	1.71
370*	—	—	4.3949	0.1436	0.1428	3.25	26.75	92.10	0.7	1.00
370	0.2	—	3.7200	0.0802	0.1190	3.20	22.54	72.69	+	+
370	1	—	2.2861	0.1812	0.1748	6.11	13.43	22.33	+	+
370	2	—	0.9722	0.1408	0.0690	7.12	5.14	16.95	+	+
740	—	—	7.0710	0.1994	0.2333	3.31	43.64	141.09	0.6	0.86
740	0.2	—	4.1703	0.2142	0.1000	2.40	25.33	81.88	+	+
740	1	—	2.3026	0.1361	0.1327	5.77	13.55	43.71	1.3	1.86
740	2	—	1.2353	0.1559	0.0829	6.71	6.80	21.98	0.9	1.29
370	—	—	3.7805	0.3081	0.1100	2.91	22.87	73.92	+	+
370	0.2	1	4.1755	0.3087	0.1340	3.21	25.36	8.98	+	1.00
370	1	1	4.1348	0.1785	0.1427	3.45	25.10	81.15	+	+
370	—	2	2.8420	0.0688	0.1196	4.21	16.98	54.77	0.8	1.14
370	0.2	2	3.4456	0.2203	0.1530	4.44	20.75	67.09	0.6	0.86
370	1	2	3.3877	0.1444	0.1426	4.21	20.39	65.90	+	+
370	2	2	1.8218	0.0889	0.1042	5.72	10.50	33.95	+	+
740	—	1	3.3192	0.1560	0.0903	2.73	19.94	64.32	+	+
740	0.2	1	4.0584	0.1085	0.1502	3.70	24.62	84.44	+	+
740	1	1	4.0196	0.2349	0.1568	3.91	24.38	83.95	0.5	0.71
740	2	1	2.2646	0.1446	0.0692	3.06	13.30	45.70	+	+

+ = Quantitatively not precisely measurable alkaloid content; ^a initial mass of transferred tissue inocula: $\bar{x} = 0.1602$, $s_k = 0.0050$ (the cultures were weighed at the age of 7 weeks); R = nicotine content/nicotine content of control (ratio); * Control

creased by citric acid, since in the absence of aluminium it complexes magnesium, decreasing its effect in stimulating growth. When both aluminium and magnesium are present in the medium, it is evident from the complex stability coefficients that citric acid preferentially complexes aluminium (antagonizing its toxicity), and only when the aluminium has been depleted will magnesium follow. This is probably why the growth of the cultures is slightly decreased by 2 mmol/dm³ citric acid (as compared with 1 mmol/dm³).

To summarize, analysis of the growth parameters of tobacco callus cultures confirms that magnesium is an antagonist of aluminium. Aluminium tolerance increases in parallel with increasing magnesium concentration. These results support the observations of Kiss (1986, 1987), who reported that magnesium inhibited the uptake and toxicity of aluminium in wheat and bean plants.

When the medium is supplemented with citric acid, this complexing the aluminium, the toxic effect of the latter is suppressed. The uptake, binding to membranes and therefore toxicity of complexed aluminium is decreased or even eliminated, as only free ionic aluminium is able to bind to membranes.

Similarly to camomile, in tobacco tissue cultures too magnesium modifies the special metabolism of the tissues. In consequence of the administration of MgSO₄, the nicotine content of the tissues is decreased which is highly advantageous from the aspect that tobacco varieties and cigarettes with low nicotine content are currently increasingly desirable.

References to Chapter 3

3.1. The relationship of magnesium with natural vegetation

- Babalonas, D., Karataglis, S., Kabassakalis, V. (1984): The ecology of plant populations growing on serpentine soils. III. *Phyton* (Austria) **24**, 225.
- Babalonas, D., Reeves, R. (1988): Kationen-Akkumulation durch Silene-Arten auf Serpentinböden Griechenlands. *Phyton* (Austria) **28**, 229.
- Berki, I., Holes, L. (1988): Lokale industrielle Emission und Waldschäden in Nordungarn II. Mineralstoffgehalt des Bodens und der Blätter von *Quercus petraea* S. L. *Acta Bot. Hung.* **34**, 25.
- Bergseth, H. (1975): Veränderung von Magnesium und Kalzium in Waldböden durch Hydrogenionen. *Acho. Agricult. Scand.* **25**, 225.
- Bredow, von B., Buggert, A., Eckhoff, A., Holstein, B., Neumann, M., Schindel, R., Weber, A., Zeck, S., Glavac, V. (1986): Vergleichende Untersuchung der Boden-, Wurzel- und Blatt-Mineralstoffgehalte von Bäumen verschiedener Schadstufen in einem immissionsbelasteten Altbuchenbestand. *Allg. Forstzeitschrift* **41**, 551.
- Bublinec, E. (1980): Flux of nutrients in a hornbeam-oak forest. *Abstracta Botanica* **6**, Suppl. 1, 79.
- Faragó, T., Iványi, Zs., Szalai, S. (eds) (1990): *Climatic Variability and Changes*, 1. Hung. Meteorol. Service. (In Hung.)
- Fekete, G., Tölgyesi, Gy., Horánszky, A. (1989): Dolomite versus limestone habitats: a study of ionic accumulation on a broader floristic basis. *Flora* **183**, 337.

- Gambi, O. V., Gabrielli, R., Pancaro, L. (1982): Nickel, chromium and cobalt in plants from Italian serpentine areas. *Acta Oecologica* **3**, 291.
- Glatzel, G., Sonderregger, E., Kazda, M., Buxbaum, M. (1983): Bodenveränderungen durch Schadstoff angereicherte Stammablaufniederschläge in Buchenbeständen des Wiener Waldes. *Allg. Forstzeitschrift* **26/27**, 693.
- Glavac, V., Jochheim, H., Koenies, H., Rheinstädter, R., Schäfer, H. (1985): Einfluß des Stammablaufwassers auf den Boden im Stammflußbereich von Altbuchen in unterschiedlich immissionsbelasteten Gebieten. *Allg. Forstzeitschrift* **51/52**, 1397.
- Glavac, V., Koenies, H. (1986): Kleinräumige Verteilung der pflanzenaufnehmbaren Mineralstoffe in den vom Stammablaufwasser beeinflussten Bodenbereichen alter Buchen verschiedener Waldgesellschaften. *Düsseldorfer Geobot. Kolloqu.* **3**, 3.
- Glavac, V., Krause, A., Wolf-Sraub, R. (1970): Über die Verteilung der Hainsimse (*Luzula luzuloides*) im Stammflußbereich der Buche im Siebengebirge bei Bonn. *Schriftenr. Vegetationskunde* **187**.
- Greune, A., Fengel, D. (1984): Elementgehalt im Holz einer gesunden und einer vom „Waldsterben“ beschaffenen Fichte. Pärchenvergleich mit Hilfe der Röntgenspektroskopie. *Forstwiss. Cbl.* **103**, 297.
- Grünhage, L., Jäger, H. J. (1988): Entwicklung der Nährstoff- und Schwermetallgehalte in Fichtennadeln aus dem Rhein-Main-Gebiet. *Angew. Botanik* **62**, 85.
- Hippeli, P., Branse, C.H. (1992): Veränderungen der Nährelementkonzentrationen in den Nadeln mittelalter Kiefernbestände auf pleistozänen Sandstandorten Brandenburgs in den Jahren 1964 bis 1988. *Forstwiss. Cbl.* **111**, 44.
- Horváth, L., Mészáros, E. (1984): The composition and acidity of precipitation in Hungary. *Atmospheric Environm.* **18**, 1842.
- Jakucs, P. (1985): Summarizing the trends of element-movement in the forest. In: Jakucs, P. (ed.): *Results of "Síkfőkút Project"*. Budapest, 511. (In Hung.)
- Jakucs, P., Kovács, M., Mészáros, I., B. Papp, L., Cs. Szabó, M., Tóth, J. A. (1981): Trends in the element movement of the "Síkfőkút Project" forest ecosystem. *MTA Biol. Oszt. Közl.* **24**, 67. (In Hung.)
- Jochheim, H. (1985): Der Einfluß des Stammablaufwassers auf den chemischen Bodenzustand und die Vegetationsdecke in Altbuchbeständen verschiedener Waldgesellschaften. *Ber. Forschungszentrum Waldökosysteme (Waldsterben)* **13**, 225.
- Jochheim, H. (1986): Einfluß des Stammablaufwassers auf den Pflanzenbewuchs und den chemischen Bodenzustand im Oberboden von Altbuchenbeständen. *Verhandl. Gesellsch. Ökologie (Hohenheim, 1984)* **14**, 299.
- Jochheim, H., Schäfer, H. (1988): Die „Baumfuß-Methode“ dargestellt anhand einer Untersuchung der Immissionsbelastung von nordwest-jugoslawischen Buchenwäldern. *Z. Pflanzenernähr. Bodenk.* **151**, 81.
- Johnson, D. W., Richter, D. D. (1984): Effects of atmospheric deposition on forest nutrient cycles. *Tappi Journal* **67**, 84.
- Karataglis, S., Babalonas, D., Kabasakakis, B. (1982): The ecology of plant populations growing on serpentine soils II. *Phyton (Austria)* **22**, 317.
- Kinzel, H., Weber, M. (1982): Serpentin-Pflanzen. In: Kinzel, M.: *Pflanzenökologie und Mineralstoffwechsel*. E. Ulmer Verlag, Stuttgart, 381.
- Klumpp, A., Guderian, R. (1990): Leaching von Magnesium, Kalzium und Kalium aus immissionsbelasteten Nadeln junger Fichten *Picea abies* (L.) *Karst. Forstwiss. Cbl.* **109**, 13.
- Kovács, M. (1975): *Beziehung zwischen Vegetation und Boden. Die Vegetation ungarischer Landschaften*. Bd. 6. Budapest, 1.
- Kovács, M. (1985): Dynamics of elements in the soil. In: Jakucs, P. (ed.): *Results of "Síkfőkút Project"*. Akadémiai Kiadó, Budapest, 497.

- Kozák M., Mészáros, E. (1971): The chemical composition and agricultural significance of rainwater in Hungary. *Agrokémia és Talajtan* **20**, 329. (In Hung.)
- Láng-Kovács, E. (1966): Comparative soil and plant analysis on dolomite and limestone rockturfs. *Botan. Közlem.* **53**, 175. (In Hung.)
- Leonardi, S., Flückiger, W. (1986): Zur Auswaschung von Nährstoffen aus der Baumkrone. *Allg. Forstzeitung* **41**, 825.
- Leonardi, S., Flückiger, W. (1988): Der Einfluß einer durch saure Benebelung induzierten Kationenauswaschung auf die Rhizosphäre und die Pufferkapazität von Buchenkeimlingen in Nährlösungskultur. *Forstwiss. Cbl.* **107**, 160.
- Matzner, E. (1983): Balances of element fluxes within different ecosystems impacted by acid rain. In: Ulrich, B., Pankratz, J. (eds): *Effects of Accumulation of Air Pollutants in Forest Ecosystem*. Reidel Publ. Co., Dordrecht – Boston – London, 147.
- Mengel, K., Lutz, H. J., Breininger, M. Th. (1987): Auswaschung von Nährstoffen durch sauren Nebel aus jungen intakten Fichten (*Picea abies*). *Z. Pflanzenernähr. Bodenk.* **150**, 61.
- Mészáros, L. I. (1985): Nutrient content of herbs. In: Jakucs, P. (ed.): *Results of "Síkfőkút Project"*. Akadémiai Kiadó, Budapest, 348.
- Papp, B. (1985): Nutrient content of woody plants. In: Jakucs, P. (ed.): *Results of "Síkfőkút Project"*. Akadémiai Kiadó, Budapest, 321.
- Reemtsma, von J. B. (1986): Der Magnesium-Gehalt von Nadeln niedersächsischer Fichtenbestände und seine Beurteilung. *Allg. Forstzeitung* **157**, 196.
- Stefanovits, P. (1986): Some additional data on the acidification of soils. *Magyar Tudomány* **11**, 339. (In Hung.)
- Stumm, R., Morgan, J. J., Schnoor, J. L. (1983): Saurer Regen, eine Folge der Störung hydrogeochemischer Kreisläufe. *Naturwissenschaften* **70**, 216.
- Szabó, M. (1985): Amount and element content of precipitation, reaching the forest soil. In: Jakucs, P. (ed.): *Results of "Síkfőkút Project"*. Akadémiai Kiadó, Budapest, 385.
- Turcsányi, G., Fangmeier, A. (1990): Blei- und Kadmiumgehalt von Buchenwurzeln (*Fagus silvatica* L.) in Stammfuß- und Zwischenstammbereichen. *Z. Pflanzenernähr. Bodenk.* **53**, 197.
- Turcsányi, G., Kovács, M., Büttner, S., Penksza, K. (1991): The effects of stemflow water onto the element accumulation of beech roots. *Vllth International Conference Bioindicators Deteriorationis Regionis*. CSER, Ceske Budejovice, September 15.
- Ulrich, B. (1983): Interaction of forest canopies with atmospheric constituents: SO₂, alkali and earth alkali cations and chloride. In: Ulrich, B., Pankratz, J. (eds): *Effects of Accumulation of Air Pollutants in Forest Ecosystem*. Reidel Publ. Co., Dordrecht – Boston – London, 33.
- Wentzel, K. F. (1982): Immissionen oder saurer Regen — Wovon sterben Wälder und Seen. *Der Forst- und Holzwirt.* **37**, 410.
- Wittig, R., Neite, H. (1983): Sind Säurezeiger im Stammfußbereich der Buche Indikatoren für immissionsbelastete Kalk-Buchenwälder? *Allg. Forstzeitschrift* **38**, 1232.
- Zech, W., Porp, E. (1983): Magnesiummangel, einer der Gründe für das Fichtensterben in NO-Bayern. *Forstwiss. Cbl.* **102**, 50.
- Zólyomi, B. (1942): The Central-Danubian floristic divide and the dolomite phenomenon. *Botan. Közlem.* **39**, 209. (In Hung.)

3.2. The physiological role of magnesium and its effects on cultivated plants

- Aloni, R. (1980): Role of auxin and sucrose in the differentiation of sieve and treachary elements in plant tissue cultures. *Planta* **150**, 255.
- Anron, D., Franzke, W. E., Johnson, C. M. (1942): *Plant Physiol.* **17**, 515.
- Ballschmitter, K., Katz, J. J. (1969): An infrared study of chlorophyll-chlorophyll and chlorophyll-water interactions. *J. American Chem. Soc.* **91**, 2661.
- Bassham, J. A., Sharp, P., Morris, I. (1968): The effect of Mg^{++} concentration on the pH optimum and Michaelis constants of the spinach chloroplast ribulose-diphosphate carboxylase (carboxybismutase). *Biochim. Biophys. Acta* **153**, 998.
- Bergmann, W. (1979): *Occurrence and Identification of the Nutritional Disorders of Crop Plants*. Mezőgazdasági Kiadó, Budapest. (In Hung.)
- Bergmann, W. (1986): *Farbatlas, Ernährungsstörungen bei Kulturpflanzen*. VEB G. Fischer Verlag, Jena.
- Beringer, H., Forster, H. (1981): Einfluß variierter Mg-Ernährung auf Tausendkorngewicht und P-Fractionen des Gerstenkorns. *Z. Pflanzenernähr. Bodenk.* **144**, 8.
- Bodrawy, A. A., Bussler, W. (1968): *Potash Review Subject* **15**, 1.
- Copeland, B. E., Sunderman, F. W. (1952): *J. Biol. Chem.* **197**, 331.
- Couvillon, G. A. (1982): Leaf elemental content comparisons of ownrooted peach cultivars to the same cultivars on several peach seedling rootstocks. *J. Amer. Soc. Hort. Sci. (Alexandria)* **107**, 555.
- Davies, J., Gilbert, W., Gorini, L. (1964): The effect of magnesium ions on biological activities of streptomycin in bacterien. *Proc. Nat. Acad. Sci. USA* **51**, 883.
- Deleers, M., Servais, J. P., Wülfert, E. (1986): Neurotoxic cations induce membrane rigidification and membrane fusion at micromolar concentration. *Biochim. Biophys. Acta* **855**, 271.
- Durlach, J. (1985): *Le magnésium en pratique clinique*. Ed. Médicales, Paris.
- (Dzhnumov, D. A., Bocharov, E. A., Klimov, S. V.) Джнумов, Д. А., Бочаров, Е. А., Климов, С. В. (1982): Влияние температуры на содержание липидов в первом листе проростков озимой пшеницы. *Физиол. раст.* (Москва) **29**, 1067.
- Ebert, K. (1967): Der Einfluß von Stickstoff und Magnesium auf Ertrag und Qualität der Zuckerrübe. *Albrecht Thaer Archiv* **11**, 439.
- Eichorn, G. L. (1962): *Nature* **194**, 474.
- Elődi, P. (1983): *Biochemistry*. Akadémiai Kiadó, Budapest. (In Hung.)
- Fabian-Galau, G. (1975): The influence of N, S and Mg deficiency on the synthesis of leaf proteins. *Rev. Roum. Biol. Bucharest* **20**, 199.
- Fecenko, J., Francaková, H. (1979): Vplyv ronzych foriem horcia na sacharidovy komplex sladovniceho jaemena. *Polnohospodárstvo* (Bratislava) **25**, 784.
- Fischer, G. L., McNeill, Democko, C. J. (1986): Trace element interaction affecting pulmonary macrophage cytotoxicity. *Environmental Research* **39**, 164.
- Fleury, B., Dipietro, A., Goinet, C., Gauthere, D. C. (1980): Role of magnesium of kinetic-parameters of soluble FI-ATP-ase from pig heart mitochondria. *Biochimie* **62**, 733.
- Gallaher, R. N., Jellum, M. D. (1976): Elemental and/or cation ratio efficiency of corn hybrids grown on infertile soil in adequate in magnesium. *Comm. Soil Sci. Plant Anal.* **7**, 653.
- Gilly, A., Király, Z. (1980): The effect of induced juvenility on necrosis formation by facultatively parasitic fungi. *Növényvédelem* **16**, 1. (In Hung.)
- Gilly, A., Kiss, A. S. (1982): Different forms of nitrogen have different effects on the resistance of host plants to facultative parasites. The probable explanation of the difference. *Növényvédelem* **18**, 486. (In Hung.)

- Grimme, H., Braunschweig, L. C. (1974): Beziehungen zwischen K, Ca und Mg bei Aufnahme und Ertragsbildung. *Landw. Forsch.* (Frankfurt a.M.) **30/II**, 93.
- Guiet-Bara, A., Bara, M., Durlach, J. (1990): Magnesium: a competitive inhibitor of lead and cadmium. *Magnesium Research* **3**, 31.
- Jacob, A. (1955): *Magnesium der fünfte Pflanzenhauptnährstoff*. Ferdinand Enke Verlag, Stuttgart, 51.
- Jakab, S. (1976): Verbal communication.
- Kirby, E. A., Mengel, K. (1976): The role of magnesium in plant nutrition. *Z. Pflanzenernähr. Bodenk.* **209**.
- Kiss, A. S. (1972): Characterization of different degrees of magnesium sensitivity in plants. *Acta Agr. Acad. Sci. Hung.* **21**, 404.
- Kiss, A. S. (1973): Nitrogen fertilizer supplemented with magnesium and its agricultural and biochemical effects. C. Sc. Thesis, Budapest – Kazincbarcika. (In Hung.)
- Kiss, A. S. (1975): Correlation between the magnesium and protein contents of various parts of the leaf blade. *Botan. Közlem.* **62**, 117. (In Hung.)
- Kiss, A. S. (1977): Magnesium effect on the synthesis of embrional gibberelline. *Proc. 17th Hung. Ann. Meet. Biochem.*, Kecskemét 119.
- Kiss, A. S. (1979a): Germination stimulation by magnesium, and the mechanism of action. *Acta Agr. Acad. Sci. Hung.* **28**, 384.
- Kiss, A. S. (1979b): Data on pollen germination. *Kertgazdaság* **11**, 64. (In Hung.)
- Kiss, A. S. (1980a): The effect of magnesium on the auxin-content of plants. *Proc. 20th Hung. Ann. Meet. Biochem.*, Siófok 239.
- Kiss, A. S. (1980b): Regulation of catalase activity in plants by magnesium. *Hohenheimer Magnesium-Symposium*, Stuttgart M-8.
- Kiss, A. S. (1981a): The effects of nitrogen and magnesium fertilization on wheat straw and its lodging. *Agrokémiai Tájékoztató* **6** (3), 27. (In Hung.)
- Kiss, A. S. (1981b): Das Magnesium und dessen Rolle in den Pflanzen. *Magnesium-Bull.* **2** (1a), 6.
- Kiss, A. S. (1983): *Magnesium Fertilization, Magnesium in Biology*. Mezőgazdasági Kiadó, Budapest. (In Hung.)
- Kiss, A. S. (1984a): Auswaschbarkeit von endogenem und exogenem Magnesium. 7. *Hohenheimer Magnesium-Symposium*, M-2.
- Kiss, A. S. (1984b): The effect of magnesium deficiency on the crop elements and stem stability of barley. *Növénytermelés* **33**, 559. (In Hung.)
- Kiss, A. S. (1988): Effect of magnesium on juvenility and rejuvenescence of plant cells, and its possible mechanism. *Magnesium Research* **1**, 177.
- Kiss, A. S. (1989): Effect of magnesium ions on the anion uptake of plants. *Acta Agron. Hung.* **38**, 23.
- Kiss, A. S. (1989a): Antagonism of magnesium and aluminium in bean and wheat. *Acta Agron. Hung.* **38**, 219.
- Kiss, A. S. (1990): Nitrate content of plants by magnesium fertilizers. *Magnesium Research* **3**, 263.
- Kiss, A. S. (1991): Unpublished data.
- Kiss, A. S., Dombovári, J., Oncsik, M. (1991): Magnesium inhibits harmful effects of some elements. 3rd European Congress on Magnesium. Geneva, 1990. *Magnesium Research* **4**, 3.
- Kiss, A. S., Horváth, L., Pozsár, B. (1960-1970): The stimulating effect of agronite on the magnesium content and photosynthetic carbon dioxide fixation of the leaves of winter wheat Besostaya. 1. *Búza termesztési Kísérletek* (Budapest) 106. (In Hung.)
- Kiss, A. S., Mustárdy, L. (1985): Effect of magnesium deficiency on chloroplasts and mitochondrie in red pepper leaves. *Magnesium-Bull.* **4**, 152.
- Kiss, A. S., Oncsik, M., Dombovári, J., Veres, S., Ács, G. (1990): Arsenic uptake of spring

- barley and onion and its decrease by magnesium fertilization. *Hungarochem. Congress* (Keszthely), 83. (In Hung.)
- Kiss, A. S., Pejtkó, I., Osváth, D. (1976): The significance of the magnesium content of agronite in the germinative ability of sowing-seed. *Agrokémiai Tájékoztató* 1 (2), 28. (In Hung.)
- Kiss, A. S., Pozsár, B. I. (1975): Stimulative effect on protein synthesis of magnesium applied by foliage spray. *Acta Agron. Sci. Hung.* 24, 61.
- Kiss, A. S., Pozsár, B. I. (1977): Danger of excessive nitrogen fertilization and magnesium deficiency as carcinogenic factors. *Magyar Kémikusok Lapja* 32, 175. (In Hung.)
- Klein, L. B., Chandra, S., Mondy, N. I. (1981): Effect of magnesium fertilization on the quality of potatoes, yield, discoloration, phenols and lipids. *J. Agric. Food Chem.* 29, 384.
- Kuderev, T., Babulka, N. (1975): The influence of magnesium insufficiency on the fraction of easily soluble protein and on the isoenzyme composition of certain dehydrogenases. *Agrochimica* (Pisa) 19, 336.
- Kumar, V., Bhatia, B. K., Chukia, V. C. (1981): Mg and Zn relationship in relation to dry matter yield and concentration and uptake of nutrients in wheat. *Soil Sci.* 131, 151.
- Lakatos, B. (1972): Metal complexes of adenosine phosphates. *Acad. Sci. Hung. KKKI*, Budapest, 214. (In Hung.)
- Lang, A. (1970): Gibberellins: Structure and metabolism. *Ann. Review Plant Physiol.* 21, 537.
- Leszek, G., Del Campo, O. (1985): Role of magnesium in the dietotherapy of degenerative diseases. In: *Magnesium Deficiency, First Eur. Cong.* (ed. by Halpern and Durlach). Karger, Basel, 239.
- Ligeti, E. (1980): *Cation transport, proton pump and membrane state transitions in isolated mitochondria*. C. Sc. Thesis, Budapest. (In Hung.)
- Litynski, T. (1973): Rola magnezu w zyciu roslin zwierzat i ludzi. *Zeszyty Probl. Postepow NAUK* (Warszawa) 23.
- Loch, J. (1970): *Correlation between the magnesium content of the soil and the amount of magnesium available to plants*. C. Sc. Thesis, Debrecen. (In Hung.)
- Loch, J. (1990): Effects of magnesium fertilization on the yield and on mineral content of plants. *Magnesium Research* 3, 48.
- Madhok, O. P., Walker, R. B. (1969): Magnesium nutrition of two species of sunflower. *Plant Physiol.* 44, 1016.
- Maitra, P., Mukherji, S. (1979): Effect of lead in nucleic acid content of rice and interaction with Ca. *Indian J. Exp. Biol.* 17, 929.
- Mándy, Gy., Kiss, A. S. (1976): Ecophysiological effect of magnesium on wheat. *Növénytermelés* 25, 23. (In Hung.)
- Moller, I. M., Schwitzgebel, J. P., Palmer, J. M. (1982): Binding and screening by cations and effect on exogenous NAD(P)/H oxidation in *Neurospora crassa* mitochondria. *Eur. J. Biochem.* 123, 204.
- Mudd, J. B. (1959): *Nature* 183, 900.
- Neales, T. F. (1955): *Nature* 175, 429.
- Palade, G. E. (1955): *J. Biophys. Biochem. Cytol.* 1, 59.
- Patócs, I. (ed.) (1989): Nutritional disorders and diseases of plants. *Agroinform* (Budapest) 232.
- Pfützer, G., Pfaff, C., Roth, H. (1952): Vitamin Inhibition von Magnesiummangel. *Landw. Forsch.* 4, 105.
- Poirier, L. A., Theiss, J. C., Arnold, L. J., Shimkin, M. B. (1984): Inhibition by Mg- and Ca-acetates of lead subacetate induced lung tumors in strain A Mice. *Cancer Research* 44, 1520.
- Pozsár, B. I., Kiss, A. S., Oros, Gy. (1973): *Proceedings of the Conference on Chemical Processes in agriculture*. Keszthely, 88. (In Hung.)
- Repka, J., Jurenková, Z. (1981): Heterogeneity of the maize leaf blade in characteristics, respiration, mineral nutrient contents and growth substances. *Biol. Pl.* (Praha) 23, 145.

- Ricciardi, R. P., Hollomon, D. W., Gottlieb, D. (1974): Age dependent changes in fungi: ribosomes and protein synthesis in *Rizoctonia solani* mycelium. *Arch. Microbiol.* (Berlin) **95**, 325.
- Rigby, M. G., Berry, W. L., Olson, B. H. (1983): Mobility of cadmium in soil-plant-insect food chain as influenced by native and amended soil cadmium levels. *Internat. Conf. Heavy Metals Environm.* Heidelberg, **2**, 753.
- Rigó, J., Szelényi, I. (1969): The role of magnesium in the pathology of circulation. *Orvostud. Aktuális Problémái* (Budapest), 69. (In Hung.)
- Rousselet, F., Durlach, J. (1971): Techniques analytique et exploration pratiques du métabolisme magnésium en clinique humaine. *First Internat. Magnesium Symp.* Vittel, 75.
- Roychondhury, R., Datta, A., Sen, S. P. (1969): RNA in developing plant cells. *Biochim. Biophys. Acta* **107**, 346.
- Rubin, H. (1975): Central role for magnesium in coordinate control of metabolism and growth in animal cells. *Proc. Nat. Acad. Sci. USA* **72**, 3551.
- Saigusa, M., Shoji, S., Takahashi, T. (1980): Plant root growth in acid soils from Japan. *Soil Sci.* (Japan) **130**, 242.
- Schiltz, P., Coussairat, J. C. (1978): Influence exercée par le magnésium sur les manifestations héréditaires de la plante de tabac. *Annal. Biol.* (Paris) **17**, 169.
- Schimansky, C. (1973): Untersuchung zur Translokation von Magnesium in Sonnenblumenpflanzen. *Z. Pflanzenernähr. Bodenk.* **136**, 68.
- Schuffelen, A. C. (1974): Aspects of potassium and magnesium uptake by oats. *Neth. J. Agric. Sci.* (Wageningen) **22**, 237.
- Schumacher, R., Frankhauser, F. (1974): Stippenbildung und Mineralstoffgehalt von Apfel in Abhängigkeit von ihrer Stellung in der Baumkrone. *Schweiz. Landw. Forsch.* (Bern) **13**, 353.
- Sen, N. K., Patra, H. K., Mishra, D. (1984): Phytochrome regulation of biochemical and enzymatic change: during senescence of excised rice leaves. *Z. Pflanzenphysiol.* **113**, 95.
- Simmonds, J. A., Dumbroff, E. B. (1974): High energy charge as a requirement for axis elongation in response to gibberellic acid and kinetin during stratification of *Acer saccharum* seeds. *Pl. Physiol.* (Washington) **53**, 91.
- Stanev, V. P., Pandev, S., Kudrev, T. (1982): Influence of macroelement deficiency on photosynthesis and respiration in sunflower. *Dokl. Bolg. A. N.* **35**, 217.
- Subramanian, A. R., Ron, E. Z., Davis, B. D. (1968): A factor required for ribosome dissociation in *Escherichia coli*. *Proc. Natl. Acad. Sci. (USA)* **61**, 761.
- Szer, W., Ochoa, S. (1964): Complexing stability and coding properties of synthetic polynucleotides. *J. Mol. Biol.* **8**, 823.
- Ward, G. M., Miller, M. J. (1969): *Canad. J. Plant. Sci.* **49**, 53.
- Williams, R. J. P. (1971): *Inorg. Chim. Acta Rew.* **5**, 137.

3.3. The effects of magnesium on biomass formation and special metabolism in plant tissue culture

- Ahmad, F., Tan, K. H. (1986): Effect of lime and organic matter on soybean seedlings grown in Al-toxic soil. *Soil Sci. Soc. Am. J.* **50**, 656.
- Allen, G. V. (1987): Influence of aluminium and magnesium metabolism. In: *Magnesium in Cellular Processes and Medicine*. (Eds: Altura, Durlach, Seelig.) Karger, Basel, 50.
- Breinlich, J., Scharnagel, K. (1968): Pharmakologische Eigenschaften des En-In-Dicycloäthers aus *Matricaria chamomilla* L. *Arzneimittel-Forsch.* **18**, 429.

- Cambraia, J., Galvani, F. R., Estevac, M. M., Santanna, R. (1983): Effect of Al on organic acid, sugar and amino acid composition of the root system of sorghum. *J. Plant Nutr.* (New York) **6**, 313.
- Cartoni, G., Goretti, G., Russo, M. V., Zacchei, P. (1990): Microcapillary gas-chromatographic analysis of camomile. *Ann. Chim.* **80**, 523.
- Conner, A. J., Meredith, C. P. (1985a): Simulating the mineral environment of Al toxic soils in plant cell culture. *J. Exp. Botany* **36**, 870.
- Conner, A. J., Meredith, C. P. (1985b): Large-scale selection of aluminium-resistant mutants from plant cell culture: expression and inheritance in seedlings. *Theor. Appl. Genet.* **71**, 159.
- Gilbertson, G., Koenig, T. R. (1981): Essential oils and related products. *Anal. Chem.* **53**, 61.
- Guerrier, G. (1979): Adsorption des éléments minéraux en présence d'aluminium. *Plant Soil* **51**, 275.
- Hüttermann, A. (1983): Auswirkungen saurer Deposition auf die Physiologie des Wurzelraumes von Waldökosystemen. *Allgem. Forstzeitung* **26/27**, 663.
- Janku, I., Zita, C. (1954): Protizánětlivé účinky nektary látek z hermanku II. *Czechoslov. Farmac.* **3**, 93.
- Kiss, A. S. (1983): *Magnesium Fertilization, Magnesium in Biology*. Mezőgazdasági Kiadó, Budapest 173. (In Hung.)
- Kiss, A. S. (1986): The acidification of soil increases aluminium toxicity which is antagonized by magnesium. *16th Agricultural Chemicalization Congress*, Keszthely, 11. (In Hung.)
- Kiss, A. S. (1987): Magnesium and aluminium in plant and human biology; the inhibition of aluminium toxicity. *17th Agricultural Chemicalization Congress*, Keszthely, 35. (In Hung.)
- Kiss, A. S. (1989): Effect of magnesium ions on the anion uptake of plants. *Acta Agron. Hung.* **38**, 23.
- Matsumoto, H., Morimura, S. (1980): Repressed template activity of cromatin of pea roots treated with aluminium. *Plant Cell. Physiol.* **21**, 951.
- Motl, O., Repčák, M., Sedmera, G. (1978): Weitere Bestandteile des Kamillenöls. 2. *Mitt. Arch. Pharm.* (Weinheim) **311**, 75.
- Motl, O., Repčák, M. (1979): New components from camomile essential oil. *Planta Med.* **36**, 272.
- Murashige, I., Skoog, F. (1962): A revised medium for rapid growth and bio-assays with tobacco tissue cultures. *Physiol. Plant.* **15**, 473.
- Ojima, K., Ohira, K. (1985): Reduction of Al toxicity by addition of a conditioned medium from Al-tolerant cells of carrot. *Plant Cell Physiol.* **26**, 281.
- Schmialek, P. (1961): Die Identifizierung zweier in Tenebriokot und in Hefe vorkommender Substanzen mit Invenilhormonwirkung. *Z. Naturforsch.* **16b**, 461.
- Szőke, É., Shavarda, A. L., Kuzovkina, I. N. (1979): Effect of culturing conditions on essential oil formation in callus tissue of wild chamomile inflorescences. *Soviet Plant Physiology* **26**, 579.
- Szőke, É., Kiss, A. S., Kursinszki, L., Petri, G. (1989): Effect of magnesium ions on the camomile tissue cultures. *Magnesium Research* **2**, 227.
- Szőke, É., Kiss, A. S., Kursinszki, L., Petri, G. (1992a): Inhibition of aluminium toxicity by magnesium and citric acid in tobacco tissue culture. *Magnesium Research* **5**, 83.
- Szőke, É., Kiss, A. S., Kursinszki, L., Petri, G. (1992b): Physiological effects of magnesium on the camomile tissue cultures. *Magnesium Research* **5**, 240.
- Tan, K. H., Binger, A. (1986): Effect of humic acid on aluminium toxicity in crop plants. *Soil Sci. Baltimore* **141**, 20.
- Wagatsuma, T. (1983): Effect of nonmetabolic conditions on the uptake of Al by plant roots. *Soil Sci. India* **53**, 882.
- Wallace, S. K., Anderson, I. C. (1984): Aluminium toxicity and DNA synthesis in wheat roots. *Agron. J.* **76**, 5.

4. Possibilities of magnesium addition to soils and plants

The discovery that magnesium is essential for plant growth dates back to the middle of the 19th century. The magnesium needs of plants can be met by means of fertilization or chemical soil amelioration. In the course of fertilization, the magnesium needed for the dry matter production is added to the soil year by year, the amount generally being adjusted to the needs of the given plant. Elimination of the acidity of acid soils deficient in magnesium and increase of the magnesium content of soils can be achieved together through application of ameliorating materials containing magnesium, such as dolomite (see Section 4.2).

4.1. Magnesium fertilization

Magnesium fertilization in soils deficient in magnesium increases both the yields of crops and their magnesium content, whereas a magnesium deficiency can lead to a yield loss. The magnesium supply of plants subsequently affects animal and human nutrition through the food chain.

Garner et al. (1922–1923) found that the chlorosis of tobacco and other plants in acid sandy soils could be traced back to a magnesium deficiency. Anderson and Swanback (1929) confirmed that the symptoms could be avoided by magnesium fertilization.

Carolus (1933) described the deficiency symptoms in the case of potato, while others examined them in fruit trees, including an account of premature defoliation (Hill and Johnston, 1939; Wallace, 1939; Kidson et al., 1940; Mulder, 1950).

Despite the early discovery of the role of magnesium, magnesium fertilization did not rapidly become widespread. Schilling (1957) stated that the necessity for magnesium fertilization acquired more importance when agricultural production became more intensive. The addition of nitrogen, kalium and potassium fertilizers to the soil in larger quantities increased yields, and the widespread application of potassium fertilizers with a high active ingredient but a low magnesium content contributed to the decrease in the available magnesium content of soils.

A magnesium deficiency is primarily characteristic of acid sandy soils with a low nutrient-supplying capacity where the acidity also hinders magnesium uptake (Stenuit, 1959).

Plants respond to a low magnesium supply by displaying specific deficiency symptoms. Because of decreased chlorophyll formation, chlorosis appears on the older leaves. Comprehensive studies of the deficiency symptoms of different plant species were reported by Jacob (1955) and Bergmann (1961, 1988). Of the Hungarian researchers, Husz (1941) described the deficiency symptoms of tobacco and apple, while Surányi and Mándy (1955) specified the deficiency symptoms of maize.

In the case of cereals, a local chlorophyll accumulation resembling a string of pearls can be found on the surface of the light-green leaves. A magnesium deficiency in maize results in the leaves becoming striped. On the leaves of dicotyledons, the veins remain green, while chlorosis occurs on intervein areas. Apple trees and grapes occasionally produce purplish-red leaves as a result of anthocyanin development. Leaf necrosis and premature defoliation may also occur. The magnesium content of a plant suffering from a lack of magnesium is usually much lower than that of the healthy plant.

Besides the magnesium deficiency inherent to soils poor in magnesium, an induced magnesium deficiency can also occur due to the potassium-calcium-magnesium antagonism. Since the magnesium uptake by plants is affected by the proportions of the cations in the soil solution, the magnesium uptake can be reduced by the presence of larger amounts of potassium and calcium (Michael, 1941; Scharrer and Mengel, 1958; Mengel, 1960; Kirkby and Mengel, 1976).

Mulder (1956) found that the magnesium uptake is also hindered by the ammonium ion. Schachtschabel (1959) observed that on the regular fertilization of crops with high needs for magnesium, the potassium and ammonium antagonism became minimal. Welte and Werner (1963) concluded that potassium reduced the magnesium uptake only in soils absolutely deficient in magnesium.

Because of the partially contradictory observations, the potassium-calcium-magnesium antagonism was examined in multifactorial experiments. These revealed that certain cations promote the uptake of other cations to a certain extent and only doses exceeding the optimal level reduce the uptake of the element at a minimum (Loch et al., 1986; Loch, 1989, 1990).

Magnesium fertilization provides the magnesium needed for dry matter production on soils deficient in magnesium and on soils lacking adequate readily mobilizable reserves.

The magnesium balance of soils depends on the properties of the given soil and on the mode of cultivation. The amount of magnesium in the soil is increased by magnesium fertilizers, manures and plant residues, whereas it is decreased by the losses due to plant growth. The non-application of magnesium fertilizers results in a negative balance: losses due to plant growth are higher than the amount returned to the soil, indeed they are occasionally higher than the amount mobilized in the same year.

Magnesium losses due to plant growth depend on the amount of the crop and on its magnesium content. This quantity can provide a guide in the estimation of the need for magnesium fertilizers. *Table 4.1* lists the average magnesium contents of different crops. These data mean that the following quantities of magnesium are extracted from the soil by the average yields of the crops: cereals 15–20, maize 30–40, sunflower 20–25, potato 20–25, and sugar beet 45–50 kg/hectare/year. About 20–40% of the quantities taken up by the plants is returned to the soil. The calculations of Henriksen (1970) show that the annual magnesium loss amounts to about 5 kg/hectare if organic ferti-

Table 4.1. Magnesium needs of field crops
(Jacob, 1955; Finck, 1979)

Crops	Magnesium needs
	<i>kg/t main crop</i>
Cereals	2.5– 3.0
Maize	4.0– 5.0
Sunflower	8.0–10.0
Rape	5.0– 6.0
Soybean	6.0– 8.0
	<i>kg/10 t main crop</i>
Sugar beet	10.0–12.0
Fooder beet	6.0– 8.0
Potato	8.0–10.0
Maize for silage	5.0– 6.0

lizers are added to the soil regularly, whereas without such fertilizers the magnesium loss is about 20 kg/hectare.

In Hungary, regular organic fertilization is carried out only on few farms. Animal stocks are especially scarce on sandy soils deficient in magnesium, which contributes to further magnesium deficiencies.

Besides the magnesium supply in the soil, the effect of magnesium fertilization in achieving higher yields also depends on the acid, neutral, or alkaline nature of the soil, as well as on the NPK supply. Jaskowski (1965) pointed out that the desired effect of magnesium fertilization might not be achieved on soils deficient in magnesium if the supply was estimated only by examination of the topsoil, or if the NPK supply was not adequate. His findings were confirmed by Loch (1975).

It is not possible to provide a comprehensive picture of the effects of magnesium fertilization within the framework of the present book. Accordingly, merely some characteristic examples will be mentioned.

Numerous data are available concerning the magnesium fertilization of potato. In Hungary, Kemenesy et al. (1961, 1963) achieved favourable effects on leached brown forest soils in the county of Somogy. In response to magnesium fertilization, both the yield and the starch content of potato increased. In long-term experiments in the Nyírség region, Láng (1973) examined the effects of NPK and NPK + Mg fertilization on brown forest soils with residual carbonate. Magnesium fertilization increased the potato yield in certain years.

Kádár and Szemes (1989) achieved good results from the magnesium fertilization of sunflower. The addition of magnesium to the soil increased the yield 3-fold.

In another long-term experiment, Márton (1989) studied the effects of magnesium fertilization on potato, maize, sunflower, and horse bean yields. He found that the nutrient response varied with the plant species, variety and years. Magnesium fertilization resulted in higher horse bean and sunflower yields. Of the potato varieties, Boglárka responded to most favourably magnesium addition.

The magnesium needs of sugar beet are also high. Sugar beet is usually produced on loam and clay soils, where a magnesium deficiency may occur. Lachowski and Weselowski (1964) achieved the best effects on soils in which the amount of silt and

clay particles in the cultivated layer exceeded 50%, while the available magnesium content was lower than 7.5 mg/100 g soil. Voigtländer (1965) made similar observations. In Hungary, beneficial effects on sugar beet production were achieved on chernozem soil by Bocz (1962) and on brown forest soil by Kiss (1972).

Magnesium addition to meadows and pastures is important because of the magnesium supply of the grazing animals. Forage low in magnesium leads to grass tetany (hypomagnesaemia) in cattle. Todd (1962), Wolton (1963), Welte and Werner (1964) found that the low magnesium content of the grass in early spring can be increased by magnesium fertilization.

Geissler and Kurnoth (1959) studied the needs of 18 vegetables for magnesium, and established that these were relatively high. On soils with average productivity, these needs can be met only by magnesium fertilization. It should also be taken into consideration that appreciable potassium too is used in the fertilization of vegetables.

Magnesium fertilization is likewise increasingly necessary in fruit production. This is related in part to potassium application on a large scale. Gruppe (1961a, b), Bingham (1963) and Gärtel (1959) studied the magnesium needs of apple, pear and grapes, and all recommended magnesium addition.

4.2. Magnesium fertilizers and their application

Both magnesium compounds and chemical fertilizers containing magnesium can be used for magnesium fertilization. The most important magnesium fertilizers are presented in *Table 4.2*.

The magnesium compounds are by-products of potassium fertilizer production and originate from enrichment and purification of crude potassium salt. Kieserite ($\text{MgSO}_4 \cdot \text{H}_2\text{O}$) is a constituent of crude potassium salt. Kieserite is used to produce anhydrous magnesium sulphate (MgSO_4) by heating, and Epsom salt ($\text{MgSO}_4 \cdot 7\text{H}_2\text{O}$) by recrystallization.

Table 4.2. Magnesium fertilizers and N, P, K fertilizers containing magnesium

Fertilizers	Mg%
Epsom salts ($\text{MgSO}_4 \cdot 7\text{H}_2\text{O}$)	10.0
Kieserite ($\text{MgSO}_4 \cdot \text{H}_2\text{O}$)	16.0
Anhydrous magnesium sulphate (MgSO_4)	20.0
Agronit ($\text{NH}_4\text{NO}_3 + \text{CaCO}_3 \cdot \text{MgCO}_3$)	2.0
Kardonit ($\text{CO}/\text{NH}_2/2 + \text{CaCO}_3 \cdot \text{MgCO}_3$)	5.0
Magnesium ammonium phosphate (MgNH_4PO_4)	14.0
Korn-Kali (KCl, MgSO_4)	3.6
Kamex (KCl, MgSO_4)	3.6
Patentkali ($\text{K}_2\text{SO}_4 \cdot \text{MgSO}_4$)	6.0
Magnesia-Kainit (crude potassium salt) (KCl, NaCl, MgSO_4)	3.0
Plantosan 4D (NPK+Mg fertilizer)	3.6
Volldünger Linz (NPK+Mg+micronutrient fertilizer)	0.6

Epsom salt dissolves fully even in cold water. Kieserite dissolves in cold water slowly and not completely. Anhydrous magnesium sulphate can be dissolved by heating. Because of the above properties, Epsom salt is primarily applied to the leaves, and Kieserite is mainly as a soil fertilizer. The application of anhydrous magnesium sulphate (calcined) had not become widespread because of its hygroscopic nature and since it dissolves with difficulty.

Some N, P, K fertilizers are produced with the addition of magnesium compounds. Of the N fertilizers, calcium ammonium nitrate may contain magnesium if the ammonium nitrate is mixed with dolomite instead of calcium carbonate. In Hungary, such fertilizers are produced by BVK (Borsodi Vegyi Kombinát): Agronit, which contains 28% N and 2% Mg; and Kardonit, a mixture of urea and dolomite, containing 28% N and 5% Mg. The magnesium content of dolomite dissolves only in an acidic medium.

Magnesium ammonium phosphate is a fertilizer containing 8% N, 40% P and 14% Mg. It is soluble in mild acids. Thermophosphates containing magnesium can also be used for magnesium fertilization.

Magnesium sulphate is added to some K fertilizers (see *Table 4.1*). Their advantage is that they contain magnesium in a water-soluble form. Of the multicomponent N, P, K fertilizers, Plantosan 4D and Volldünger Linz contain magnesium.

Foliar application

Plants usually take up the necessary nutrients from the soil through the roots, but nutrients applied to the leaves are also utilized. The advantage of foliar application in the growing season is that in this way the metabolic processes can be influenced by small amounts of fertilizers utilized directly by the plant. However, foliar application cannot replace soil fertilization, especially on soils with a low nutrient content.

Only dilute solutions can be used for foliar application. For magnesium fertilization, the repeated application of 400 dm³ 5% Epsom salt solution (0.5% Mg) per hectare is generally recommended. In farming practice higher concentrations up to 10% are also used in cases of severe magnesium deficiency.

The effectiveness of foliar fertilization is highly dependent on the timing. The best results can usually be achieved in the period of intensive growth. When noticeable deficiency symptoms occur, spraying should be repeated weekly until these disappear. Magnesium sulphate can be mixed with most pesticides, and thus chemical plant protection and magnesium addition can be achieved simultaneously.

The development phases recommended for the spraying of various crops are as follows:

wheat, barley, oat:	from first node to early milky ripe
maize:	from the four-leaf stage on
rape:	from the beginning of shooting to flowering
sugar beet:	inter-row leaf cover onwards
potato:	inter-row leaf cover onwards
meadow-pasture:	one day after moving
peas, beans:	ground-cover to pre-flowering
grapes:	after blossoming

Foliar feeding of cereals deserves special interest according to Grimme (1986), who observed that foliar application of an Epsom salt solution to cereals favourably affected growth, thousand grain weight and grain yield. Hence, magnesium is essential for both growth and translocation of assimilates, and foliar fertilizer application is therefore recommended at two different times: first in the tillering phase, at the beginning of shooting and then after blossoming until ripening.

The magnesium spray applied in the first period is necessary because the magnesium uptake cannot keep up with the rapid plant growth in the phase of shooting. Consequently, the magnesium concentration in the plants decreases to a great extent and deficiency symptoms occur.

The second critical period is the phase after blossoming. This is the time when the starch produced in the leaves migrates into the grains. The longer the flag leaf stays green, the better the graining will be. Cereals take up only a small proportion of the magnesium accumulated in the grain from the soil; most of it is translocated from the stalk and the leaves. This is why late magnesium sprays can increase the thousand grain weight.

Soil fertilization

The effectiveness of soil fertilization is influenced decisively by the properties of magnesium fertilizers and the applied dose.

In the choice of a magnesium fertilizer, its solubility and nutrient content, and the pH conditions of the soil should be taken into consideration. The advantage of magnesium sulphate and fertilizers containing magnesium sulphate is that they are water-soluble and can be applied to acidic, neutral or alkaline soils. The magnesium content of fertilizers to which dolomite is added dissolves only in an acidic medium. *Figure 4.1* shows, how to choose the adequate magnesium form for different site conditions (Andres, 1992).

For the correct determination of fertilizer doses, the needs of the given crop for magnesium and the magnesium supply of the soil in question should be known. Soil scientists differentiate three categories of soils according to their nutrient supply: soils with a poor, fair and good nutrient content (see sections 2.3 and 9.1).

Magnesium fertilization is generally recommended only on soils with a poor or fair supply. In the latter case, the magnesium needed for dry matter production should be added to the soil, whereas for soils with a poor supply, more should be added, so that the magnesium content of the soil can also be increased. On soils with a high potassium or clay content, increased magnesium doses are recommended. High potassium fertilizer doses may also necessitate an increase of the magnesium doses. With regard to all the above aspects, the magnesium doses recommended in the international literature on fertilization are 20–40 or 60 kg/ha. The addition of higher doses to the soil is possible only with magnesium compounds, e.g. Kieserite.

Because of their low nutrient content N, P, K fertilizers containing magnesium are primarily suitable for the regular addition of small doses of magnesium to the soil; application of the recommended doses to the soil is problematic. For example, when the fertilizer Agronit (28% N and 2% Mg) is used, 20 kg magnesium can be added to the soil only together with 280 kg N, which is not necessary on low-productivity

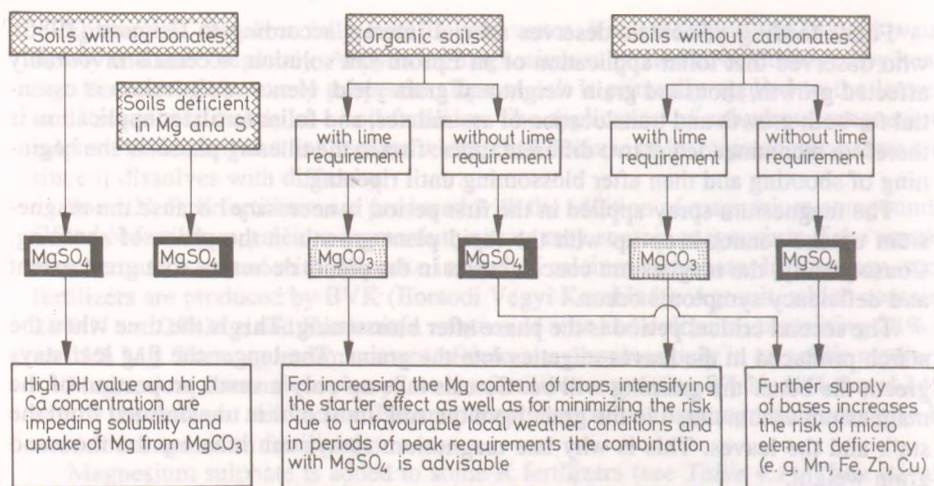


Fig. 4.1. Agrochemical conditions for the use of MgSO_4 and MgCO_3 in agriculture (Andres 1992)

sandy soils, and it may even have a damaging effect. The nitrogen : magnesium ratio in Kardonit is more favourable.

Similarly, the magnesium content in potassium fertilizers is usually very low (3–4%). It is favourable, however, that crops with a high need for magnesium (beets, potato, vegetables and fruits) at the same time, demand considerable potassium, and these two elements can therefore be added to the soil in harmonic proportions. In the earlier discussion of the needs of various plant species for magnesium, it was mentioned that in some cases a magnesium deficiency occurs because of the high potassium doses applied to the soil. In such cases in particular, the use of potassium fertilizers containing magnesium is recommended on endangered areas. As far as the magnesium fertilization of meadows and pastures is concerned, the use of fertilizers containing potassium, sodium and magnesium can also be beneficial.

To summarize the effects of magnesium fertilization, it may be concluded that on soils deficient in magnesium such fertilization may increase yields and improve quality (e.g. carbohydrate production), and always increases the magnesium content of the product. The beneficial effects of magnesium fertilization may be associated with the multiple physiological role of magnesium (see Chapter 3). Besides its direct effects, the role of magnesium in eliminating toxic elements (e.g. aluminium) is considerable. The non-performance of magnesium fertilization on soils deficient in magnesium leads to a yield loss and results in unbalanced mineral proportions.

One-sided human intrusions such as excessive liming or potassium fertilization is equally harmful from the aspects of dry matter production and mineral matter content. Multifactorial experiments have demonstrated that the potassium, calcium and magnesium supplies must be harmonized on these soils (Loch, 1990).

4.3. Increasing the magnesium supply by chemical soil improvement

In Hungary, there are 2.3 million hectares of acid soils, 500,000 hectares of which have low magnesium supplies. A low magnesium supply for plants in Hungary occurs mainly in acid, magnesium-deficient soils. The low magnesium status of the soils can be explained by their physical and chemical characteristics and by genetic factors (Loch, 1970, 1983).

In these highly acid soils, there is an ever-increasing leaching of calcium and magnesium (released by weathering and other processes), which disturb the balance of the minerals and decreases nutrient utilization. Since the course of such leaching is determined by the solubility of these elements, acidic sandy soils poor in calcium tend to develop a magnesium deficiency as well.

In acid soils, the availability of the small amounts of magnesium is further restricted by the increased H^+ ion concentration of the soil solution.

In these soils, the conventional application of lime to control soil acidity will not correct a magnesium deficiency; indeed, the antagonism exerted by the applied calcium doses will make the magnesium uptake of the plants even worse.

Stefanovits (1981) emphasized that, in soils short of carbonatic lime, acidic air pollution enhances the calcium and magnesium leaching by acidifying fertilizers. The ammonium and potassium ions from fertilizers cause the shrinkage of the swelling clay minerals in the soil. The high amount of potash alters the ion ratios in the soil solution and the magnesium uptake by plants will be reduced even at relatively low levels of acidity.

A national study on the possibilities of long-term biomass utilization initiated by the Hungarian Academy of Sciences (Láng, 1985) revealed that, in proportion with the growth of the amount of biomass, the uptakes of macro, meso and micro elements are increased. Certain elements may therefore be reduced to such low levels as to cause deficiency symptoms in plants. To make up for the alkali losses in soils with little buffering capacity, the increased and systematic application of calcium and magnesium-containing soil-improving materials must be instituted.

In countries where there is a high proportion of highly acid and strongly leached soils, a wide range of such magnesium-containing materials are used, natural or heat-treated dolomites of various genetic origins predominating. Pure dolomite contains equal molecular amounts of $CaCO_3$ and $MgCO_3$, their mass ratio being 54.3% $CaCO_3$ to 45.7% $MgCO_3$.

Pettyjohn (1957) reported that dolomitic and calcitic limestones can be divided into the following types:

dolomite	11.7 – 13.1% Mg
calcitic dolomite	6.5 – 11.7% Mg
dolomitic limestone	1.3 – 6.5% Mg
limestone	0.6 – 1.3% Mg

The solubility of a dolomite in the soil is determined by its geological origin, crystal structure and surface, and the acidity and water content of the soil. Since the

Table 4.3. Effects of liming and ameliorative calcium and magnesium replacement on the yields of various field crops (1983–1986)

Group A

Treatment	1st year potato	2nd year sunflower	3rd year potato	4th year horse bean	Total yield	Yield gain
	t/ha	t/ha	t/ha	t/ha	CU t/ha	%
1. Untreated	25.9	1.64	17.2	1.80	17.22	—
2. Lime powder	27.4	1.86	19.1	2.10	18.89	9.7
3. Lime powder + $\text{MgCO}_3 \cdot 3\text{H}_2\text{O}$	28.9	2.03	20.0	2.25	20.01	16.2
4. Lime from magnesium pr.	29.6	2.15	20.5	2.20	20.47	18.9
5. Self-p. dolomite	33.6	1.93	21.2	2.20	21.59	25.4
6. Self-p. dolomite + $\text{MgCO}_3 \cdot 3\text{H}_2\text{O}$	32.2	1.95	21.0	2.20	21.17	22.9

Group B

Treatment	1st year sunflower	2nd year maize	3rd year maize	4th year maize	Total yield	Yield gain
	t/ha	t/ha	t/ha	t/ha	CU t/ha	%
1. Untreated	1.55	3.53	3.20	3.76	12.51	—
2. Lime powder	1.79	4.10	3.60	3.90	13.93	11.4
3. Lime powder + $\text{MgCO}_3 \cdot 3\text{H}_2\text{O}$	1.98	4.30	3.70	4.03	14.60	16.7
4. Lime from magnesium pr.	1.88	4.40	3.80	4.16	14.80	18.3
5. Self-p. dolomite	2.04	4.50	4.80	4.05	16.00	27.9
6. Self-p. dolomite + $\text{MgCO}_3 \cdot 3\text{H}_2\text{O}$	2.17	4.45	4.80	3.93	16.00	27.9

solubility of dolomite is lower than that of calcitic limestone, the fineness of grinding of the former should be higher to achieve satisfactory efficiency.

Bear and Allen (1932) found that the solubility of dolomites in the soil is determined by the proportion of particles with diameters of 0.25–0.45 mm. Sloma (1971) concluded that the best efficiency is achieved with dolomite powder containing particle smaller than 0.1 mm. In his pot experiments with Hungarian acidic soils, Debreczeni (1982) also found the fraction size < 0.1 mm to have the highest efficiency. The data of Darab and Mrs Rédly (1981) on the chemical solubilities of various calcium and magnesium-containing materials indicate that the various dolomite types exhibit great differences in solubility constant (between 3.6×10^{-17} and 2.7×10^{-20}). The differences were explained in part by Jakucs (1950) and Vitális (1974), who showed that the changes in crystal structure of dolomites at certain excavation sites were due to strong hydrothermic effects. Mineral microscopy observations demonstrated that the loose crystal structure, which is attributed to metastomatic effects, and consequent pulverization are present in a significant proportion of the dolomitic minerals in Hungary.

In his model and field experiments on magnesium-deficient acid sands, Balogh (1984, 1988) found that the solubility of self-pulverizing dolomites is higher than that of ground dolomites and is nearly as high as that of heat-treated (half-calcined) dolomites.

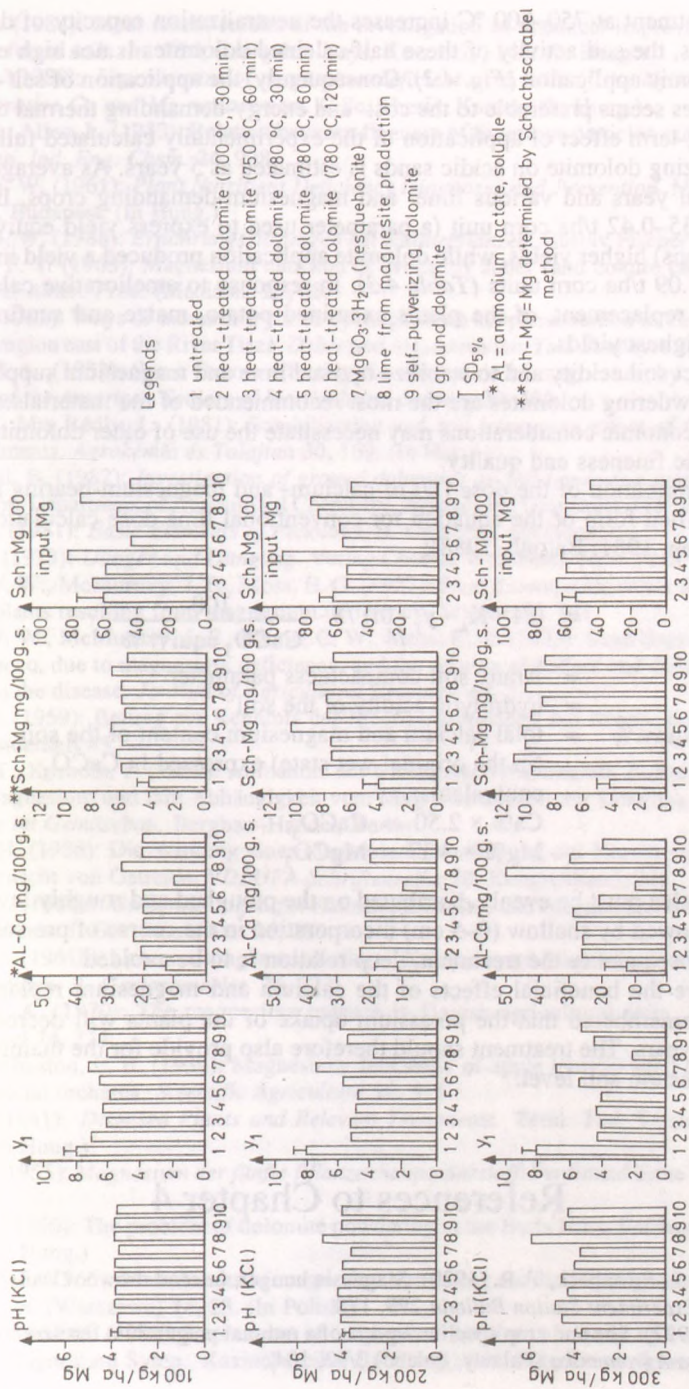


Fig. 4.2. Effects of various magnesium additives on the chemical properties of magnesium-deficient soil in model pot-experiment

Heat treatment at 750–800 °C increases the neutralization capacity of dolomites. Nevertheless, the soil activity of these half-calcined dolomites is not high enough to allow economic application (Fig. 4.2). Consequently, the application of self-pulverizing dolomites seems preferable to the cost- and energy-demanding thermal treatment.

The long-term effect of application of the experimentally calculated full doses of self-pulverizing dolomite on acidic sands is estimated as 5 years. As averages for the experimental years and various lime- and magnesium-demanding crops, liming resulted in 0.35–0.42 t/ha corn unit (a parameter used to express yield equivalents of different crops) higher yields, while dolomite application produced a yield increase of only 0.52–1.09 t/ha corn units (Table 4.3). In response to ameliorative calcium and magnesium replacement, of the plants examined potato, maize and sunflower produced the highest yields.

To correct soil acidity and to stabilize optimal lime and magnesium supplies in the soil, self-powdering dolomites are the most recommended of the materials available. However, economic considerations may necessitate the use of other dolomites of certified particle fineness and quality.

For determination of the dose (D) of calcium- and magnesium-bearing soil additive, a modified form of the equation for conventional lime dose calculation can be applied (Filep, 1981; Balogh, 1988):

$$D \text{ (t/ha)} = 0.1 \cdot K_A \cdot y_1 \cdot 0.173 \cdot \frac{100}{\text{CaCO}_3 \text{ equiv. \%}}$$

K_A = Arany soil compactness parameter

y_1 = hydrolytic acidity of the soil

$\text{CaCO}_3 \text{ equiv. \%}$ = total calcium and magnesium content of the soil (in the original wet state) expressed in CaCO_3 equivalents:

$$\text{Ca\%} \times 2.50 = \text{CaCO}_3,$$

$$\text{Mg\%} \times 4.17 = \text{MgCO}_3$$

The additive must be evenly distributed on the ploughed and roughly levelled soil surface, followed by shallow (0–5 cm) incorporation in the course of pre-sowing cultivation. Subsequent to the treatment, deep rotation is to be avoided.

To ensure the beneficial effects of the calcium and magnesium replacement, it should be remembered that the potassium uptake of the plants will decrease in the subsequent years. The treatment should therefore also provide for the maintenance of a good potassium soil level.

References to Chapter 4

- Anderson, P. J., Swanback, T. R. (1929): Magnesia hunger, or sand drown. *Connecticut Agricultural Experiment Station Bulletin* 299, 178.
- Andres, E. (1992): Site and crop specific aspects of a rational magnesium fertilization strategy. *Fragmenta Agronomika* (Pulawy, Poland) 3/92, 104.

- Balogh, I. (1984): Most recent results of the investigation of chemical improvement of acid brown forest soils. In: *26th Georgikon Days*, Keszthely, 143. (In Hung.)
- Balogh, I. (1988): *Improvement of magnesium-deficient acid soils of the Nyírség region by ameliorative Ca and Mg replacement*. C.Sc. Thesis, Karcag. (In Hung.)
- Bear, F. E., Allen, L. (1932): Relation between fineness of limestone particles and their rates of solution. *Ind. Eng. Chem.* **24**, 998.
- Bergmann, W. (1961): *Plant Nutrient Deficiency Diagnoses and Prevention*. Mezőgazdasági Kiadó, Budapest. (In Hung.)
- Bergmann, W. (1988): *Ernährungsstörungen bei Kulturpflanzen*. Gustav Fischer Verlag, Jena.
- Bingham, F. T. (1963): Magnesium nutrition of avocados under sand culture conditions. *Soil Sci. Soc. Amer. Proc.* (Madison) **27**, 58.
- Bocz, E. (1962): Ways of increasing yields by magnesium supplementation in chernozem soils of the region east of the River Tisza. *Debreceni Mg. Akadémia Tud. Évkönyve* **7**, 3. (In Hung.)
- Carolus, R. L. (1933): Some factors affecting the absorption of magnesium by potato plants. *Proc. of the American Society of Horticultural Science* **30**, 480.
- Darab, K., Mrs Rédy, L. (1981): Solubilization and soil improving effect of Ca-containing amendments. *Agrokémia és Talajtan* **30**, 169. (In Hung.)
- Debreczeni, B. (1982): *Investigation of ground dolomites as soil-improving materials*. Working copy. Department of Agricultural Chemistry, Agricultural University, Gödöllő. (In Hung.)
- Filep, Gy. (1981): *Basic Elements of Pedology, II*. Debrecen. (In Hung.)
- Finck, A. (1979): *Dünger und Düngung*. Verlag Chemie Weinheim, New York.
- Garner, W. W., McMurtrey, J. E., Moss, E. G. (1922): Sand drown, a chlorosis of tobacco and other plants resulting from magnesium deficiency. *Science* **56**, 341.
- Garner, W. W., McMurtrey, J. E., Bacon, C. W., Moss, E. G. (1923): Sand drown, a chlorosis of tobacco, due to magnesium deficiency, and the relation of sulfate and chloride of potassium to the disease. *Journal of Agricultural Research* **40**, 27.
- Gärtel, W. (1959): Beitrag zur Kenntnis des Magnesiummangels bei Reben. *Landw. Forsch.* **13**, Sonderheft 45.
- Geissler, T., Kurnoth, P. (1959): Aufnahme der wichtigsten Gemüsearten an Kalium, Kalzium und Magnesium und ihre Abhängigkeit vom Magnesiumgehalt der Düngung. In: *Mineraldünger im Gemüsebau*. Bergbau-Handel, Berlin.
- Grimme, H. (1986): Die Wirkung einer Magnesiumblattdüngung auf Korntrag und Einzelkorngewicht von Getreide. *VDLUFA-Schriftenreihe* **20**, Kongreßband, 243.
- Gruppe, W. (1961a): Untersuchungen zur Kalium-, Kalzium- und Magnesiumernährung junger Apfelbäume. I. *Gartenbauwiss.* **26**, 288.
- Gruppe, W. (1961b): Untersuchungen zur Kalium-, Kalzium- und Magnesiumernährung junger Apfelbäume. II. *Gartenbauwiss.* **26**, 373.
- Henriksen, A. (1970): The magnesium balance in Danish agricultural soils. *Tidsskrift for Planteavl* **74**, 224.
- Hill, H., Johnston, F. B. (1939): Magnesium deficiency of apple trees in sand culture and in commercial orchards. *Scientific Agriculture* **20**, 516.
- Husz, B. (1941): *Diseased Plants and Relevant Treatments*. Term. Tud. Társulat, Budapest 182. (In Hung.)
- Jacob, A. (1955): *Magnesium der fünfte Pflanzenhauptnährstoff*. Ferdinand Enke Verlag, Stuttgart.
- Jakucs, L. (1950): The problem of dolomite powdering in the Buda Hills. *Földtani Közlöny* **80**, 361. (In Hung.)
- Jaskowski, Z. (1965): Main results of magnesium fertilizing and liming experiments with rye. *Nov. Roln.* (Warszawa) **14**, 23. (In Polish.)
- Kádár, I., Szemes I. (1989): Importance of magnesium fertilizer on sandy acid soil. 3rd Hungarian Magnesium Symp., Kazincbarcika. (In Hung.) Ref. *Magnesium Research* **2**, 221.

- Kemenesy, E., Nyéki, J., Molnár, I. (1961): Magnesium application to sandy soils. *Magyar Mezőgazdaság* **16**, 9. (In Hung.)
- Kemenesy, E., Nyéki, J. (1963): Results of magnesium application to sandy soils in the Somogy area. *Növénytermesztés* **12**, 211. (In Hung.)
- Kidson, E. B., Askew, H. O., Chittenden, E. T. (1940): Magnesium deficiency of apples in the Neslon district of New Zealand. *N. Z. Journal of Science and Technology* **21**, 305A.
- Kirkby, E. A., Mengel, K. (1976): The role of magnesium in plant nutrition. *Z. Pfl.-ernähr. Düng. Bodenk.* **139**, 209.
- Kiss, A. S. (1972): Experiments with the magnesium-containing nitrogenous fertilizer "Agronit". *Agrokémia és Talajtan* **21**, 377. (In Hung.)
- Lachowski, J., Wesolowski, F. (1964): Magnesium in soil profile and the yields of sugar beet. *Roczn. Nauk Roln. Ser A.* (Warszawa) **88**, 835. (In Polish.)
- Láng, I. (1973): *Fertilizer duration experiments in sandy soils*. D. Sc. Thesis, Budapest. (In Hung.)
- Láng, I. (1985): *Possibilities for Complex Utilization of the Biomass*. Mezőgazdasági Kiadó, Budapest. (In Hung.)
- Loch, J. (1970): *Relations between the soil magnesium content and the uptake by plants*. C. Sc. Thesis, Debrecen. (In Hung.)
- Loch, J. (1975): *Untersuchung der Magnesiumaufnahme in Gefäßversuchen. Le contrôle de l'alimentation des plantes cultivées*. Akadémiai Kiadó, Budapest 125.
- Loch, J. (1983): Readily soluble Mg content of the soils in Szabolcs-Szatmár County. In: *Studies on the Utilization of Sands*. (Proc.) Westsik Vilmos tudományos emlékülés kiadványa, 153. (In Hung.)
- Loch, J. (1989): Factors influencing the effects of magnesium fertilization. (In Hung.) Ref. *Magnesium Research* **2**, 221.
- Loch, J. (1990): Determining optimal K-, Ca-, and Mg-doses in multifactorial pot experiments. *10th World Fertilizer Congress of C.I.E.C. Oct. 21-27, 1990*, Nicosia, Cyprus.
- Loch, J., Biczók, Gy., Tolner, L. (1986): Mg-fertilization and the K-Ca-Mg antagonism. *NEVIKI Conference, Keszthely. The Chemicalization of Agriculture I*, 62. (In Hung.)
- Márton, A. (1989): Effects of magnesium applied to the soil in particular crops. 3rd Hungarian Magnesium Symp., Kazincbarcika. (In Hung.) Ref. *Magnesium Research* **2**, 221.
- Mengel, K. (1960): Der Einfluß einer variierten K- und Mg-Düngung auf die Mg-Versorgung und den Mineralstoffgehalt von Lihoraps. *Landw. Forsch.* **13**, 253.
- Michael, G. (1941): Über die Aufnahme und Verteilung des Magnesiums und dessen Rolle in der höheren grünen Pflanze. *Z. Pfl.-ernähr. Düng. Bodenk.* **25**, 65.
- Mulder, D. (1950): Magnesium deficiency in fruit trees on sandy soils and clay soils in Holland. *Plant and Soil* **2**, 145.
- Mulder, E. G. (1956): Nitrogen-magnesium relationships in crop plants. *Plant and Soil* **7**, 341.
- Pettyjohn, F. G. (1957): *Sedimentary Rocks*. (2nd ed.) Harper, New York.
- Schachtschabel, P. (1959): Umsetzung von magnesiumhaltigen Kalken im Boden. *Landw. Forsch.* **13**, Sonderheft 29.
- Scharrer, K., Mengel, K. (1958): Über den Kalium-Magnesium-Antagonismus bei Mais und Sonnenblumen. *Z. Pfl.-ernähr. Düng. Bodenk.* **83**, 149.
- Schilling, G. (1957): *Magnesium ein universeller Pflanzennährstoff*. Bergbau-Handel, Berlin.
- Sestić, S. (1965): *Kolicina, pristupacnost i dinamika zammenljivog magnezijuma u glavnum tipovima zemljista Srbije*. C. Sc. Thesis, Belgrade.
- Sloma, M. G. (1971): The effect of the particle distribution of the ground dolomite on the agrochemical properties of podsollic soils. *Agrokimiya* (Moscow) 135. (In Russian.)
- Stefanovits, P. (1981): Some theoretical problems of soil acidity. In: *Circular of the Proceedings "Improvement of forest soils in Hungary"*, 41. (In Hung.)

- Stenuit, D. F. (1959): Beziehungen zwischen Magnesiumgehalt und Ertrag belgischer Böden. *Landw. Forsch.* **13**, Sonderheft 23.
- Surányi, J., Mándy, Gy. (1955): *Maize (The culture flora of Hungary.)* Akadémiai Kiadó, Budapest. (In Hung.)
- Todd, J. R. (1962): Magnesium in forage plants. III. Magnesium content. *J. Agric. Sci. London* **58**, 277.
- Vitális, Gy. (1974): Hydrothermic alterations in the rock on the dolomite area near the Danube andesite Mountain. *Hidrológiai Közlöny* **12**, 562. (In Hung.)
- Voigtländer, G. (1965): Ein Beitrag zur Frage der Magnesiumdüngung auf schweren Böden. *Z. Acker. Pflbau* (Berlin - Hamburg) **121**, 116.
- Wallace, T. (1939): Magnesium deficiency in fruit trees. *Journal of Pomology and Horticultural Science* **17**, 150.
- Welte, E., Werner, W. (1963): Potassium-magnesium antagonism in soils and crops. *J. Sci. Food Agric. London* **14**, 180.
- Welte, E., Werner, W. (1964): Über die Magnesium-Anreicherung des Weidefutters durch Düngungsmaßnahmen. *Landw. Forsch.* **18**, Sonderheft 112.
- Wolton, K. M. (1963): Fertilizers and hypomagnesaemia. *N.A.A.S. Quarterly Review* (London) **14**.

5. The role of magnesium in animal life

5.1. The role of magnesium in physiological processes and in feeding

Out of the 94 naturally occurring elements, 32 are present in the animal organism. As concerns the 28 elements that may be detected in the ash formed upon ignition for chemical analysis, the roles of 16 essential elements are known (*Table 5.1*), whereas

Table 5.1. Mineral composition of fat-free body substance, averaged for several animal species (Kakuk and Schmidt, 1988)

Component	Unit of measure	Content in 1 kg of fat-free body substance	mmol/kg body mass	Percentage distribution on molar basis
H ₂ O	g	630.0	—	—
N	g	330.0	—	—
Ca	g	15.01	375.250	44.243
P	g	8.51	274.516	32.366
Na	g	1.55	67.391	7.945
K	g	2.89	74.103	8.737
Cl	g	1.27	35.775	4.210
Mg	g	0.46	19.166	2.259
Fe	mg	80.00	1.429	0.168
Zn	mg	3.23	0.489	0.0577
Cs	mg	0.17	0.0027	0.0003
I	mg	0.40	0.0031	0.0004
Mo	mg	1.50	0.0156	0.0018
Mn	mg	0.20	0.0036	0.0004
Se	mg	0.20	0.0025	0.0003

those of a further 5 essential elements have not been fully revealed. The 7 remaining elements are incorporated into the animal organism as impurities. On the basis of the role they play within the organism, elements are classified as those of static function, those preserving homeostasis, and those with an enzyme function. According to this classification, magnesium is grouped among the elements preserving homeostasis.

The role of magnesium in biochemical processes

Magnesium plays a role in three main groups of biochemical processes (Kiss, 1983; Schneider, 1983):

- the synthesis of macroerg compounds,
- the synthesis of the proton and electron transmitters of redox reactions, and
- the synthesis and activation of enzymes.

Magnesium is essential in animal nutrition, primarily because of its role as an enzyme cofactor. It is well known that magnesium is a cofactor of the ATPase in the energetic processes of the body (Karlson, 1972). It has been shown that Ca^{2+} and Mg^{2+} -ATPase activities of the mitochondrial and microsomal fractions are significantly higher in the uterus of egg-laying hens and quails than in the uterus of sexually inactive birds. Bain (1954) established a functional relationship between magnesium and thyroxine, magnesium inhibiting the effect of thyroxine on oxidative phosphorylation.

Experiments to support this have been conducted in many laboratories. Hyperthyroid rats have been shown to exhibit symptoms of magnesium deficiency, as an indication that hyperthyroidism increases the magnesium requirements (Vitale et al., 1957). Magnesium alters membrane permeability and thereby affects oxidative phosphorylation (Tapley and Cooper, 1956).

Corradino and Parker (1962) kept rats on a magnesium-free diet and observed a small but statistically significant enlargement of the thyroid glands. Their results led them to assume that regulation of the thyroid function demands an optimal balance of thyroxine and magnesium.

Meißner (1962) studied the effect of a magnesium deficiency and excess magnesium on the lipid content of blood plasma in rabbits. The animals were either fed with the usual rabbit fodder and magnesium was added to their drinking-water, or they were kept on a synthetic magnesium-free diet. Magnesium had a positive effect on lipid metabolism. The administration of magnesium was accompanied by decreases in the triglyceride and in the total and free cholesterol content of blood plasma, and by an increase in the HDL-cholesterol level. Magnesium reduced the formation of fat deposits and sclerotic foci in the aorta. Larvor et al. (1964, 1965) described that in calves the level of both alkaline phosphatase in blood serum and glucose-6-phosphate-dehydrogenase (G-6PDH) in red blood cells were decreased in magnesium deficiency.

Low magnesium levels stimulate the activity of endocrine glands. Porta et al. (1989) found that low levels of magnesium increase both the synthesis and the excretion of insulin in rats, while adrenaline has a reverse effect. Their observations suggested that prolonged stress may bring about a magnesium deficiency, but the effect on insulin may compensate for the adrenaline secretion caused by decreased glycogen levels in the liver.

Müller et al. (1982) studied the glucose, free fatty acid, insulin, calcium, phosphorus and magnesium contents and the alkaline phosphatase activity of the blood plasma, and also the correlation of these parameters, in Jersey cows at different stages of lactation. They established that the magnesium content and the alkaline phosphatase activity of blood plasma are closely interrelated, since this enzyme activity is influenced by magnesium concentration.

The role of magnesium in the structure of the animal organism

The animal organism contains approximately 0.05% mass/% magnesium. Nearly 60% of the magnesium is found in the bones, about 40% in the cells of the soft tissues, and ca. 1% is in the extracellular fluid (Rook and Storry, 1962; Table 5.2).

The amount of magnesium mobilizable from the bones decreases with increasing age. In the event of a sufficient supply of magnesium, the magnesium concentration of the blood plasma is 0.9 mmol/dm³ in bull-calves and 1.0 mmol/dm³ in cows in milk. The average magnesium content of the blood plasma for cows in milk is 1.9 mg/100 cm³ (Boling et al., 1979; Samsom et al., 1982).

Molnár (1989) reported that the values indicative of the optimal magnesium provision in cattle are 2.4–3.0 g/100 cm³, in the blood serum and 0.04–0.10 g/100 g in the coarse hair. Naturally, the magnesium content of blood plasma is influenced by a number of factors, among them the magnesium content of the fodder factors influencing absorption, and variations in temperature which affect the activity of the thyroids and thereby the magnesium level of blood plasma via the correlation between magnesium ions and thyroxine.

In an evaluation of the magnesium content of the blood plasma, it is also important to consider the Ca:Mg, P:Mg and (Ca+Mg):P ratios. The age and variety of the animals are known to influence the levels of these minerals in blood serum significantly. The concentration of magnesium is slightly higher in cerebrospinal fluid than in blood plasma.

In sheep, the magnesium content of blood plasma lies between 0.97 and 1.20 mg/100 cm³, depending upon the age of the animal (Chicco et al., 1973).

The blood plasma of pigs contains 3.5 mg magnesium/100 cm³ (Günther and Mohme, 1985).

Magnesium contained in the skeleton is the result of a process of heteroionic exchange between the inorganic surface of the bones and the body fluids. It is mostly bound in the form of Mg²⁺ and MgOH⁺, by means of electrostatic attraction. When magnesium is excreted in young animals, 30% of the magnesium content of the bones is mobilized. Blaxter (1956) considered that the entire skeleton participates in the mobilization of magnesium for excretion, while Smith (1961) found upon analysis of the skeleton that mobilization occurs primarily in the phalanges, the vertebrae, the bones and the ribs. This was proven by intravenous administration of magnesium to

Table 5.2. Average Ca, P and Mg contents (g) of the skeleton, the soft tissues and the blood of cows in milk (500–550 kg live mass) (Rook and Storry, 1962)

Elements	Skeleton (ca. 40%)	Physiologically mobilizable (ca. 20% of total amount)	Soft tissues (ca. 180–200 kg)	Blood (ca. 40 dm ³)
Calcium	6800–7500	1360–1500	75–100	2.5–3.0
Phosphorus	3300–3650	660–730	700–750	7.0–8.0
Magnesium	130–150	26–30	60–70	1.5–2.0

sheep, after which significant differences were observed in the specific activities of the individual bones. With increasing age, the amount of mobilizable magnesium decreases. In pigs the magnesium content of the osseous tissues is 0.30% (Günther, 1985).

In response to the administration of toxic amounts of magnesium, the tibiae of baby chicks are shortened and thickened, and microscopy of the bone plates reveals symptoms characteristic of rachitis, with very low numbers of osteoblasts (Lee et al., 1980).

The magnesium supply also influences the magnesium contents of the vital internal organs and the muscles. In the event of normal supply levels, the magnesium content of the dry *M. long. dorsi* in pigs is 0.066%, while that of cardiac muscle is 0.072% (Günther and Mohme, 1985).

Hypomagnesaemia particularly affects the neuromuscular system. In sheep and cattle that perished due to diseases of the digestive and respiratory systems under conditions of low magnesium intake, the magnesium content of cardiac muscle was found to be extremely low (Kershaw and Wilson, 1969).

Similarly, in cows that perished or were subjected to emergency slaughter as a consequence of grass tetany, the magnesium content of the tissues was lower than that in beef cattle. Decreases in the magnesium and potassium contents of the various parts of the brain, with a concomitant increase in sodium content, are observed. These changes in the potassium and sodium contents can be traced back to the decrease in the activity of $(\text{Na}^+, \text{K}^+)\text{-ATPase}$ (Kolb, 1985).

The excretion of magnesium from the body

The excretion of magnesium in the milk

As concerns the minerals, significant amounts of calcium and phosphorus, but relatively low quantities of magnesium are excreted in the milk. The amounts of magnesium excreted daily in the milk of domesticated mammals are shown in Table 5.3.

Of course, the requirements are influenced significantly by the daily yield of milk during lactation and the milking period.

Table 5.3. Magnesium excretion in milk of domestic animals as a function of their daily milk production (Meyer, 1981)

Species	Magnesium content of milk (mg/kg)	Amount of milk (kg/day)	Amount of magnesium excreted in milk (mg/day)
Horse	80	18.0	1440
Cattle	110	25.0	2750
Sheep	170	1.5	255
Pig	170	7.0	1190
Dog	100	0.3	35
Cat	90	0.1	11
Rabbit	340	0.1	51

Table 5.5. Calcium, phosphorus and magnesium requirements of cows in milk

Production level	Live mass (kg)	Ca	P	Mg	References
		(g/day)			
Sustenance requirement	600	24	24	12	Weis (1986)
	650	26	26	13	Weis (1986)
	700	28	28	14	Weis (1986)
1 kg of milk (4% fat)		3.2	1.7	0.6	Weis (1986)
Production requirement					
+ 5 kg of milk	650	42	34	16	Weis (1986)
+ 10 kg of milk	650	58	43	19	Weis (1986)
					Pallauf (1975)
+ 15 kg of milk	650	74	51	22	Weis (1986)
					Pallauf (1975)
+ 20 kg of milk	650	90	59	25	Weis (1986)
					Pallauf (1975)
+ 25 kg of milk	650	106	68	29	Weis (1986)
					Pallauf (1975)
+ 30 kg of milk	650	122	76	32	Weis (1986)
					Pallauf (1975)
+ 35 kg of milk	650	138	84	35	Weis (1986)
					Pallauf (1975)
Dry period					
1st stage	550	62	38	16	Pallauf (1975)
2nd stage	550	69	42	16	Gütte (1975)

The prevailing geological characteristics lead to the vegetation in Hungary having a high magnesium content. With the exception of a few minor regions, therefore, Hungarian cattle are in general well provided with magnesium.

In Hungary, grass tetany (grazing tetany) amounts to only 0.9% (Tölgyesy et al., 1972), whereas in the West European countries the corresponding value is considerably higher. The cause of the disease is the low magnesium content of the grass. Although the intensive application of fertilizers containing potassium and nitrogen increases the mass of herbage the high potassium content, the lower energy to protein ratio and the low fibre fodder all impair the utilization of magnesium (Jonas, 1982; Gönye, 1987).

The magnesium requirements of stabled cows are satisfied by the winter feeding. From the time grazing starts or the switch to green forage occurs, however, the magnesium content of fresh fodder which is low because of the factors discussed above, does not meet the needs of the animals. The magnesium content of the milk is relatively stable and, when milk is intensively produced under conditions of suboptimal magnesium supply, the missing amount is mobilized from the bones.

Symptoms emerge when the ion balance of the blood is upset in consequence of decrease in magnesium level leading to a relative excess of potassium and sodium ions. Spasms and symptoms of tetany arrive when the magnesium level of the blood falls below 0.4 mmol/dm³ (Gönye, 1987). Grass tetany is also promoted by other

predisposing factors. These may include the stress caused by driving to the pasture; metabolic stress brought about by the low energy content of the grass; or rough, rainy weather, which decreases the ingestion of food with low protein and magnesium content (Gunhold, 1967; Ondersheka, 1967; Jonas, 1982).

Besides grass tetany, parturient paralysis is likewise a notable metabolic abnormality. One of the many factors leading to the development of this disease is magnesium deficiency. It is imperative that the Ca:P ratio of 3:1 ensured during the gestation period of milking cows be decreased to 1–1.5; 1, 2–3 weeks before the expected time of calving, as otherwise the parathyroids remain inactive and do not produce enough parathormone, which is responsible for calcium mobilization. This is important because, at the time milk production starts after calving, the organism has to mobilize large amounts of calcium to meet the demands of milk secretion. In addition to an inappropriate Ca:P ratio, other factors leading to calving paralysis include fodder with very high protein (160–170 g/kg) and phosphorus (>7 g/kg) contents, easy, fast calving and a high milk production.

A decrease in the concentration of free calcium ion in the blood increases the neuromuscular excitability of the tissues, which leads first to tremors and then to spasms, but this effect is overcome by the relative excess of magnesium resulting from high calcium excretion, which causes stupor. The frequent occurrence of either grass tetany or parturient paralysis is currently not to be expected in Hungary, though the effects of extensive fertilization on the one hand and the production characteristics of the now most popular dairy cow variety, the Holstein Friesian (high milk yield, fast and easy calving), on the other may lead to a higher incidence of these diseases. In sheep, grass tetany (grazing tetany) resulting from hypomagnesaemia is caused mainly by ameliorated spring pastures, but may also be induced by scanty feeding, especially in older ewes that year two or three lambs (Hemmingway et al., 1960; Michael et al., 1962; Kolb et al., 1981).

The magnesium requirement of fully developed sheep is 1.0–1.5 g/kg, while that of lambs is 0.8 g/kg dry mass.

Table 5.6. Magnesium requirement of pigs

Type of pig	Mg (g/animal/day) (Günther, 1985)	Mg (g/kg fodder dry mass) (Meyer, 1981)
Brood-sow (up to day 90 of gestation)	2.00	—
Brood-sow (3–4 weeks before farrowing)	3.00	0.60
Suckling sow	6.00–7.00	0.67
Suckling piglet (up to 10 kg live mass)	0.25	0.44
Weaned piglet (up to 20 kg live mass)	0.50	0.40
Porker (up to 50 kg live mass)	1.50–2.00	—
Porker (up to 100 kg live mass)	2.00–3.00	0.63

Table 5.7. Mineral requirements of domestic fowl (N.R.C., 1984)

Type of fowl	Ca (%)	P (utilizable) (%)	K (%)	Mg (mg/kg)
Broiler				
1-3 weeks	1.00	0.45	0.40	600
3-8 weeks	0.80-0.90	0.35-0.40	0.30-0.35	600
Hybrid layer				
0-6 weeks	1.00	0.40	0.26	600
6-14 weeks	0.83	0.35	0.22	500
14-20 weeks	0.67	0.30	0.17	400
Brood-hen	3.40	0.32	0.16	500

Pigs are well provided with magnesium when their food contains 0.3-0.5 g/kg of magnesium (A.R.C., 1966). Besides the average requirement, the levels at various ages and in various production periods have also been determined (Table 5.6).

As regards the mineral requirements of domestic fowl and turkey the magnesium supply must be considered together with the calcium and phosphorus requirement: excess magnesium relative to these two elements may decrease the hardness of the egg-shell, and this is of great importance in egg production as concerns both breeding and egg sales (Table 5.7). The magnesium requirement of young and brood turkeys is 600 mg/kg (N.R.C., 1984).

5.2. The magnesium content of fodders

Domestic animals are supplied with magnesium via the concentrate feed and the forage fed to them. The contents of calcium, phosphorus and magnesium in the most frequently used fodders are listed in Table 5.8.

5.3. Interactions of magnesium with other minerals in the animal organism

The magnesium concentration of blood is influenced primarily by parathormone through its regulation of the calcium level of the blood. Calcium levels lower than 2.2 mmol/dm³ are accompanied by magnesium levels higher than 1 mmol/dm³ (Gönye, 1987).

If the calcium content of pig fodder is slightly increased, the magnesium content of the bones of the animals decreases, whereas the magnesium content of the blood increases. These phenomena are explained by the effect of the calcium dosage on the phosphorus metabolism (hypophosphataemia) rather than by a direct interaction of

Table 5.8. Average mineral contents of various fodders (D.L.G., 1973)

Fodder	Dry matter (%)	Ca	P	Mg
		(g/kg dry mass)		
<i>Green forages</i>				
Grasses: pasture	19	6.6	3.9	1.9
lawn	21	9.1	2.7	1.9
alfalfa	22	20.9	2.8	2.7
red clover	22	15.3	2.5	3.6
rape	14	19.9	4.2	2.9
<i>Silages</i>				
maize silage	22	3.9	2.6	2.3
grass silage	30	6.6	3.3	1.6
<i>Hay</i>				
grasses	85	9.1–11.4	2.8–3.1	2.1–2.9
red clover	85	18.8	2.5	3.2
alfalfa	85	16.0	3.1	3.1
<i>Seeds</i>				
maize		0.3	3.6	1.4
wheat		0.9	3.5	1.3
barley		0.8	3.9	1.3
oats		1.2	3.5	1.4
rye		1.0	2.7	1.6
<i>Legumes</i>				
peas		1.0	4.5	1.5
broad bean		1.5	4.8	1.8
lupine		2.7	5.1	2.4
<i>Oil seeds</i>				
extracted soybean flour		3.1	7.0	3.0
extracted sunflower flour		4.4	8.3	5.2
<i>Industrial by-products</i>				
wheat bran		1.1	8.9	4.9
<i>Feeding yeast (Torula)</i>				
		4.3	16.0	2.1

calcium with magnesium (Pointillart, 1989). There is a significant correlation between the calcium and magnesium concentrations of blood serum. This correlation for 3- and 5-week-old pigs is: $r = 0.36-0.88$; $P \geq 0.01\%$ (Miller et al., 1965). A correlation between phosphorus and magnesium has also been observed in the case of chickens: when the food is supplemented with phosphorus, the content of magnesium must also be increased, as otherwise the phosphorus is not effective. At low magnesium and high phosphorus levels, the egg production declines rapidly (Edwards and Nugara, 1968). With regard to isolated rumen conditions in young cattle, a potassium concentration of 119 mmol/dm³ and a sodium concentration of 30 mmol/dm³ led to an hourly magnesium absorption amounted to only 0.75 mmol/dm³. In the opposite case (20 mmol potassium/dm³ and 130 mmol sodium/dm³), the magnesium absorption increased (2 mmol/dm³/hour) (Heggemann, 1980).

Under similar physiological conditions, the same phenomenon is observed in sheep, i.e. at high potassium (120 mmol/dm³) and low sodium concentrations (30 mmol/dm³) the absorption of magnesium decreases (Blume, 1980).

5.4. The effects of magnesium supplementation

In veterinary practice, grass tetany in cows is treated by the combined administration of magnesium and calcium, since hypomagnesaemia is accompanied by hypocalcaemia. The latter is caused by large calcium losses due to milk production under conditions of low calcium and magnesium ingestion. Earlier medical preparations contained a relatively high amount of calcium ($7.32 \text{ g}/500 \text{ cm}^3$), while the magnesium content was $1.77 \text{ g}/500 \text{ cm}^3$. Such a composition had deleterious effects on the renal function and also on other organs. In modern preparations, the ratio of the two elements is reversed: they contain $5.70 \text{ g}/500 \text{ cm}^3$ magnesium and $3.23 \text{ g}/500 \text{ cm}^3$ calcium (Kolb et al., 1981, 1985).

The most important measures to be taken in order to prevent grass tetany are as follows (Seidel and Gürtler, 1974):

- treatment of the soil with a dressing that contains magnesium easily accessible for plants;
- supplementation of the fodder with a magnesium preparation;
- spreading a material such as magnesit on the grass before the animals are put out to pasture;
- supplementation of the diet from the first days of grazing up to 1–2 weeks with hay or other fodder rich in fibres, which blocks the extensive formation of ammonium ions in the caw.

In the case of pigs, it is not necessary to supplement the fodder with magnesium if the aim is to satisfy the official standard. Nevertheless, the digestion coefficients of fodders exhibit better results with rather than without additional magnesium.

In the course of a metabolic study on pigs, Günther and Mohme (1985) supplemented the fodder providing the basic requirements with 1.7 g magnesium oxide/kg or 1.7 g magnesium fumarate/kg. Supplementation started in the 9th week of fattening. Both the inorganic magnesium oxide and the organic salt magnesium fumarate improved the digestibility of the raw proteins and fibres in the fodder. Supplementation with 0.3% of either magnesium oxide or magnesium citrate gave a similar result. The utilization and N-metabolism are also improved by the addition of magnesium citrate (Gaál-Kovács, 1989).

The magnesium content of the fodder influences the reproductive performance. Additional magnesium (15 and 30 mg magnesium citrate/kg live mass/day) improved the fecundity rate of young sows (11.3 and 14.7%). The number of live piglets per litter increased by 11.9 and 12.9%. It seems especially advantageous that the interval within which young sows that had not conceived returned to heat was 19 days shorter than that of the control group (Gaál-Kovács and Szerdahelyi, 1987).

Experience shows that the more intensive and more sensitive pig varieties and hybrids with the capacity for a higher yield and better quality have increased magnesium requirement. In varieties with different constitution (e.g. the pietrain, a variety with a weak constitution, and the German large white, a variety with a sturdy, robust constitution), different calcium and magnesium levels are observed in blood plasma after stress provoked by ACTH administration. The average calcium concentration of the blood plasma is $10.30 \text{ mg}/100 \text{ cm}^3$ for the pietrain and $10.42 \text{ mg}/100 \text{ cm}^3$ for the

large white; the average magnesium concentration is 1.47 and 1.60 mg/100 cm³, respectively. The sturdy variety exhibited a higher mineral content of the blood even after stress (Thielscher, 1990). It is worth considering that, in order to prevent foreseeable stress or when certain breeding procedures are applied, special fodders with high magnesium content might prove beneficial.

Schneider (1983) concluded that it is justified to administer magnesium in excess of the basic requirements

- at the time of herding and transfer,
- in order to prevent cannibalism,
- in order to prevent transportation losses,
- in order to inhibit the formation of PSE meat (Sair et al., 1970; Campion et al., 1971).

A study of a number of parameters that determine carcass quality, and of factors influencing meat quality, together with monitoring of the biochemical parameters of the blood, the mass and ratio of the endocrine glands and the state of the vital internal organs revealed that the administration of magnesium has a positive effect on some parameters but little influence on the meat quality (Kuhn et al., 1981).

The mineral requirements of poultry depend on the keeping conditions, the age, the sex and the intensity of egg production, and are therefore difficult to estimate. The factor primarily determining the requirement is the egg production. The average magnesium content of the egg (without the shell) of domestic fowl, guinea fowl, Pekinese and regular duck, goose and turkey is 0.4 mg/g. From the aspect of the hardness of the egg-shell, the anion-cation ratio within the minerals fed is extremely important (WPSA, 1984).

Administration of magnesium in excess of the basic requirements increases the number of eggs (Edwards and Nugara, 1968; Gaál-Kovács, 1981), the mass (Hajj and Sell, 1969; Vogt, 1971) and the hatchability of the eggs (Hajj and Sell, 1969).

The role of magnesium in preventing unfavourable effects is demonstrated by the observation that laying-hens fed extra magnesium accommodate to battery-keeping technology faster than those that are not (Cox and Sell, 1967).

In the case of fattening broiler chickens, magnesium supplementation in excess of 0.4% has a mild laxative effect, decreases the ash content of the tibia and increases the probability of the occurrence of foot deformities (Günther, 1966; Bronsch and Kehrer, 1969; Lee et al., 1980). These deleterious phenomena can be corrected by phosphorus supplementation. At the same time, it is not advisable to administer extra magnesium during the first 3–4 weeks of fattening because the gain in mass is not improved, whereas the danger of the above-mentioned negative effects increases (Gaál-Kovács, 1986). For broiler fattening, the degree of hardness and the magnesium content of the drinking water should also be taken into consideration (Atteh and Leeson, 1983).

References to Chapter 5

- A. R. C. (1966): *The Nutrient Requirements of Farm Livestock*, No. 3, Pigs, H. M. Stationary Office, London.
- Atteh, J. O., Leeson, S. (1983): Influence of increasing the calcium and magnesium content of the drinking water on performance and bone and plasma minerals of broiler chickens. *Poult. Sci.* **62**, 869.
- Bain, J. A. (1954): The effect of magnesium upon thyroxin inhibition of phosphorylation. *J. Pharmacol.* **110**, 2.
- Blaxter, K. L. (1956): The magnesium content of bone in hypomagnesaemic disorders of livestock. *Bone Struct. Metab., Ciba Found. Symp.* 1955, 117.
- Blume, R. (1980): *Prü- und postduodenale Verdaulichkeit von Mg und von Ca bei laktierenden Kühen*. Vet.-med. Diss., Hannover.
- Boling, J. A., Okolo, T. O., Gay, N., Bradley, N. W. (1979): Effect of magnesium and energy supplementation on blood constituents of fall-calving beef cows. *J. Anim. Sci.* **48**, 5, 1209.
- Bronner, F., Thompson, D. D. (1961): *J. Physiol.* **157**, 232.
- Bronsch, K., Kehr, A. (1969): Richtzahlen zum Mineralstoffbedarf des Geflügels. *Landwirt. Forschung* **22**, 160.
- Campion, D. R., Marsh, B. B., Schmidt, G. R., Cassens, R. G., Kaufmann, R. G., Briskey, E. J. (1971): Use of whole-body perfusion in the study of muscle glycolysis. *J. Food Sci. Campaign* **36**, 545.
- Chicco, C. F., Ammerman, C. B., Loggins, P. E. (1973): Effect of age and dietary magnesium on voluntary feed intake and plasma magnesium in ruminants. *J. Dairy Sci.* **56**, 6, 822.
- Corradino, R. A., Parker, H. E. (1962): Magnesium and thyroid function in the rat. *J. Nutrition* **77**, 455.
- Cox, A. C., Sell, J. L. (1967): Magnesium deficiency in the laying hen. *Poult. Sci.* **46**, 675.
- D. L. G. (1973): *Futterwerttabellen der DLG, Mineralstoffe*. DLG-Verlags-GmbH, Frankfurt am Main.
- Edwards, H. M., Nugara, D. (1968): Magnesium requirement of the laying hen. *Poultry Sci.* **47**, 963.
- Gaál-Kovács, K. (1981): The effects of magnesium administration on some characteristics of eggs. *ATE Mezőgazdaságtudományi Kar Közleményei* (Mosonmagyaróvár) **23**, 181. (In Hung.)
- Gaál-Kovács, K. (1986): The effects of magnesium supplementation on the feeding results of broiler chickens. *Baromfitenyésztés és -feldolgozás* **2**, 87. (In Hung.)
- Gaál-Kovács, K. (1989): Effect of magnesium supplement on digestibility and biological value of feed in pigs. *Magnesium Research* **2**, 228.
- Gaál-Kovács, K., Szerdahelyi, A. (1987): The effects of magnesium supplementation on the reproductive power of intact sows. *Állattenyésztés és takarmányozás* **36**, 441. (In Hung.)
- Gönye, S. (1987): Mineral balance and its disorders. In: *Poisoning and Diseases of the Metabolic Balance of Cattle*. (Eds: Brydl, E., Gönye, S., Haraszi, J., Kutas, F., Sályi, G., Sas, B., Ványi, A.). Mezőgazdasági Kiadó, Budapest, 142. (In Hung.)
- Gunhold, P. (1967): Zur Frage hypomagnesiämischer Tiererkrankungen in Intensiv- und Extensivbetrieben. *Der Förderungsdienst* **15**, 373.
- Günther, K. (1966): Ernährungsphysiologische Studien über Magnesiumwirkungen auf die Calcium- und Phosphorverwertung. *Zentralbl. Veterinärmed.* **13**, 1.
- Günther, K. (1985): Mineralstoffbedarf und -versorgung von Zucht- und Mastschweinen. *Kraftfutter* **6**, 204.
- Günther, K., Mohme, H. (1985): Zur ernährungsphysiologischen Wirksamkeit von Magnesiumfumarat in der Ernährung des Schweines während der Mast. *Kraftfutter* **5**, 1.

- Gütte, J. O. (1975): Schätzung des Calcium-, Phosphor und Magnesiumbedarfes der Milchkuh. *Bayer. Landw. Jahrbuch* **3**, 353.
- Hajj, R. N., Sell, J. L. (1969): Magnesium requirement of the laying hen for reproduction. *J. Nutr.* **97**, 441.
- Heggemann, G. (1980): *In-vivo-Untersuchungen über den Einfluß des Na/K-Verhältnisses auf die Mg-Absorption aus dem Pansen von 5 bis 10 Monate alten Jungrindern*. Vet.-med. Diss., Hannover.
- Hemmingway, R. G., Inglis, J. S. S., Ritchie, N. S. (1960): *British Veterinary Association Conference on Hypomagnesaemia*. London, 58.
- Jonas, K. (1982): Ergebnisse mehrjähriger Untersuchungen zu den Ursachen und zur Prophylaxe der Weidetetanie. *Mh. Vet.-Med.* **37**, 379.
- Kakuk, T., Schmidt, J. (1988): *Animal Nutrition Science*. Mezőgazdasági Kiadó, Budapest, 122. (In Hung.)
- Karlson, P. (1972): *Biochemistry*. Medicina Kiadó, Budapest, 230. (In Hung.)
- Kershaw, G. F., Wilson, A. A. (1969): *Vet. Res.* **84**, 525.
- Kiss, A. S. (1983): *Magnesium Fertilization, Magnesium in Biology*. Mezőgazdasági Kiadó, Budapest. (In Hung.)
- Kolb, E. (1985): Neuere biochemische Erkenntnisse zum Mg-Stoffwechsel der Wiederkäuer sowie zur Entstehung und Behandlung der Hypomagnesämie unter besonderer Berücksichtigung des Präparates Tetamag. *Mh. Vet.-Med.* **40**, 615.
- Kolb, B., Gründel, G., Kouider, S., Schmidt, U., Teuffert, D., Teuffert, J. (1981): Untersuchungen über den Gehalt des Blutplasmas von Rindern mit Hypomagnesämie an Laktat, an freien Fettsäuren und an Chlorid vor und nach Infusion einer Mg-Ca-Lösung. *Mh. Vet.-Med.* **36**, 366.
- Kuhn, G., Nowak, A., Otto, E., Albrecht, V., Gaßmann, B., Sandner, E., Przybiski, H., Zahn, L. (1981): Untersuchungen zur Beeinflussung der Fleischbeschaffenheit mit Hilfe spezieller Behandlungsverfahren beim Schwein. *Arch. Tierzucht* (Berlin) **24**, 217.
- Larvor, P., Girard, A., Brochart, M. (1964): Etude de la carence expérimentale en Mg chez le veau. II. Interférence entre la carence en Mg et le métabolisme du Ca. *Ann. Biol. Anim. Biochim. Biophys.* **4**, 371.
- Larvor, P., Kwiatrowski, T., Lamand, M. (1965): Etude de la carence expérimentale en Mg chez le veau. IV. Mise en évidence de phénomènes hémolytiques et de modifications enzymatiques (glucose 6 phosphate-déshydrogénase et transaminase glutamique-oxalacétique). *Ann. Bio. Anim. Biochem. Biophys.* **5**, 389.
- Lee S. R., Britton, W. M., Rowland, G. N. (1980): Magnesium toxicity: bone lesion. *Poult. Sci.* **59**, 2403.
- Meißner, D. (1989): Magnesium, lipoprotein metabolism and atherosclerosis. *Mengen und Spurelementen. Arbeitstagung*, Karl-Märx-Universität (Leipzig), 240.
- Meyer, H. (1981): Mg-Bedarf und Mg-Versorgung bei Haustieren. *Magnesium-Bulletin* **1**, 13.
- Michael, R. L., Whitehair, C. K., Keahey, K. K. (1969): *J. Am. Vet.-Med. Assoc.* **155**, 50.
- Miller, E. R., Ullrey, D. E., Zutaut, C. L., Baltzer, B. V., Schmidt, D. A., Hoefer, J. A., Luecke, R. W. (1965): Magnesium requirement of the baby pig. *J. Nutrition* **85**, 13.
- Molnár, I. (1989): Concluding of mineral supply in cows. *Vágóállat és hústermelés* **5**, 24–26. (In Hung.)
- Murdaugh, H. V., Robinson, R. R. (1959): *J. Clin. Invest.* **38**, 1065.
- Müller, I., Gottschild, C., Kolb, E., Seidel, H., Ziemke, G. (1982): Untersuchung über den Gehalt an Glukose an freien Fettsäuren, an Insulin, an Ca, an P und an Mg sowie über die Aktivität der alkalischen Phosphatase im Blutplasma von 10 laktierenden Jersey-Rindern über einen Zeitraum von 24 h. *Mh. Vet.-Med.* **37**, 103.
- Nanni, G. (1958): Opsonic activity of properdin. *Experientia* **14**, 23.
- N. R. C. (1984): *Nutrient Requirements of Poultry*. 5th ed. National Academy Press, Washington.

sorption of magnesium is a process displaying linear saturation. This is therefore the process responsible for the adaptive change following variation in intake.

On the other hand, indirect mechanisms, which are not connected with an insufficient intake, may also participate in the warding-off of a magnesium deficiency. Experiments in rats indicated that the absorption of magnesium is increased if its renal secretion is enhanced following the administration of diuretics, e.g. furosemide, or if the renal clearance is enhanced by triiodothyronine (Peerenboom et al., 1980).

The essentials of these regulatory mechanisms are not known, with the exception of the decrease in the intestinal transit time. The latter is the only mechanism which appears in a magnesium deficiency and is capable of inducing the intestinal absorption of magnesium (Bueno et al., 1980).

It may be assumed that a local hormonal regulation involving polypeptidolytic hormones also plays a role in magnesium absorption: magnesium influences the secretion of these hormones, some of which are able to modify its absorption.

The increased magnesium absorption in cases of magnesium depletion is not always a constant-regulatory mechanism, since this mechanism does not function in the experimental magnesium deficiency of man (Dunn and Walser, 1966).

There is no doubt that the homeostasis of the blood level of magnesium depends primarily on the renal function (Grünzig et al., 1983), and secondarily on the effectivity of intestinal absorption. Nevertheless, these two processes alone do not satisfactorily explain the constancy of the level of magnesium in the blood. The presence of feedback mechanisms regulating these two processes and the distribution of the magnesium ion in the organism must also be assumed.

Intestinal methods of examination of magnesium absorption

It is obvious from an analysis of the diagnostic problems relating to magnesium deficiency that magnesium-loading tests are of essential importance.

Of course, as concerns the evaluation of tolerance tests, it must always be taken into consideration that a positive result is not absolutely necessary for the establishment of a deficiency. These tests are generally negative in cases of magnesium depletion, i.e. when the deficiency is caused by a disturbance of the factors controlling the magnesium metabolism. In these cases of depletion, the diagnosis is easy if the cause can be revealed and effective therapy is employed which is capable of inducing a regression of the functional disturbance by suspending the magnesium deficiency. Examples of this condition include the magnesium deficiency in cirrhosis (requiring aldosterone-antagonist treatment) and that in the various clinical forms of diabetes.

Loading tests are most important in deficiency states, in which diagnosis is relatively easy, but an exact pathophysiological diagnosis is necessary to reveal the corrective mechanisms.

Magnesium loading tests

Apart from those dynamic tests in which hormones and pharmacodynamic agents are used to examine the magnesium metabolism, mainly two types of tolerance tests are applied in clinical practice. These are *quick parenteral test* and the *slower oral test*. As will be seen later, these two tolerance tests are adequate methods for examination of the magnesium metabolism rather than satisfying the criteria of the classical tests of intestinal absorption.

Parenteral magnesium loading test. This method is based on the increased cellular requirement in a magnesium deficiency. In experimental animals with a magnesium deficiency, 90% of the intraperitoneally administered magnesium is retained within 6 hours, as opposed to the 4% retained in the controls. This means that, in animals with a magnesium deficiency, 10% of the administered magnesium is excreted by the kidneys (Caddell et al., 1980; Achilles and Schefel, 1983.) In man, the retention of intravenously administered magnesium should be less than 20% after 4 hours, or 10% after 24 hours. A retention in excess of these values (positive Thoren test) is indicative of a magnesium deficiency (Thoren, 1963).

The result of the loading test is influenced essentially by the involvement of the kidney. If the urinary excretion of magnesium is faster than its accumulation during the test, the result is 'false negative' (Harris and Wilkinson, 1971).

Oral magnesium loading test. This is the basic practical diagnostic test for the assessment of a magnesium deficiency (Nicar, 1981; Nicar and Pak, 1982). Its clinical aspects may be interpreted much more easily than those of the parenteral tolerance test. If magnesium is administered in physiological oral doses, its pharmacodynamic features are completely absent. During the test period, magnesium is given in a daily dose of 0.2 mmol or about 5 mg per kg body weight, in the form of a well-absorbable salt. The effect of this dosage is evaluated monthly. Observation of a positive effect (i.e. an increase in the magnesium level) is taken as the starting-point of treatment (Durlach, 1961, 1963, 1969; Elin and Johnson, 1983; Elin and Hossein, 1984).

Magnesium deficiency as a consequence of malabsorption

Malabsorption may be the cause of primary and secondary magnesium deficiencies. The primary form, neonatal hypomagnesaemia (hereditary magnesium malabsorption), is a rare disease in which magnesium absorption is selectively impaired, while in the secondary forms the malabsorption of magnesium is a symptom accompanying the syndromes of generalized malabsorption.

Hereditary magnesium malabsorption

This is a rare autosomal recessive congenital disease, a congenital disturbance of the metabolism (Holtmeier, 1968; Paunier, 1979, 1980; Teebi, 1983). It is manifested at an early age by convulsions and tetany. Its symptoms were initially thought to be a

consequence of hypocalcaemia, but they did not disappear following the intravenous administration of calcium. Since even the chronic administration of vitamin D also proved ineffective, attention turned to magnesium. The symptoms are rapidly influenced by orally or parenterally administered magnesium.

By means of radioactive magnesium, it was demonstrated that 90% of the administered quantity was not absorbed even after 96 hours and that only 1.5% was excreted with the urine. These values are in sharp contrast with the respective values of 46% and 14% measured in the controls. Furthermore, the serum magnesium and calcium levels are decreased; the latter may be corrected by an increased calcium intake. The plasma phosphate level is elevated. Since the condition is improved by the administration of a large amount of magnesium, the specific transport mechanism is not impaired. This finding is consistent with the experimental observation that magnesium is transported normally by diffusion, along an electrochemical gradient. Following the suspension of magnesium administration, the symptoms reappear.

Causes of magnesium deficiency due to malabsorption

Magnesium malabsorption may be a consequence of anatomical, physicochemical or functional damage of the intestines.

Reduction of the absorptive surface. Since magnesium is absorbed mainly in the ileum (primarily in its distal segment) and also in the colon, a reduction in the absorptive surface is followed by a decreased absorption of magnesium from the food. The resection of an ileal segment, a jejunoileal bypass (Hessov et al., 1982) or inflammation of the intestinal wall (due to toxins or irradiation) also result in a decreased magnesium absorption (Nichini et al., 1973; Tansy and Kendall, 1981; Hessov et al., 1983).

Diarrhoea and steatorrhoea. Diarrhoea, independently of whether it is an acute or chronic, intensive or profuse form (Hanna et al., 1960; Thoren, 1963; Hessov et al., 1983) increases the loss of magnesium via the intestinal tract, considerably mainly because of the decreased intestinal transit time, since this time is correlated with the passive absorption of magnesium (MacIntyre and Robinson, 1964). In steatorrhoea, the same mechanism is accompanied by a significant magnesium loss with the faeces because of the formation of nonabsorbable magnesium soaps (Booth et al., 1963; Graham, 1982; Graham and Sackman, 1983). If the magnesium deficiency induces exudative enteropathy, a true vicious circle develops, which is maintained by diarrhoea and steatorrhoea on one side, and a magnesium deficiency on the other.

The impairment of facilitated diffusion. $1.25\text{-(OH)}_2\text{D}$, insulin and the peptide hormones of the intestinal tract all play roles in the enhancement of magnesium absorption by facilitated diffusion. In certain conditions, such as insulin-dependent diabetes (Foert et al., 1980; Paschen et al., 1981), especially if this is accompanied by haemochromatosis, rickets and osteomalacia or renal insufficiency, the magnesium deficiency decreases the absorption of magnesium by decreasing its facilitated diffusion (Mountokalakis et al., 1976).

There can be no doubt that the above mechanisms are often closely interrelated. It would be arbitrary to consider any one of them as the main cause of the magnesium deficiency developing in malabsorption.

Magnesium deficiency in iatrogenic malabsorptions

Magnesium deficiency following surgical intervention. Two types of surgical intervention may lead to an iatrogenic magnesium deficiency:

- a) extensive resection of the small intestine, and
- b) jejunioileal bypass.

Resection of the small intestine is performed in Crohn disease, volvulus and intestinal infraction (Booth et al., 1963; Homeida et al., 1979; Hesso et al., 1983). Jejunioileal bypass may be the method of choice in severe cases of obesity (Hesso et al., 1982). The level of magnesium in the serum decreases if the length of the resected intestinal segment exceeds 75 cm (Hesso et al., 1983). In these cases of malabsorption, the decrease in the magnesium content of the urine correlates well with that of the muscles, and measurement of the amount of magnesium excreted in the urine may therefore be a method of surveillance. By contrast, the Thoren test may give misleading results, for example in cases with a retention of less than 10% (Hesso et al., 1982). It appears that correction of the magnesium deficiency following ileal resection by means of the oral administration of magnesium is much more effective if the magnesium is given in solution rather than as tablets (Haddad, 1982).

Enteritis following irradiation. The intestinal complications of abdominal irradiation reflect chronic intestinal lesions which most frequently induce a severe magnesium deficiency. While significant hypomagnesaemia is observed in only half of the cases of extensive ileal resection, it develops in 70% of enteritides induced by chronic irradiation. The magnesium deficiency is much more severe in radiation enteritis than in the short-bowel syndrome. This peculiarly severe complication of radiation enteritis is a consequence of the loss of magnesium via the faeces which points either to a specific malabsorption or to the development of a genuine exudative enteropathy. Under experimental conditions, the effects of acute abdominal irradiation and those observed in a subacute magnesium deficiency reveal similarities such that the role of abdominal irradiation in the development of a magnesium deficiency seems unambiguous (Tansy et al., 1971, 1980; Nichini et al., 1973; Tansy and Kendall, 1981).

Iatrogenic enterocolitis. All forms of treatment-induced diarrhoea and steatorrhoea may cause a magnesium deficiency. Large doses of antacids, such as aluminium carbonate, calcium carbonate or magnesium oxide, result in the loss of magnesium by two mechanisms: a phosphate deficiency and steatorrhoea. On binding to the phosphates in the food, magnesium forms insoluble and nonabsorbable complexes. The precipitation of poorly absorbable soaps and conjugated biliary acids leads to an enhanced loss of fats via the faeces, which in turn induces a further magnesium loss (Graham, 1982; Graham and Sackman, 1982).

Magnesium deficiency due to spontaneous malabsorption

Acute diarrhoea. A magnesium deficiency develops only in severe cases of diarrhoea, e.g. in Asiatic cholera or in bacterial enterocolitis accompanied by a serious condition. In such cases, the dehydration results in an apparently increased serum magnesium level, which conceals the intracellular ion deficit. Following rehydration, however, the magnesium deficiency is clearly revealed.

Chronic states of diarrhoea. The chronic states of diarrhoea may lead to magnesium deficiencies of various degrees. The severity and frequency of the magnesium deficit in Crohn disease may vary widely, depending mainly on the extent of the intestinal impairment. The malabsorption of magnesium is especially considerable if both the terminal segment of the ileum and the colon are involved. On the other hand, some forms of chronic enteritides, such as coeliac disease, Whipple disease, disaccharide intolerance, certain types of lymphangiectasia and diffuse mastocytosis, decrease the magnesium level only if persisting for a long time (Goldman et al., 1962; Booth et al., 1963; Harris and Wilkinson, 1971; Paunier, 1979, 1980).

Magnesium deficiency is caused also by the diarrhoeal form of megacolon, diverticulitis and ulcerative colitis. Steatorrhoea and probably the sequestration of magnesium in the pancreatic substance are the underlying mechanisms of magnesium deficiency in acute and chronic pancreatitides, independently of their origin, and also in mucoviscidosis (Edmondson et al., 1952; Paunier, 1980).

Endocrine dysfunctions. In some forms of endocrine dysregulations, malabsorption may be a concomitant symptom which may lead to a magnesium deficiency. This is the case in diabetes (Nath et al., 1974), rickets and magnesium-dependent osteomalacia, in which vitamin D has a substantial influence on the absorption of magnesium. On the other hand, the role of magnesium malabsorption in postmenopausal and senile osteoporosis has not yet been clarified (Cohen et al., 1983 a, b; Levine et al., 1979, 1980; Avakian et al., 1984; Brown et al., 1984).

Chronic renal diseases. The mechanism of magnesium malabsorption in chronic renal insufficiency is still unknown. It has been proved that the absorption of magnesium is reduced; in man, this is a consequence of the decreased renal activation of 1,25-dihydroxycalciferol. On the other hand, animal experiments have revealed that the change induced in the jejunal magnesium transport by subtotal nephrectomy could not be influenced by 1,25-dihydroxycalciferol (Mountokalakis et al., 1976; Devone and Ryan, 1983; Ahmad et al., 1984).

Consequences of magnesium deficiency due to malabsorption

In malabsorption, every manifestation of magnesium deficiency may be observed. Magnesium deficiency plays a role in the development of gastrointestinal symptoms and humoral disturbances. This role deserves special attention in malabsorption.

The role of magnesium deficiency in the general symptoms of malabsorption

The magnesium deficiency observed in states of malabsorption is closely correlated with the signs of neuromuscular hyperexcitability, i.e. fatigue, paraesthesia, and the development of tetanic spasms, convulsions and decreased isometric contraction in the quadriceps muscle (Eisinger, 1983).

The cardiovascular consequences of a magnesium deficiency should be considered especially in pathological obesity treated by jejunoileal bypass (Arsura et al., 1984). The ECGs of these patients reveal typical changes in ventricular repolarization, due to the decreased level of magnesium in the plasma.

Gastrointestinal and humoral consequences of magnesium deficiency in malabsorption

The most frequent causes of a magnesium deficiency are exudative enteropathy, diarrhoea and steatorrhoea. The correction of the magnesium deficiency in intestinal hyperperistalsis, protein loss and fat malabsorption may help in revealing those cases in which magnesium is responsible for the intestinal anomalies (Fletcher et al., 1960; Homeida et al., 1973).

The development of a magnesium deficiency in Crohn disease plays a role in the manifestation of the disease. The plasma level of magnesium is negatively correlated with an inflammation-specific glycoprotein reaction (Augusti et al., 1973).

Hypocalcaemia, hypoparathyroidism and hypokalaemia may be consequences and accompanying signs of a magnesium deficiency; the subsides if the state of deficiency is corrected (Borkenstein and Dambacher, 1981; Homeida et al., 1979). Nevertheless, it should be emphasized that all the above disturbances of the ion metabolism may sometimes be directly related with the generalized malabsorption. The nature and site of the intestinal impairment determine the magnesium deficiency and the severity of the accompanying primary or secondary hypocalcaemia. In cases of massive ileal resection sparing only the duodenum and the upper part of the jejunum, the balance and radioisotope examinations reveal a massive change in the magnesium level, a significant change in the potassium level, and a negligible change in the calcium level. This also proves that in man calcium and magnesium are absorbed mainly in the proximal and distal parts, respectively, of the small intestine part.

A magnesium deficiency may increase the malabsorption of other substances, and in cases of joint occurrence may result in an enhancement of the deficiency, e.g. in polyneuritis due to vitamin B₁ deficiency, in anaemia due to vitamin B₁₂ deficiency, and in osteomalacia due to vitamin D deficiency (Levine et al., 1979, 1980; Moussavian and Nichas, 1979; Mosekilde et al., 1980).

6.2. Recommended magnesium intake and magnesium in human nutrition

Magnesium is the fourth most important cation in the human body, but it ranks second as an intracellular cation. Around 40% of the 20–28 g of magnesium in the organism is situated in the muscular and visceral tissues and only 1% is in the cells. The remaining magnesium is in the bones. The average plasma magnesium level is 0.85 mmol/dm³, the range being 0.65–1.0 mmol/dm³. The plasma magnesium level is under the control of a not yet fully understood mechanism, which is rather unstable.

Since almost 70% of the plasma magnesium is not bound to protein and 30% can be filtered, the plasma magnesium level must be stabilized by renal regulation. The magnesium in the bones serves a buffer to balance the fluctuations in the intracellular magnesium level.

Magnesium serves several functions in the human body. It plays a basically important role in biosynthetic processes, and in glycolysis, it is indispensable for the transmission of genetic codes and the transport function of energy-dependent membranes, and it is necessary for the activation of more than 300 enzymes (Wester, 1987). The indispensable role of magnesium was first proved by Leroy 65 years ago in mouse, and the symptoms of magnesium deficiency in rat have been known for almost 60 years, but a magnesium deficiency in humans or the possibility of its development and the importance of its detection, treatment and prevention are taken into consideration by only few clinicians (Gums, 1987; Durlach, 1989).

A magnesium deficiency can be life-threatening, and its identification and rapid diagnosis in time are therefore mandatory. Since a magnesium deficiency cannot be diagnosed easily (the serum magnesium level is only a rough indicator of the magnesium supply of the human body, and its checking by biochemical methods will not help to identify the danger of development of the complications of a magnesium deficiency), it is very important to be aware of those conditions which can result in mild or serious forms of magnesium deficiency. The diseases and risk factors resulting in magnesium deficiency can in general be classified in four groups:

- a) conditions involving malabsorption, and diseases of the digestive system with serious fluid and electrolyte loss;
- b) renal diseases with reduced cation reabsorption;
- c) general malnutrition and alcoholism;
- d) iatrogenic (nosocomial) causes.

Serious diseases involving chronic enteral inflammation, among them gliadin enteropathy, diseases with fistulas, e.g. Crohn disease, and all other conditions leading to steatorrhoea, may belong in the first group. A magnesium deficiency may also be caused by other forms of intestinal villous atrophy, e.g. pathological changes caused by diseases of the immune system or by irradiation. Besides these diseases of the gastrointestinal system, a magnesium deficiency can develop in other enteral diseases too.

In chronic renal diseases, dysfunction of the renal tubules may be seen, but a magnesium loss can develop in response to medicines (digoxin reduces the renal reabsorption of magnesium, and the magnesium-discharging effect of some diuretics is well known). Diabetes mellitus is one of the most frequent diseases associated with a magnesium deficit, possibly determined by the intake, the gastrointestinal absorption, the redistribution in the body and the urinary excretion (Garland, 1992).

Certain endocrine diseases likewise lead to a magnesium deficiency: hyperaldosteronism, hyperthyroidism and hyperparathyroidism.

Malnutrition is a well-known causative condition of a magnesium deficiency. Definite symptoms of this may be seen in its most serious form: protein energy malnutrition (inanition). A familiar consequence of alcoholism is a marginal magnesium deficiency (Durlach, 1989). A magnesium deficiency can develop during long-term parenteral feeding, and in diseases accompanied by an increased catabolism (hyperthyroidism and cancer). A long duration of breast feeding can similarly lead to the development of magnesium deficiency.

As concerns medicines, symptoms suggestive of a magnesium deficiency may be observed during the long-term use of aldosterone, amphotericin, calcitonin, carbenicillin, digoxin, diuretics, gentamycin, tobramycin, growth hormone and thyroxine (Gums, 1987; Shils, 1988).

Primary idiopathic hypomagnesaemia belongs among the familial magnesium deficiencies of genetic origin, together with the magnesium-deficient state of the children of diabetic mothers.

In connection with the prevalence of magnesium deficiency, examination of 2300 hospitalized patients revealed an abnormal magnesium status in 12.5%, and the incidence of hypomagnesaemia in two studies was 7% and 11% (Wong et al., 1983; Whang et al., 1984). Accordingly, it seems reasonable to look for a magnesium deficiency in cases involving other electrolyte disturbances: hypomagnesaemia has been identified in 42% of hypokalaemia, 29% of hypophosphataemia, 23% of hyponatraemia and 22% of hypocalcaemia cases (Whang et al., 1984). A magnesium deficiency is a common problem in critically ill patients: Ryzen (1939) found a 65% prevalence and considered that the actual occurrence of a magnesium deficiency in critically ill patients may be even higher and may contribute to the pathogenesis of cardiac arrhythmias.

Durlach (1989) estimates that a marginal primary magnesium deficit affects an appreciable proportion (15–20%) of the population.

As a result of the fact that hypomagnesaemia commonly develops and is present unobserved, two very important questions arise:

- a) Is there any chance of the development of a primary magnesium deficiency from an insufficient intake?
- b) How can the magnesium intake be evaluated and compared with the recommended intake?

Answers to these questions may be sought indirectly, primarily from the results of surveys, human observations and balance studies. Nutrition-epidemiological surveys involving study of the correlation between magnesium intake and blood pressure may serve as the starting-point.

Magnesium effectively inhibits the contractions of the arterial smooth muscles, decreases the peripheral vascular resistance and, by virtue of its vasodilator effect, may play a role in the regulation of blood pressure. The relationship between magnesium intake and high blood pressure has long been studied. Observations and clinical trial experience suggest the possibility that magnesium may have both physiologic and pharmacologic roles in patients with essential hypertension. Unfortunately, the evidence from epidemiological studies is inconsistent and many clinical examinations were not extensive enough or were methodologically imperfect (Whelton and Klag, 1989). The effects of any one nutrient, including magnesium, in hypertension should be considered within the context of the overall nutrition in each patient. The magnesium ion plays a part in smooth muscle contraction and, since magnesium is mainly situated in the inner surface of the cell membranes, it could contribute to the membrane permeability for sodium and calcium, which is important in the pathogenesis of hypertension. A magnesium deficiency predisposes to an increased arterial contractility and a magnesium excess can modulate the smooth muscle contractility caused by angiotension II (Singh et al., 1989b). Magnesium loading was found to blunt the rise in blood pressure and the aldosterone-stimulating effect of angiotensin II, but

magnesium depletion significantly enhanced these angiotensin II effects (Rude et al., 1989).

An inverse relation has been observed between the serum magnesium level and the blood pressure in 60-year-old men and women, and a similar relation has been found between the amount of magnesium excreted with the urine and the diastolic blood pressure (Sangal and Beevers, 1982; Kesteloot, 1984b). A significant negative correlation was demonstrated between the dietary magnesium intake and the systolic blood pressure in women in a randomized epidemiological survey in Belgium between 1979 and 1984 (Kesteloot and Joossens, 1988). Motoyama et al. (1989) suggest that oral magnesium supplementation may lower the blood pressure through the activation of a cell membrane sodium pump and Singh et al. (1989b) consider that the adequate administration of magnesium salts for an appropriate period of time would result in at least a 10/5 mm Hg decrease in blood pressure. From the results of other studies, it seems that there is no correlation between the magnesium intake and the blood pressure. The magnesium intakes of normotensive and hypertensive Scandinavian women were similar, and no relation was found between urinary magnesium excretion and blood pressure in Korea and in the NHANES II survey (Thulin et al., 1980; Harlan et al., 1984; Kesteloot, 1984a). Magnesium supplementation did not appear to have an additive hypotensive effect in mild hypertensive subjects on a reduced sodium intake (Nowson and Morgan, 1989). The current level of uncertainty is likely to persist until results from large, rigorously controlled studies become available (Whelton and Klag, 1989), but until then a diet adequate in magnesium may be used for the prevention of hypertension, and magnesium supplementation is advised only for those who are receiving diuretics (Singh et al., 1989b). Motoyama et al. (1989) is of the view that oral magnesium supplementation is appropriate non-pharmacological treatment for essential hypertension.

Population groups living in areas where the water is hard (water with a high mineral content, including magnesium) display lower than average prevalence of cardiovascular disease (Schroeder, 1960; Neri and Johansen, 1978). There is abundant literature on the correlation between the magnesium nutritional status and the myocardial function (rhythmicity) in ischaemic heart disease. These studies permit the conclusion that the lower incidence of sudden heart death in population groups living in hard-water areas is in part correlated with the magnesium status of the people, and the higher mortality among people drinking soft water may be an indicator of the importance of the marginal form of magnesium deficiency. During the past ten years, many authors have demonstrated the possibility of magnesium depletion in the population as a whole and in particular among patients receiving diuretics, and some results suggest that this magnesium depletion could play a role in the development of arteriosclerosis and could aggravate the outcome of acute myocardial infarction with a tendency to arrhythmia. However, these studies are too few and too limited to be conclusive (Frandsen and Pedersen, 1992). In a study where the magnesium intake of one group was 1.142 mg/day and that of another group was 418 mg/day (400 high-risk individuals participated in the two groups for 10 years), it was found that in the group with a very high magnesium intake the total mortality was significantly less, the incidence of sudden death was 50% less, and the number of complications was significantly less than in the other group. It was considered that an increased intake of magnesium can offer protection against cardiovascular death among high-risk individuals

(Singh, 1990). Nevertheless, it should be noted that many experts are of the view that the evidences collected is not conclusive enough to declare the necessity for an increased magnesium intake (Simopoulos, 1987), or further studies are urged (Diet and Health, 1989).

The recommended magnesium intake is debated. The only method recommended for an approach to the problem is the balance study, but neither isotopic magnesium turn-over examinations nor surveys to establish the magnesium intake are appropriate for clarification of the question. The results of magnesium balance studies suggest that 3.0–4.5 mg/kg body mass may be enough for adults which corresponds to an intake of 210–320 mg/day (Greger and Baier, 1983; Schwartz et al., 1984, 1986).

Few selected examples from various countries demonstrate that the recommended intake for adult men was somewhat higher than mentioned above: the recommended intake in Czechoslovakia and Poland in 1983 was 400 mg/day, while in the Soviet Union it was 300 mg/day (Table 6.1).

Very similar recommendations were to be found in the second half and at the end of the 1980s (Tables 6.2 and 6.3). There is a significant difference between Europe and North America as concerns the recommended intake for infants and children (Table 6.4). Recent recommendations, however, differ substantially: the recommended intake for adults is 6.0 mg/kg body mass i.e. 450 mg/day (ILSI, 1990), and Durlach (1989) considers that an intake of 4.0 mg/kg body mass is responsible for the primary marginal magnesium deficiency in 15–20% of the population.

The data from nutrition-epidemiological surveys show that the magnesium intakes of certain population groups can differ significantly from the recommended value, but the effects of this on the cardiovascular system are still a matter of debate.

In the U.S.A., the daily magnesium intake of 1–5-year-old children was reported to be 193 mg (115% of the intake recommended in 1980), while for 19–50-year-old women it was 207 mg (67% of the recommended intake) and for men of the same age

Table 6.1. Recommended magnesium intake (mg/day) (Committee 1.5 of IUNS, *Nutr. Abstr. Rev.*, 1983)

Country	Age	Infants	Children	Girls	Boys	Men	Elderly women	Pregnancy	Lactation
		4 5 months	1 2 years	13 14 years	16 17 years	26 29 years	65-69 years	23 30 years	23 30 years
	Sex	M F	M F	F	M	M	F	F	F
Canada		50	75	250	300	300	250	+25	+75
Caribbean		50	150	300	350	350	250	+50	+100
Czechoslovakia		0.8/kg	100	300	400	400	300	+100	+100
France		—	100	350	350	350	350	+50	+50
G.D.R.		80	120	300	300	250	250	+50	+100
F.G.R.		75	130	280	300	260	220	+40	+60
Italy		60	150	300	400	350	300	+150	+150
New Zealand		70	150	350	400	350	300	+150	+150
Poland		—	109–150	350	400	400–350	350	+100–150	+100–150
Spain		60	125	330	400	350	300	+120	+120
Uruguay		—	150	300	400	300	300	+150	+150
U.S.A.		50	150	300	400	350	300	+150	+150
Soviet Union		—	140	400	530	500	—	+42.5	+72.5

Table 6.2. Recommended magnesium intake*

Females

U.S.A. 1989		F.G.R. 1989		Nordic countries 1989		Hungary 1988	
age (years)	daily intake (mg)	age (years)	daily intake (mg)	age (years)	daily intake (mg)	age (years)	daily intake (mg)
11-14	280	10-12	250	11-14	300	11-14	350
		13-14	300				
15-18	300	15-18	350	15-18	300	15-18	350
19-24	280	19-35	300	19-30	300	19-30	300
25-50	280	36-50	300	31-60	300	31-60	300
51	280	51-65	300	61-75	300	61	300
		65	300	75	300		
Pregnant women							
	320		400		450		450
Lactating women							
6 months	355		450		450		450
6 months	340						

* Sources of data in Tables 6.2, 6.3 and 6.4.

U.S.A.: Subcommittee on the Tenth Edition of the RDAs, Food and Nutrition Board, Commission on Life Sciences, National Research Board: *Recommended Dietary Allowances* (1989)

F.G.R.: Deutsche Gesellschaft für Ernährung (DGE): *Empfehlungen für die Nährstoffzufuhr* (1989)

Nordic countries: Nordisk Ministerråd: *Nordic Nutrition Recommendations* (1989)

Hungary: Bíró, Gy., Linder, K.: *Tápanyagtáblázat* (Food Composition Tables) (1988)

Table 6.3. Recommended magnesium intake*

Men

U.S.A. 1989		F.G.R. 1989		Nordic countries 1989		Hungary 1988	
age (years)	daily intake (mg)	age (years)	daily intake (mg)	age (years)	daily intake (mg)	age (years)	daily intake (mg)
11-14	270	10-12	280	11-14	350	11-14	350
		13-14	330				
15-18	400	15-18	400	15-18	400	15-18	350
19-24	350	19-35	350	19-30	350	19-30	350
25-50	350	36-50	350	31-60	350	31-60	350
51	350	51-65	350	61-75	350	61	350
		65	350	75	350		

* See notes to Table 6.2.

Table 6.4. Recommended magnesium intake*

Infants, children

U.S.A. 1989		F.G.R. 1989		Nordic countries 1989		Hungary 1988	
age (years)	daily intake (mg)	age (years)	daily intake (mg)	age (years)	daily intake (mg)	age (years)	daily intake (mg)
0 -0.5	40	0 -0.2	50	0 -0.5	50	0 -0.5	50
0.5-1	40	0.3-0.5	70	0.5-1	70	0.5-1	70
1 -3	80	0.6-1	120	1 -3	150	2 -3	150
4 -6	120	1 -3	140	4 -6	200	4 -6	200
7-10	170	4 -6	200	7-10	250	7-10	250
		7 -9	220				

* See notes to Table 6.2.

Table 6.5. Magnesium intake of vegetarians and non-vegetarians (mg/day) (Diet and Health, 1989)

U.S.A., 1977-78

Sex	Age (years)	Vegetarians	Non-vegetarians
Males	>3	176	149
	3- 8	120	100
	9- 18	97	80
	19- 34	124	86
	35- 64	106	88
	≥ 65	92	80
Females	9- 18	115	103
	19- 34	87	69
	35- 64	74	76
	≥ 65	68	75
Total		95	83

it was 329 mg (94% of the recommended intake) (Diet and Health, 1989). It is very interesting to see that the changes in the diet of the population in the U.S.A. between 1909 and 1985 suggest increased intakes of energy, protein, fat, calcium and almost all vitamins, but in the same period there was a decrease in the magnesium intake from 380 mg/day/person to 320 mg/day/person (i.e. a 16% decrease) (Diet and Health, 1989).

An other analysis from the U.S.A. on the magnesium intake of adolescent girls reveals that in 1976 the magnesium intake was 238 (SD 86) mg/day (5.56 mg/kg body mass), and in 1977 it was 231 (SD 85) mg/day (4.31 mg/kg body mass), but in one-third of the girls participating in the study the intake was less than two-thirds of the recommended intake (Greger et al., 1979). At close to the same time, the magnesium intake of adult American women and men was 230 and 310 mg/day, respectively (Diet and Health, 1989). In a nutritional study of 270 U.S. Navy sea, air, and land

trainees, the mean intake of magnesium exceeded the recommended dose, but in 34% of them it did not reach this level (Singh et al., 1989a).

Balance studies yielded values of magnesium requirements ranging from 300 to 354 mg/day for American women and from 420 to 483 mg/day for men. The actual magnesium intake in the U.S.A. is about 202 mg/day for children from 1 to 5 years old, 228 mg/day for women, and 331 mg/day for men (19–50 years old) (Lichten, 1989).

During a one-year balance study in which the daily dietary data served for an estimation of the daily magnesium intake the balance for 34 men and women proved negative, with a magnesium intake of 323 and 234 mg/day, respectively, but effects were obviously exerted by other nutrients (protein and calcium) and food ingredients (dietary fibres) (Lakshmanan et al., 1984).

The importance of dietary habits on the magnesium intake is shown by the difference between the magnesium intakes of vegetarians and non-vegetarians (Table 6.5). The average daily magnesium intake of vegetarians reached 96% of the Recommended Dietary Allowance (RDA), but in the diet of non-vegetarians it was only 83% of the RDA. It was interesting that the lowest magnesium intake among the vegetarians was that of women over 65 years, but among the non-vegetarians it was that of women aged 19–34 years (Diet and Health, 1989).

A nutrition survey on a group of 2242 men and women (15–80 years) in Denmark in 1985 revealed a magnesium intake of 289 mg/day in women and 389 mg/day in men (LST, 1985).

The nutrition of 5767 men and 5204 women (25–74 years) was studied in Belgium during the period between 1980 and 1985. It was found that the average daily magnesium intake of the men in the age group 25–34 years was over 400 mg, and that the average intake for all the males approached 400 mg/day (Table 6.6), whereas the daily magnesium intake of the women was almost 100 mg less (Kornitzer and Bara, 1989).

In the Honolulu Heart Study, the correlations between magnesium intake and systolic and diastolic blood pressures were analysed. In comparison with other nutritional elements (calcium, phosphorus, dietary fibre, vegetable proteins, starch, etc.) the blood

Table 6.6. Magnesium intake in Belgium
(Nutritional survey, Kornitzer and Bara, 1989)

Belgium, 1988, $n=10,971$;
Males + females 25–74 years

Age (years)	Sex	Males	Females
	daily intake (mg)		
25–34		441	327
35–44		428	317
45–54		400	308
55–64		371	294
65–74		333	276
25–74		395	306

pressure had the closest (negative) correlation with the magnesium intake (Table 6.7; Joffres et al., 1987).

The Hungarian data presented here are from the First Hungarian Representative Nutrition Survey (1985–1988), which covered 16,641 people. The average daily magnesium intake for men and women was 387 and 309 mg, respectively. In the two youngest age groups of the male population the daily magnesium intake was over 400 mg, while in the three oldest groups it was between 400 and 311 mg. In the female population the daily magnesium intake was somewhat over 300 mg in the three lowest age groups, and below 300 mg in the two oldest age groups (Table 6.8). A magnesium intake lower than 300 mg/day was found in 26% of the males and 50% of the females (Bíró, 1992).

A survey in Japan revealed a magnesium intake of 200–300 mg/day for healthy adults, and 120–130 mg/day for children. An interesting result from the same survey was that the magnesium balance could not be influenced significantly by increasing the magnesium intake either in adults or in children (Goto 1986).

In the Netherlands, the nutrition of 201 adult people was studied by means of the most expensive, but most accurate method (each meal was prepared in two portions,

Table 6.7. Relationship between magnesium intake and blood pressure (Honolulu study, Joffres et al., 1987)

Honolulu Heart Study

Magnesium intake (mg/day)	Blood pressure (mm Hg)	
	systolic	diastolic
38– 174	139.8	81.2
175– 240	135.2	78.4
241– 330	133.5	78.9
331– 1429	133.4	78.1

Table 6.8. Magnesium intake in Hungary (Representative nutrition survey, Bíró, 1992)

Hungary, 1985–88

Age (years)	Sex	Males	Females
	daily intake (mg)		
15<18		441 ± 149	314 ± 100
19– 34		424 ± 161	323 ± 100
35– 60/55		387 ± 120	313 ± 91
56/61– 75		348 ± 113	292 ± 90
>75		311 ± 94	276 ± 90
Total		386 ± 133	308 ± 95

Table 6.9. Magnesium content of planned menus
(Zajkás et al., 1990; unpublished)

Age (years)	Winter/spring diet		Summer/autumn diet	
	energy kJ(kcal)	magnesium (mg)	energy kJ(kcal)	magnesium (mg)
19-30	9618 (2290)	408	10357 (2466)	411
31-60	10752 (2560)	404	10752 (2560)	390
>60	8458 (2014)	370	8551 (2036)	366
Menu of diabetics	7014 (1670)	350	7392 (1760)	376
Low-energy menu	4334 (1032)	278	4410 (1050)	265

one for the patient and one for chemical analysis); the daily magnesium intake was 289 mg (ranging between 127 and 653 mg/day) (Vaessen and van De Kamp, 1986). In Great Britain, statistical analysis of household budgets demonstrated an average daily magnesium intake of 267 mg in 1986 (Lewis and Buss, 1988), reflecting only a slight increase over the 249 mg/day intake in 1976. The data from household statistical surveys relate primarily to food consumed at home, but when the above value was corrected for the magnesium content of confectioneries, drinks and other foods consumed outside the home, the daily magnesium intake rose to 294 mg. In this analysis the average magnesium intake in Great Britain was 247, in England 245, in Scotland 247 and in Wales 257 mg/day. Only 1 mg difference in daily magnesium intake was found between the four groups, formulated on the basis of the income (229 and 228 mg/day).

Comparison of the above data and the present magnesium intake recommendations suggests that the insufficiency of the magnesium intake in different countries and population groups appears to be a reality.

It is relevant that the magnesium intakes of individuals and population groups are determined by the dietary patterns and the magnesium contents of the foods characteristic of the given country. Table 6.9 lists the magnesium contents of planned diets (for winter-spring, and summer-autumn, two weeks in each period) for healthy adults, obese people, and diabetics in different age groups. Regularly consumed foods in Hungary that provide over 9.6 MJ (2300 kcal) can ensure a magnesium intake of around 400 mg/day; and even in diets limited for different reasons the Hungarian recommendations can be fulfilled for adult men and women, i.e. 350 and 300 mg/day, respectively, but the low-energy diet is deficient in magnesium. Accordingly, in answer to the question raised at the beginning of this section, certain diets may involve an insufficient magnesium intake, and magnesium supplementation may therefore be necessary.

In Hungary, primarily cereals, meats and meat products, then vegetables and fruits and finally the pulses play a determining role as concerns the magnesium intake.

Evaluation of a menu plan demands a consideration of the magnesium losses caused by some food industrial technologies (e.g. milling) and the increasing effect of nutrients such as proteins, fats, cholesterol and lactose on the magnesium requirements. Fats are practically magnesium-free, and the excellent protein sources milk, dairy products and eggs are very poor in magnesium (Caddell, 1980). A diet based on the

regular intake of refined carbohydrates, chips, fatty meat and meat products, and dairy products (containing only small quantities of vegetables and fruits) can result in a marginal magnesium deficiency. However, a subclinical magnesium deficiency can be identified only with difficulty because the human body is able to compensate a moderately insufficient magnesium intake.

Magnesium depletion caused by only a moderately or marginally insufficient intake is infrequent. It can develop in the simultaneous presence of other pathological factors well known to induce magnesium depletion, such as gastrointestinal diseases with a significant water and electrolyte loss, renal diseases with reduced cation reabsorption, severe malnutrition, alcoholism and finally iatrogenic causes (Shils, 1988; Elin, 1988).

As concerns the results of some groups who have made experimental observations of human magnesium depletion, the experience of Shils (1988) deserves attention. He studied 7 patients operated on because of oral cancer, who were fed only parenterally. The diet containing an adequate quantity of magnesium was changed to one providing a 12 mg magnesium intake daily. The amount of magnesium excreted with the urine quickly decreased, and within one week magnesium could not be found in the urine, this demonstrating the efficiency of the magnesium-conserving role of the kidneys. At the same time, the magnesium content of the faeces became very low and a gradual decrease in the plasma magnesium level was also experienced. The symptoms of magnesium depletion developed on the 24th day in one patient and on the 26th day in another; the others were still free of symptoms on the 100th day, but the symptoms finally appeared in these patients too: commonly nausea, muscle weakness, spasmophilia, excitement, mental disturbances and psychotic symptoms. All these problems were eliminated on normalization of the magnesium intake.

The results of the cited study reveal that an insufficient magnesium intake is chronically compensated by several mechanisms during a period of 3 weeks to around 3 months in humans. The functioning of these mechanisms is obviously insufficient when the four pathological conditions referred to earlier coexist with a deficient intake, and in these cases there is a real danger of the rapid development of a severe form of magnesium depletion.

6.3. Magnesium deficiency syndrome

Magnesium is a ubiquitous element in Nature and comprises an estimated 2.1% of the Earth's crust (Windholz, 1983). 22.7–35 meq/kg (calculated on a wet tissue mass basis) magnesium is to be found in the human body (Widdowson et al., 1951). This is equivalent to roughly 24 g magnesium (1 meq = 12 mg, 1 mmol = 24 mg). The majority (approximately 60%) is found in the bone. Skeletal muscle (20%) and other soft tissues contain most of the remainder (e.g. 20% in the liver and heart). Exchangeable magnesium is found in the muscle and myocardium (70% and 98%, respectively) (Cohen and Kitzes, 1983). Only about 1% is present in the extracellular space: one-third of this is non-specifically bound to plasma protein, leaving the remainder as the diffusible or free ion component. Only the surface part of the bone magnesium is

exchangeable, which is the main endogenous source of magnesium. The results of equilibrium studies (Aikawa et al., 1960) using radioisotopes suggest that the labile pool of magnesium is primarily contained in the connective tissue, the skin and the soft tissues of the abdominal cavity, while the magnesium in the bone, muscle and red blood cells exchanges very slowly. Mg^{2+} is the second most abundant intracellular cation (second only to K^+) and it is the fourth most abundant total cation. Among the biologically important cations, Mg^{2+} has the smallest ionic radius. The smaller an ion is, the greater the binding energy and the tendency to form complex compounds (chelates and organometallic complexes). The formation of complex compounds is one of the major metabolic roles of magnesium, which is a metabolic cofactor in hundreds of enzymatic reactions, particularly those involving energy utilization.

The magnesium ion is necessary for reactions involving hydrolysis and transfer of a phosphate group. Specifically, the complex magnesium-adenosine triphosphate (ATP) may destabilize the terminal ATP-phosphate bond, permitting phosphate transfer. Magnesium is also a requisite for normal functioning of the (Na^+, K^+) -ATPase pump and, as such, exerts control on the intracellular potassium balance. The Ca^{2+} -ATPase pump and the proton pump require the magnesium ion.

Besides transfer, storage and utilization of energy, magnesium is needed for protein and nucleic acid synthesis and for a number of mitochondrial processes. It has an important role in maintaining the potential in human myocytes during the fourth phase of the action potential (Dyckner and Wester, 1979).

Aikawa (1981) postulated that 3.5 billion years ago the magnesium ion combined with the porphyrin ring, because of the chelating properties of Mg^{2+} , to form chlorophyll. Formation of the chlorophyll molecule permitted photosynthesis, and therefore an oxygen-rich environment. The magnesium in the chlorophyll molecule is essential for the process of capturing protons from the Sun and converting them to ATP. The complex Mg^{2+} -porphyrin, excited by the Sun, is capable of undergoing reversible photochemical oxidation or reduction, accepting or donating electrons between partner molecules. This process leads to the formation of ATP and oxygen: both are necessary for the next higher step in the evolutionary process, oxidative phosphorylation.

Geologic evidence suggests that as oxygen was formed in the photosynthetic process, the iron in the oceans, initially in the divalent state, reacted with the oxygen formed in the photosynthetic process and precipitated in the trivalent state, forming rusty layers on the ocean floor. As this process of precipitation was completed, oxygen was released into the atmosphere, setting the stage for oxidative phosphorylation, a process that utilizes oxygen and a variety of substrates to produce ATP more efficiently than can photosynthesis.

The definition and parameters of magnesium deficiency

The terms magnesium deficiency and magnesium depletion are used as synonyms, though a magnesium deficiency involves a disturbance of the basic processes of magnesium homeostasis, while a depletion is usually a secondary consequence of the action of several compounds (e.g. alcohol or diuretics) and interventions, and is said

to exist when the intracellular stores of magnesium become depleted; however, there are no available clinical measurements of this parameter. To estimate a magnesium deficiency in clinical practice (with regard to the fact that only about 1% of the total body magnesium is in the extracellular, intravascular fluid compartment), the serum magnesium level is used (normal range 0.75–1.25 mmol/dm³, 1.8–3.0 mg/100 cm³, 1.5–2.5 meq/dm³ (24-hour urinary excretion <25 mg, without any drug which influences its excretion). Measurement of the magnesium content of mononuclear cells and skeletal muscle is more precise, but it is not routinely available (Dyckner and Wester, 1984).

Thus, for the estimation of a magnesium deficiency, the patient's clinical signs and symptoms have to be taken into consideration, with comparisons of magnesium levels and urinary excretion, and pseudo-magnesium deficiency states (e.g. intracellular magnesium loss, elevation of serum magnesium, a redistribution caused by high catecholamine states or intracellular magnesium soap precipitation due to elevated concentrations of free fatty acids, and a decreased serum magnesium level). The severity of a magnesium depletion or deficiency is also estimated indirectly via oral (Dyckner and Wester, 1982) or intravenous loading tests (Ryzen et al., 1985).

The load consists of a 30 mmol infusion of magnesium sulphate in 500 cm³ of 5% dextrose in water over 8 to 12 hours. Urine is collected for 24 hours, with a criterion of the excretion of at least 60% of the load. If the patient excretes more than 60% of the load, his body magnesium stores are normal. Individuals with a magnesium deficiency will excrete less than 50% of the administered load.

Berkelhammer and Bear (1985) utilized a stepwise algorithm in determining a true magnesium deficiency. If such a deficiency is suspected, a 24-hour urinary magnesium determination should be ordered. If the urine magnesium level is normal, the patient is not magnesium-deficient, provided he also has a normal serum level. On the other hand, if a normal serum level is obtained, but the 24-hour urine magnesium level is low (1 mmol/day), a magnesium load test is suggested to determine whether this indicates a true body deficiency.

If the patient exhibits a low serum magnesium level, with a low 24-hour magnesium excretion on urine analysis, a diagnosis of hypomagnesaemia may be made (no load is necessary). However, if he has a high 24-hour urine magnesium, with a low serum magnesium level, the renal magnesium loss must be investigated.

Correlation between serum magnesium level and magnesium homeostasis

Intracellular and tissue magnesium levels correlate weakly with serum levels, and a magnesium-deficient state may coexist with a normal serum magnesium level.

The serum magnesium level has been reported to be influenced by sex and age (Lowenstein and Stanton, 1986), but other authors found no such difference (Reinhart, 1988).

Although Ryan and Ryan (1979) showed that in the magnesium-deficient rat losses of intracellular magnesium from the lymphocytes (9%) were similar to those from the cardiac muscle (10%) and the skeletal muscle (6%), the magnitudes of these losses

were less than those from the serum (71%) and the red blood cells (33%). In that study, the lymphocyte levels of sodium and calcium increased during the magnesium-deficient state. In the study by Chang and Bloom (1985) of the magnesium-deficient hamster, no reduction in level of intracellular myocardial magnesium was found, despite a fall in the serum magnesium level to about half of the control value. These authors did observe increases in the myocardial sodium and calcium levels. In a study of magnesium deficiency and myocardial infarct size in the dog, Chang et al. (1985) found similar increases in the myocardial sodium and calcium levels. The myocardial magnesium content was unaltered.

If the results of these three studies are compared, the differences found in intracellular magnesium levels could be explained by differences in species-specific metabolic patterns, or may reflect differences between the studies in the degree or rate of development of magnesium deficiency. A common denominator appears to be the intracellular sodium and calcium level increases induced by magnesium deficiency. Possibly because of its influence on the cellular membrane via the $(\text{Na}^+, \text{K}^+)\text{-ATPase}$ system, magnesium alters intracellular levels of sodium directly and those of calcium indirectly. Do the intracellular levels of sodium and calcium actually represent a more sensitive index of the effects of a magnesium deficiency than the magnesium content itself? The answer to this awaits further study.

Studies have shown the superiority of measuring the intracellular content of magnesium over measuring its serum level in determining the magnesium status of patients. In a study of patients in an intensive care unit, Ryzen et al. (1986) detected a low mononuclear blood cell content of magnesium in 53% of unselected patients. No correlation was found with the serum magnesium levels simultaneously measured in these patients. It was concluded that the incidence of intracellular magnesium deficiency in patients with cardiovascular disease is much higher than serum magnesium determinations would indicate. Elin (1988) studied serum, mononuclear blood cell, and erythrocyte magnesium levels in hyperparathyroid and hypoparathyroid patients. The results suggested that high blood concentrations of parathyroid hormone reduced the cellular magnesium contents of the erythrocytes and mononuclear blood cells, but did not alter the plasma concentrations. Finally, in patients with digitalis-induced arrhythmias, Cohen and Kitzes (1983) showed that the magnesium content of the mononuclear blood cells was a better indicator of an altered magnesium status than the serum magnesium level. Magnesium-balance studies also provide valuable information regarding the magnesium status of an individual patient. One practical method is that described by Ryzen et al. (1985), which uses a calculation of the percentage of retention of a single intravenous dose of a magnesium salt administered on a short-term basis. They concluded that this test is a more sensitive index of a magnesium deficiency than is measurement of the serum magnesium concentration.

Erythrocyte analysis has the disadvantage that the determinations are affected by the haemoglobin concentration, and muscle analysis is often inconsistent and painful for the patient. Leukocyte determinations are not affected by haemoglobin levels and offer many advantages for the study of intracellular electrolyte function (Edmondson et al., 1974).

If one considers the exchangeability coefficients previously discussed, the usefulness of intraleukocyte magnesium levels can be better understood. Skeletal muscle and bone provide exchangeability coefficients for elemental magnesium of 0.4 and

0.38 respectively. Serum values are therefore only a rough estimate of myocardial magnesium. Estimated exchangeability coefficients for leukocyte magnesium, however, range from 0.78 to 0.85. With this higher correlation, myocardial magnesium concentration can be better assessed, since heart cells readily allow magnesium to cross with a coefficient approaching 1.00.

Investigation of the magnesium metabolism under normal conditions have focussed on differentiating between slowly exchanging and rapidly exchanging pools of magnesium. When dietary intakes are adequate, magnesium levels slowly exchange between the bone, skeletal muscle and erythrocytes. The rapidly exchanging pools of magnesium are contained primarily in the heart, liver, intestine, connective tissue and skin. In a magnesium-deficient state, the rapidly exchanging pools maintain magnesium levels at the expense of the slowly exchanging pools. For example, in a hypomagnesaemic state, the heart, a component of the primary survival core, appears to capture magnesium from the slowly exchanging bone store. This is supported by the observation that rats fed a diet moderately deficient in magnesium had significantly reduced bone concentrations of magnesium (Hurley et al., 1976).

In both normal and hypomagnesaemic states, exercises appeared to exert interesting regulatory effects on the magnesium concentrations of the slowly exchanging pools. The exercise groups in both normal and hypomagnesaemic diet groups displayed significant shifts of greater magnesium levels in the skeletal muscle tissue. Exercise demonstrates the capacity to aid in the magnesium capturing or protective processes of the skeletal muscle in rat (Lorraine et al., 1989).

It is postulated that the mechanism may be due in part to the effect of catecholamines. Catecholamine levels are elevated during strenuous effort, and it has been demonstrated that catecholamines facilitate the entry of magnesium into soft tissues (Durlach and Durlach, 1984). Since catecholamines were not measured in that study, this and other possible mechanisms that enhance the entry of magnesium into skeletal muscle in response to exercise remain to be elucidated.

Hypomagnesaemia may also be related to physical activity and may be expressed as an inferior performance (Karppanen, 1981). Numerous studies have been carried out on animals fed a magnesium-deficient diet. A deficiency of magnesium is known to disrupt the carbohydrate, lipid and protein metabolisms (Rayssiguier et al., 1981; McNeill, 1983; Rayssiguier, 1986). A magnesium deficiency also interferes with oxidative phosphorylation by diminishing the production of ATP.

It is important to note that the magnesium loss at high temperature via diaphoresis may reach 10–15% of the total body stores of magnesium (Elin, 1988).

Experimental magnesium deficiency

Numerous studies describe myocardial degeneration in animals fed magnesium-deficient diets. Focal cardiac necrosis and needle-like calcification in the mitochondria were characteristic lesions found in these studies (Moore et al., 1938; Heggteit et al., 1964). Calcifications were noted to develop even before the death of the cells and were especially prone to develop when the animals were stressed in ice-water. Silver and Sordahl (1980) provided evidence that magnesium modulated the uptake of

calcium by the myocardial mitochondria. In the presence of magnesium, calcium remained in a spheroidal amorphous state. Magnesium thus appeared not only to protect the cells against the excess uptake of calcium by the mitochondria, but also to keep calcium in an amorphous non-destructive state. The structural abnormalities suggested that failure of the magnesium-dependent oxidative phosphorylation played an important role in the pathogenesis of the lesions. Whang and Welt (1963) concluded that the primary effect of a magnesium deficiency was the loss of cellular potassium, without any increase in the cellular sodium, but with an increase in the cellular calcium. This finding was used as an argument against suppression of the $(\text{Na}^+, \text{K}^+)\text{-ATPase}$ "sodium pump" as the cause of potassium loss.

A magnesium deficiency may therefore result in (1) failure to block the entry of calcium into the myocardial cells; (2) failure to extrude calcium out of the cells through magnesium-dependent $\text{Ca}^{2+}\text{-ATPase}$ activity; (3) failure to prevent the entry of calcium into and the formation of crystals in the mitochondria; and (4) failure of the sarcoplasmic reticulum to sequester excess calcium (Iseri and French, 1984).

Almost the only animal model available that resembles spontaneous human cardiomyopathy is the hereditary cardiomyopathy seen in a special breed of hamsters. These animals consistently develop focal myocardial degeneration around the 30th day of life. It is of interest that the myocardial tissue in these animals contains low magnesium and high calcium levels well before the development of degenerative changes (Bajusz and Lossnitzer, 1968).

Patients dying of ischaemic heart disease have lesions simulating an acute magnesium deficiency, and the ischaemic myocardium is known to contain decreased amounts of magnesium (Heggtveit et al., 1969).

An experimental magnesium deficiency in animals usually causes a blood pressure elevation, but this effect is not observed consistently. Hypertensive animals generally display hyperlipidaemia, atheromas and hypercalcaemia (Seelig, 1980). Acute studies (Haddy et al. 1969) seem to indicate that a low ratio of magnesium to calcium, especially in the presence of alkalosis, is required to increase vascular resistance. Regardless of the lack of consistency with which hypertension is seen during magnesium depletion, the fact remains that calcium interaction with magnesium appears to determine the final outcome (Iseri, Frenche, 1984). However, the serum magnesium levels in a group of non-azotaemic hypertensive patients have been reported to be subnormal (Albert et al., 1958).

Lehr (1966) showed that the initial changes in the myocardium following a low dose of isoproterenol (5.25 mg/kg) were a loss of magnesium and a gain of calcium before any changes in sodium or potassium take place. As a corollary to this, the liberation of catecholamines by the adrenals or by the heart muscle itself is stimulated by calcium and suppressed by magnesium (Seelig, 1980).

Hypertensive patients with a decreased renin level, whose average serum magnesium level is higher, are better treated with calcium, while patients with an elevated renin and a lowered serum magnesium level are easily treated with magnesium. At the same time, the free magnesium content of red blood cells is low in both groups (Resnick et al. 1984).

Experimental data show that magnesium has an inhibitory effect on the calcium flux in hearts stimulated by catecholamines.

Shils (1969) reported the clinical and biochemical abnormalities that occurred in experimental magnesium deficiency in 7 human subjects. The plasma magnesium levels decreased progressively to 10–30% of those in the control periods. The urine and faecal magnesium decreased to extremely low levels within 7 days. Hypocalcaemia occurred in 6 of the subjects despite an adequate calcium intake. In the majority of the magnesium-deficient subjects, hypokalaemia and a negative potassium balance developed; the serum sodium levels remained normal, but a positive sodium balance developed. Neurologic signs occurred in 5 of the 7 subjects; the most common manifestation was a positive Trousseau sign. Other neurologic abnormalities included personality change, tremor, fasciculations and generalized spasticity. Hypomagnesaemia, hypocalcaemia and hypokalaemia were consistently present in all symptomatic patients. All abnormalities reverted to normal on reinstitution of magnesium.

Etiology of magnesium deficiency

The causes of a magnesium deficiency are multiple and are divided into broad categories: nutritional, intestinal and renal causes, divided into disease-related and drug-related losses, endocrine and metabolic causes and childhood-associated conditions. These are as follows (*Table 6.1*; Whang, 1987, modified):

A) Nutritional causes

1. Prolonged parenteral fluid administration, including "total parenteral nutrition" without magnesium replacement
2. Starvation with attendant metabolic acidosis
3. Diabetic ketoacidosis (osmotic magnesium diuresis)
4. Protein calorie malnutrition and kwashiorkor
5. Alcoholism (increased renal magnesium excretion, potassium antidiuresis)
6. Gastric suction, chronic vomiting

B) Intestinal causes

1. Chronic diarrhoea from any cause — chronic ulcerative colitis, laxative abuse, villous adenoma and adenocarcinoma of rectum
2. Intestinal malabsorption
 - a) Short bowel syndrome due to extensive resection of small bowel, jejunoileal fistula, jejunoileal bypass or gastrojejunoileal fistula
 - b) Gluten enteropathy
 - c) Pancreatic insufficiency with steatorrhoea
 - d) Tropical sprue
 - e) Bulimarexia

C) Renal causes

1. Disease-related
 - a) Renal tubular acidosis
 - b) Diuretic phase of acute tubular necrosis
 - c) Chronic glomerulonephritis and pyelonephritis
 - d) Familial and sporadic renal magnesium loss
 - e) Postobstructive diuresis (polyuria)

2. Drug-related renal losses
 - a) Diuretics — furosemide and ethacrynic acid, but also thiazide sometimes
 - b) Antibiotic-induced tubular dysfunction — gentamycin, ticarcillin, carbenicillin, amphotericin B
 - c) Antineoplastic drugs — cisplatin in particular, but also combinations of gentamycin, carbenicillin and a cytotoxic agent
 - d) Cyclosporine, pentamidine
- D) *Endocrine and metabolic causes*
 1. Primary and secondary aldosteronism
 2. Hyperthyroidism
 3. Excessive lactation
 4. Pregnancy in last trimester
 5. Hypercalcaemia due to malignant disease — high serum calcium increases magnesium excretion
 6. Primary hyperparathyroidism
 - a) As a primary event due to hypercalcaemia
 - b) Immediately postoperatively in patients with osteitis fibrosa cystica ("hungry bone")
- E) *Miscellaneous*
 1. Excessive lactation
 2. Exchange transfusion
 3. Acute intermittent porphyria
- F) *Neonatal and childhood-associated conditions*
 1. Infantile convulsions with hypomagnesaemia and hypocalcaemia responsive only to magnesium therapy
 2. Genetic (male) hypomagnesaemia (specific magnesium malabsorption)
 3. Newborns of diabetic mothers
 4. Infants born of mothers with hyperparathyroidism
 5. Exchange transfusions — citrate effect for calcium and magnesium
 6. Infants born of mothers with hypoparathyroidism.

In accordance with the suggestions of Whang (1987), excessive lactation, exchange transfusions and acute intermittent porphyria are included in the miscellaneous category. Of these causes of clinical hypomagnesaemia, renal magnesuria induced by cyclosporine is one of the more recent. Spurious hypomagnesaemia may occur with trauma, stress, overhydration or hypoalbuminaemia.

It is also proposed by Whang (1987) that hypomagnesaemia is currently the most underdiagnosed electrolyte deficiency, and that greater clinical focus should be placed on routine monitoring of serum magnesium, and on the importance of magnesium repletion, or the prevention of magnesium depletion in certain patient populations with, or at high risk developing cardiac dysrhythmias in patients treated with diuretics and digitalis glycosides.

Hypokalaemia is well recognized in association with diuretic therapy and digitalis toxicity. More recently, magnesium depletion has been implicated in aggravating potassium depletion and interfering with potassium repletion.

Hypomagnesaemia with concurrent hypokalaemia occurs frequently in heart failure in subjects undergoing long-term diuretic treatment (Lim and Jacob, 1972; Wester and Dyckner, 1981), in Bartter syndrome (Baehler et al., 1980), in familial hypokalaemic alkalosis (Gullner et al., 1981), in jejunoileal bypass (Lipner, 1977; Dyckner et al., 1982) and in alcoholics (Whang et al., 1985). Lim and Jacob (1972) suggest measurement of the magnesium content of the skeletal muscle rather than the serum magnesium concentration to estimate magnesium deficiency in heart failure patients treated with long-term diuretics.

Hypomagnesaemia can be expected in 6.9–11% (Whang et al., 1980; Wong et al., 1983) of hospitalized patients when serum electrolyte determinations are performed routinely. The frequency of hypomagnesaemia appears to be greater in patients treated in the intensive care unit. Among hypokalaemic patients, 38% (Boyd et al., 1983) to 42% have concurrent hypomagnesaemia.

Hypomagnesaemia has been observed in patients with acute myocardial infarction (Rasmussen et al., 1986). A shift of magnesium from extracellular to intracellular compartments, with a consequent lowering of the serum magnesium concentration is the most likely cause of an acutely altered magnesium distribution in acute myocardial infarction. This appears to occur by increased uptake of magnesium into adipocytes following catecholamine induced lipolysis and intracellular magnesium "soap" formation with free fatty acids (Flink et al., 1981). Variation in the amount of adipose tissue and different sensitivity to catecholamines make the quantitative impact of this mechanism variable (Ott and Fenster, 1992). It is of interest that administration of intravenous magnesium prevented hypomagnesaemia and resulted in lower mortality rates (7% compared with 19%) and in a lower frequency of arrhythmias (21% compared with 47%; Rasmussen et al., 1986).

In a patient group treated intravenously with 1 g magnesium sulphate daily, the 2-week hospital mortality was half (15.3%) that in the control group (28.7%) (Kiss et al., 1986). The difference in arrhythmia incidence was not significant (41.8% and 50%, respectively). In the Horner meta-analysis of 8 randomized controlled trials including 930 patients under 70 years of age with acute myocardial infarction, administration of magnesium was associated with a 49% reduction in ventricular tachycardia and ventricular fibrillation. The incidence of cardiac arrest was reduced by 58%. The frequency of supraventricular tachycardia was also lower. Overall, there was a 54% reduction in mortality. It is concluded that intravenous magnesium is a safe, effective method of reducing the frequency of arrhythmias and of reducing mortality in acute myocardial infarction (Horner, 1992). The results of Thögersen et al. (1993) indicate that magnesium infusion may have a beneficial effect on mortality in patients with acute myocardial infarction not receiving thrombolytic therapy. No effect of magnesium infusion on ventricular arrhythmias was demonstrated; instead, they found a greater proportion of patients with short runs of ventricular tachycardias in the magnesium-treated non-thrombolytic group ($p < 0.05$), which may represent an increase in spontaneous reperfusion. No additional effect of magnesium to that of ongoing fibrinolytic therapy could be demonstrated as regards mortality, reinfarction and heart failure (Thögersen et al., 1993).

The cardiovascular pathophysiology (partly clinical and nutritional) of magnesium deficiency was first surveyed in Hungary by Rigó and Szelényi (1969).

Durlach (1988) differentiates primary and secondary magnesium deficits. Adult latent normocalcaemic tetany and mitral valve prolapse (one-third of the cases) are the primary forms, which were formerly known as spasmophilia, hyperventilation syndrome and hyperkinetic circulation. In the view of Durlach (1988), rhinitis vasomotorica (pseudoallergy; Moneret-Vautrin et al., 1980) is the primary form of magnesium deficiency, which can be differentiated from allergic rhinitis.

The secondary forms are iatrogenic (insufficient nutrition, starvation, long-term infusion therapy and diuretics), forms due to the increased consumption of magnesium (growth, pregnancy, lactation and increased physical activity), chronic alcoholism, excessive intake of tea or coffee, drug abuse, malabsorption, stress, hypo- and hyperparathyroidism and certain intoxications (beryllium, fluorine, manganese, cadmium and lead).

A very interesting iatrogenic form is the pseudo-Schwartz-Bartter syndrome, induced by clofibrate, carbamazepine or chlorpromazine treatment, with ADH-like activity, which causes dilutional hyponatraemia and (as in the case of increased ADH secretion) increased magnesium secretion (Durlach and Rayssiguier, 1983).

There are significant renal potassium and magnesium losses in the familial, rarely occurring Welt syndrome, where the severe hypokalaemia is not influenced by potassium supplementation (Gitelman et al., 1969). The distinction between the secondary tubular and magnesium depletion varieties of Bartter syndrome often demands renal biopsy.

Clinical manifestations of hypomagnesaemia

Ever since hypomagnesaemia was first discovered in 1932 through a rat model, clinicians have tended to overlook it (Gums, 1987).

The symptoms of magnesium deficiency were observed as side-effects of diuretics. Spontaneous arrhythmias are rare in patients without underlying heart disease, but are usually ventricular and difficult to control without magnesium replacement. Hypomagnesaemia also lowers the threshold for digoxin toxic arrhythmias in patients receiving digoxin therapy (Seller et al., 1970). Again, the arrhythmia is usually ventricular and characteristically difficult to control without magnesium replacement (Iseri et al., 1975).

Sheehan and White (1982) were the first to observe that hypomagnesaemia also diminishes the effect of digoxin in atrial fibrillation and this effect can be reversed by magnesium replacement. This implies that hypomagnesaemia could increase the amount of digoxin needed to control atrial fibrillation, while also increasing the risk of digoxin toxicity. However, Sheehan and White based their observations on a patient population identified as having symptoms of hypomagnesaemia such as changes in cognition, muscle weakness and refractory hypokalaemia. The incidence of hypomagnesaemia in general population of patients with symptomatic atrial fibrillation is not known (DeCarli et al., 1986).

Leicht et al. (1990) presented 4 patients with severe hypomagnesaemia, hypocalcaemia and functional hypoparathyroidism (3 patients with shortened bowel, one with alcoholism). Sequential measurements of calcium metabolism parameters were per-

formed before and during intravenous administration of magnesium. Parathyroid hormone was unmeasurably or inadequately low in all patients before magnesium injection, but rapidly rose to elevated values thereafter. Even without calcium supplements, the serum calcium rose to normal levels within 2–5 days, although the $1.25\text{-(OH)}_2\text{-vitamin D}$ levels did not rise significantly. In the patient with alcoholism, hypophosphataemia developed during the first few days after admission; the rise in serum calcium preceded the elevation of cyclic adenosine monophosphate (cAMP) in the urine. A transient rise in urinary calcium was observed in 2 patients after initiation of magnesium therapy, with a subsequent fall to subnormal levels in spite of normal serum calcium concentrations. The findings were considered to be due to partial parathyroid hormone resistance during the phase of magnesium replenishment.

Boezoboc et al. (1989) described hypomagnesaemic and hypocalcaemic coma with skeletal muscle rigidity and areflexia during carboplatine treatment. The possible cause of this syndrome is organoplatinum nephrotoxicity.

Symptoms and signs of magnesium deficiency (Reinhardt, 1988, modified) are as follow:

Neuromuscular

- muscle weakness
- muscle cramp and tremor
- positive Chvostek and Trousseau signs
- myoclonus
- dysphagia, decreased intestinal motility
- hyperreflexia, tetany, convulsions, coma (rarely, e.g. cisplatin-induced with concomitant hypocalcaemia)

Neuropsychiatric

- focal cerebral deficits (in severe hypomagnesaemia)
- apathy
- depression
- anxiety
- hallucination
- delirium
- Wernicke–Korsakoff encephalopathy

Cardiovascular

- ventricular premature beats
- prolongation of PR and QT intervals
- supraventricular extrasystoles
- atrial fibrillation, junctional tachycardia
- “torsade de pointes” ventricular tachycardia
- ventricular fibrillation
- coronary artery spasm (possible)
- enhanced sensitivity to digitalis glycosides
- possible greater size of myocardial infarction
- possible enhanced susceptibility to ventricular fibrillation and sudden death in ischaemic heart disease

Metabolic

refractory hypokalaemia
hypocalcaemia

Epidemiologic studies

It was discovered two decades ago in epidemiologic surveys that ischaemic heart disease is more frequent in those populations who consume drinking water with a low content of minerals, especially magnesium (soft water). The role of magnesium was underlined by data showing the low magnesium content of the myocardium in patients who died from an acute myocardial infarction (Heggteit et al., 1969). Turlapaty and Altura (1980) stressed the importance of a low serum magnesium level in the development of ischaemic heart diseases and the preventive role of an elevated serum magnesium level.

Bíró (1990) discussed the relation between Hungarian nutrition and the cardiovascular morbidity risk. In Hungary the daily magnesium intake was 10–16 mmol (236–380 mg) in the elderly and the young. He observed an inappropriate intake of magnesium in females (8–9.5 mmol, 197–231 mg) in an investigation of a 0.2% sample of the total population of Hungary, i.e. 17,000 persons above 14 years of age. Relative to the recommended daily potassium intake (51–128 mmol, 2–5 g), the actual intake was 89–64 mmol (3.5–2.9 g) in males and 65–54 mmol (2.4–2.1 g) in females, and the sodium/potassium ratio was undesirable (average 4.12 ± 3.71). A very low intake of potassium was frequent in elderly people.

Rinner et al. (1989) investigated the correlations between the serum levels of sodium, potassium, magnesium and hypertension in a 1% sample of the population of a small town (200 males and females, 20–59 years old). The serum potassium exhibited an inverse correlation, and the serum calcium a positive correlation with the systolic blood pressure, though the latter was not significant. On the other hand, in females there was an inverse correlation with both systolic and diastolic blood pressure. The serum magnesium correlated significantly with the systolic and the diastolic blood pressure and was nearly significant with respect to diastolic hypertension. Multivariate statistical analysis revealed a positive correlation only between the serum calcium level and the systolic blood pressure. A moderately significant inverse correlation was found between the serum potassium level and the diastolic blood pressure.

Petersen et al. (1977) demonstrated a clear-cut significant inverse correlation between the serum magnesium level and the systolic blood pressure.

Some important magnesium deficiency states

Primary hypomagnesaemia

Primary hypomagnesaemia or hypomagnesaemic tetany is a rare genetic disorder, manifested in early infancy (Dudin and Teebi, 1987), from the age of 2 weeks up to 4 months, but a late onset has been described in a teenage girl with mild symptoms. It is

characterized by severe hypomagnesaemia and secondary hypocalcaemia. Prior to the onset of convulsions, irritability, with poor sleeping or latent tetany occurs. There is an incomplete response to calcium therapy, while magnesium supplementation alone in a dose of 4–20 times the normal daily requirements leads to reversal of hypomagnesaemia, hypocalcaemia and the clinical symptoms. Hypomagnesaemia is caused by selective magnesium malabsorption (Skyberg et al., 1968). Thus, the condition is distinguished from the hereditary impairment of renal tubular reabsorption of magnesium (Suh et al., 1973), in which state a high oral magnesium dose can bypass the defect in Mg-absorption and corrects the hypomagnesaemia. The hypocalcaemia secondary to magnesium depletion is considered to be due to the impaired synthesis or secretion of parathyroid hormone, presumably as a result of the deficient activity of magnesium-dependent enzymes (Evans et al., 1981). Naturally, this inherited defect persists for life, with a progressive fall in serum magnesium levels whenever magnesium supplementation is discontinued. Inheritance of this condition was suggested to be autosomal recessive in some cases and X-linked in others, on the basis of a striking male preponderance (the ratio of males to females among the reported cases is approximately 4:1).

It can be suggested that the process of intestinal absorption of magnesium is regulated by the collaboration of two genes (an autosomal recessive and an X-linked), and a defect in either will affect the whole process of magnesium absorption.

It is also suggested that several genetic factors account for the inter-individual variability of both red blood cell and plasma magnesium, with distinct genetic factors regulating these correlating variables (Darlu et al., 1983). The distinction between selective intestinal malabsorption and primary hypomagnesaemia with the available methods is very difficult, hypomagnesaemia being one of the hereditary manifestations of possible heritable disorders.

Correlation between magnesium depletion and diabetes mellitus

Mild hypomagnesaemia is common in diabetes mellitus. It may occur in a quarter of diabetic outpatients (Mather et al., 1979), and the plasma magnesium concentration varies inversely with the blood glucose concentration in these patients. During the treatment of diabetic ketoacidosis, the plasma magnesium concentration may fall so severely that magnesium supplementation is required (Winter et al., 1979). Hypomagnesaemia is often asymptomatic, but may manifest as tremor, tetany, delirium, hallucinations or, when severe, generalized seizures. In such instances, it is usually associated with hypocalcaemia (Brenton and Gordon, 1984).

Manthey et al. (1986) observed a 69-year-old housewife who presented with a 3-day history of headache and confusion. For 12 years she had suffered from non-insulin-dependent diabetes, rheumatoid arthritis and migraine. There was no history of epileptic fits or transient ischaemic attacks. She was taking glibenclamide, prednisolone and furosemide.

On examination, she was found to be obtunded with left homonymous hemianopia and left sensory inattention. On the day of admission, she suffered at least 12 episodes of involuntary head and eye turning (mainly to the left), with associated periods of absence lasting up to 2 minutes.

A parieto-occipital infarct with associated focal fits was diagnosed initially. Despite control of her blood glucose concentration with an insulin infusion and phenytoin (a loading dose of 1 g in the first 24 hours), 48 hours after admission her serum magnesium concentration was 0.29 mmol/dm^3 , (0.7 mg/100 cm^3), and this was verified on four successive occasions within 24 hours (normal range $0.7\text{--}1.0 \text{ mmol/dm}^3$, $1.7\text{--}2.4 \text{ mg/100 cm}^3$). Magnesium sulphate (3 g) was infused over 4 hours, and within 12 hours her fits had become less frequent. They had stopped altogether by 30 hours, after a further infusion of 2 g.

It is suggested that the possibility of hypomagnesaemia be borne in mind when a diabetic presents with unexplained focal neurological signs. It may occur in the absence of other electrolyte disturbances and ketosis. Prompt replacement of this essential ion will lead to rapid resolution of the neurological deficit.

Magnesium deficiency in Prinzmetal (vasospastic) angina pectoris

To study whether a magnesium deficiency was present in patients with variant angina, the 24-hour retention of a low dose of magnesium (0.2 meq/kg body mass) administered intravenously over 4 hours in 20 patients with variant angina was examined by Goto et al. (1990). No patient had received calcium antagonists before or during the study. All had attacks of chest pain associated with an ST-elevation on the electrocardiograms. Twenty-one subjects without ischaemic heart disease were studied as control subjects. Ten patients with variant angina were restudied 10 to 529 days (mean 235 ± 30) after the treatment with calcium antagonists (diltiazem $120\text{--}240$, or nifedipine $40\text{--}80 \text{ mg/day}$), which resulted in complete suppression of the anginal attacks. The mean serum magnesium concentrations in the patients with variant angina and the control subjects were 2.1 ± 0.05 and $2.1 \pm 0.03 \text{ mg/100 cm}^3$, respectively (difference not significant). However, the 24-hour magnesium retention in the patients with variant angina was $60 \pm 5\%$, while that in the control subjects was $36 \pm 3\%$ ($p < 0.001$), suggesting that a magnesium deficiency is present in at least some patients with variant angina. The mean serum magnesium concentrations before and after calcium antagonist treatment in 10 patients with variant angina were 2.1 ± 0.09 and $2.1 \pm 0.07 \text{ mg/100 cm}^3$, respectively (difference not significant). However, the 24-hour magnesium retention decreased significantly ($p < 0.01$) from 60 ± 6 to $34 \pm 7\%$ after the treatment. There is a magnesium deficiency in many patients with variant angina and it is corrected after treatment with calcium antagonists.

Magnesium has been shown to compete with calcium for the membrane and intracellular binding sites, eventually affecting the availability of calcium for the development of tension (Altura and Altura, 1984; Iseri and French, 1984). The clinical conditions that may lead to a magnesium depletion were not found in any of the patients with variant angina. A reduced intake due to inadequate dietary habits could not be excluded as a possible cause of magnesium deficiency in the patients. The acute stress of the attacks with elevated levels of catecholamines and subsequent changes in the renal handling of magnesium or an increased intracellular precipitation of insoluble magnesium soaps could also lead to magnesium deficiency in these patients, as in patients with acute myocardial infarction (Flink et al., 1979; Rasmussen et al., 1986).

Magnesium deficiency and sudden death in coronary heart disease (CHD)

Deficiency states of several essential metals, due to a low dietary intake or the failure of homeostatic control mechanisms, have been suggested as causes of CHD and/or sudden death. It has also been assumed that an excessive intake of various elements such as copper and cadmium may contribute to regional differences in cardiovascular mortality. Furthermore, there are regional differences in the death rate caused by CHD that are not fully understood. In the search for other causes of CHD, attention is being focussed on metal and trace element imbalances.

A deficiency or an excessive intake of metals with cardiovascular effects is suspected of being involved in the pathogenesis of CHD and sudden death. Therefore, in 106 patients undergoing coronary arteriography, the serum levels of 6 essential metals (magnesium, chromium, copper, manganese, selenium and zinc) and the whole blood concentrations of 2 elements without known essential functions (cadmium and lead) were measured by means of using atomic absorption spectrophotometry, including the flameless technique, or neutron activation analysis (Manthey et al., 1981).

The patients were classified into three groups according to the severity of CHD, as assessed by coronary angiography: those without coronary lesions ($n = 31$) and those with moderate ($n = 34$) or severe CHD ($n = 41$). Patients with severe CHD had lower mean serum magnesium and higher serum copper and manganese levels than those without CHD. In contrast, the metal concentrations in patients with moderate CHD did not differ significantly from the control values. There was no significant association between the prevalence and severity of CHD and the other elements investigated. The analysis of associations between metal concentrations and clinical characteristics revealed markedly elevated blood cadmium levels in cigarette smokers as compared with non-smokers. A correlation was noted between cadmium levels and the number of cigarettes smoked per day. These results suggest that a deficiency of magnesium, but not of the other metals studied, may be present in patients with severe CHD; elevated serum copper and manganese levels do not play a role in the development of CHD in the sample of patients studied; and cigarette smoking may be associated with increased serum cadmium levels, which may explain in part the contribution of smoking to the risk of sudden death in patients with CHD (Manthey et al., 1981).

Depressed serum magnesium levels were observed only in patients with severe CHD and left ventricular dysfunction. The left ventricular function as assessed via the ejection fraction showed a highly significant correlation with the serum magnesium levels. It may therefore be speculated that an impaired left ventricular function is responsible for the depressed serum magnesium levels in patients with severe CHD, rather than an inadequate dietary intake, as suggested in epidemiologic studies. Whether the low serum magnesium levels in these patients are a consequence of humoral compensatory mechanism in heart failure (such as stimulation of the renin-angiotensin system or of the sympathetic nervous system) or a consequence of digitalis or diuretic therapy cannot be definitely answered.

Recent experimental studies have shown that 9–15 minutes of global ischaemia results in a 3–6-fold increase in intracellular free magnesium ion concentration. Furthermore, on reperfusion, Murphy et al. (1989) found that the free magnesium ion

concentration does not return to normal, but remains elevated. This increase may contribute to the mechanical dysfunction associated with myocardial stunning because such an increase in free magnesium ion concentration has been shown to decrease the calcium sensitivity of normal skinned cardiac cells (Fabiato and Fabiato, 1975).

The effects of cadmium on the development of arterial hypertension are controversial. Glauser et al. (1976) found that hypertensive patients had higher blood cadmium levels than normotensive subjects. Recently, long-term exposure to small doses of cadmium was found to decrease the content of high-energy phosphate in the rat heart (Kopp et al., 1978).

Cardiovascular consequences of magnesium deficiency

The electrocardiographic patterns and arrhythmias of mitral valve prolapse that are like those seen in magnesium deficiency are those present in a condition frequently observed in many patients with latent tetany of magnesium deficiency (Galland et al., 1986). The finding of decreased red blood cell magnesium levels in patients with the human leukocyte antigen hypotype HLA-Bw35 (Braun et al., 1977), which has been associated with mitral valve prolapse (Henrotte, 1980), supports the premise that there is a relation. Additional theories as to how magnesium deficiency might participate in the pathogenesis of this disease have been considered.

In congestive heart failure, the compensatory mechanisms resulting from the reduced cardiac output cause an increased secretion of vasoconstrictor and volume-regulating hormones: catecholamines, renin-angiotensin-aldosterone and antidiuretics (Francis, 1985). Catecholamine and aldosterone secretion is increased by an underlying magnesium deficiency, which is increased by both diuretic and digitalis therapy, which further stimulates the neurohormones. The loss of potassium and magnesium caused by diuretics and aldosterone increases arrhythmias, which are intensified by the angiotensin-induced stimulation of aldosterone secretion and potentiation of the sympathetic nervous system.

The correction of the losses of both K^+ and Mg^{2+} induced secondarily by aldosterone and by treatment is responsible for the immediate favourable response of heart failure patients with digitalis arrhythmias (Seeling, 1989). When both cations are deficient, repletion of magnesium is necessary for the repair of tissue magnesium and potassium levels and the dysrhythmias (Dyckner and Wester, 1979). Infusion of potassium before magnesium infusion had a much weaker antiarrhythmic effect than did magnesium infusion alone; in several patients, the potassium infusion actually caused more ectopic beats, which were largely corrected by the magnesium infusion (Dyckner and Wester, 1981).

A very similar observation was made by Kiss and Fazekas (1979): in a 50-year-old man suffering from severe barium polysulphide intoxication, the supraventricular and ventricular bigeminy did not cease during intravenous potassium-substitution, but they were eliminated and did not reappear later during the continuous administration of magnesium sulphate. In the meantime, the patient's elevated blood pressure and low serum potassium level (3.0 mmol/dm^3) also normalized. It is interesting that in another case (a 60-year-old man suffering from severe barium polysulphide intoxica-

tion) with hypertension (250/130 mm Hg), ventricular bigeminy and tetraplegia. The latter also resolved during continuous magnesium sulphate infusion, despite residual hypokalaemia (serum potassium level: 2.9 mmol/dm³ after preceding potassium administration). The hypokalaemia accompanying barium-intoxication is probably transfer hypokalaemia, which comes about because of the redistribution of the K⁺ and its influx from the extracellular into the intracellular space (from the plasma into the skeletal muscles and the electrocytes). It is possible that, similarly as in digitalis intoxication, Mg²⁺ reactivates the myocardial cell membrane Na⁺-K⁺-ATPase (Seller, 1971).

Rapid electrolyte depletion might explain the precipitation of lethal arrhythmias in patients with left-sided heart failure with myocardial fibrosis, ventricular wall stress and elevated circulating neurohormones. Hypokalaemia is most often recognized in this condition and in patients with congestive heart failure resuscitated after in hospital cardiac arrest. It has been suggested that the only antiarrhythmic intervention needed to prevent recurrence of cardiac arrest may be repletion of potassium and magnesium.

It has been found that magnesium infusions to patients with congestive heart failure with hyponatraemia, increased muscle levels of sodium and chloride, subnormal muscle levels of potassium and magnesium and increased resistance to diuretics, corrected the electrolyte abnormalities (Dyckner and Wester, 1981). Comparable results were obtained with oral magnesium supplementation in patients with congestive heart failure and in hypertensive patients taking long-term diuretics (Dyckner and Wester, 1983).

Magnesium deficiency and arteriosclerosis

Atherosclerosis is frequently produced by feeding animals diets high in fat-cholesterol. The magnesium deficiency-induced lesions of the small and medium-sized arteries in several animal species are characterized by oedematous and thickened intima, and thinned, split and fragmented internal elastica, sometimes with lipid droplets (Seeling and Haddy, 1980). Coronary arteriopathy: hyperplasia of the smooth muscle cells, fibrinoid necrosis and chronic medial and adventitial inflammation develop in the hamster, a rodent that is particularly vulnerable to magnesium deficiency, when fed a magnesium-deficient diet (Bloom, 1985). When, in addition to low magnesium, the diet includes excesses of saturated fat or calcaemic agents, or both, larger arteries are affected and atherosclerosis develops. The lesions are intensified over those seen in the absence of magnesium deficiency.

Magnesium deficiency and blood coagulation

The possibility that the early lesions of atherosclerosis are mediated by organization and fatty changes in mural thrombi at sites of arterial damage calls attention to the possible role of a magnesium deficiency, which increases intraarterial coagulation. Animals deficient in magnesium displayed significantly shorter thrombus clotting times than those of the controls. Hypercoagulability caused by a thrombogenic diet rich in fat was counteracted by oral magnesium chloride supplementation (Szelényi et al., 1967). The effect of high doses (50 mg/kg) of intravenously administered mag-

nesium sulphate (25%) on platelet deposition, in arteries with suture ligation causing 40–60% constriction, has recently been reported (Gertz et al., 1987). Dogs with a narrowed major coronary artery, and rabbits with a narrowed carotid artery, pretreated with magnesium, exhibited a marked diminution of platelet aggregation at the site of constriction, and the absence of microthrombi in the arteries distal to the ligation. It has been suggested that these findings have potential therapeutic or prophylactic implications in Prinzmetal's variant angina, where arterial spasm is the principal factor, and in coronary thrombosis. There is some evidence that these findings may be applicable to the clinical situation.

Correlation between alcohol consumption and magnesium depletion

Ethanol increases magnesium needs, even when taken in moderate quantities, through its enhancement of renal magnesium excretion (Kalbfleisch et al., 1963). The efficacy of magnesium treatment of the neuromuscular and cardiac disorders of alcoholism was early attributed to correction of the magnesium deficiency (Flink et al., 1954). Chronic alcoholics become profoundly magnesium-depleted as a result of long-term magnesiuressis, superimposed on a poor intake; those with cirrhosis also lose magnesium as a result of secondary aldosteronism (Horton and Biglieri, 1962; Flink, 1986). During the stress of alcohol withdrawal, the fatty acids released as a result of catecholamine-induced lipolysis magnify the problem by binding serum and cellular magnesium (Flink et al., 1979). Unless the concomitant magnesium deficiency is repaired during the treatment of alcoholism (which entails the repair of thiamine deficiency), there may be a faulty response to administered vitamin B₁ because of the magnesium dependence of thiamine-activated enzymes (Zieve, 1969). In thiamine- and magnesium-deficient rats, thiamine administration without correction of the magnesium deficiency intensifies tissue magnesium depletion (Itokawa et al., 1972).

Magnesium deficiency and lipid metabolism

Both magnesium content and plasma high-density lipoprotein cholesterol (HDL) have been shown to be inversely correlated with cardiovascular risk (Davis et al., 1984). Studies have investigated whether a relationship exists between magnesium and blood lipids. In an open, uncontrolled study, Davis et al. discovered that a preparation of magnesium chloride (17.92 mmol for 118 days) significantly lowered the total cholesterol and very low-density lipoproteins (VLDL), plus low-density lipoproteins (LDL), while increasing the HDL fraction over prestudy levels. The 16 patients examined had abnormally high levels of VLDL and LDL on entry, as well as abnormally low levels of HDL. The authors suggested that magnesium therapy be considered as a first choice for the treatment of atherogenic disease in certain patients.

The mechanism of a potential interaction between magnesium and lipid metabolism is unclear, but several explanations exist. Magnesium may diminish lipolysis through partial activation of catecholamine release by the suprarenal glands and the sympathetic nerve endings (Reyes and Leary, 1983). Magnesium can also increase

the activity of lipoprotein lipase. With inhibition of the lipase and stimulation of the lipoprotein lipase activity, magnesium could decrease VLDL + LDL and possibly decrease the total cholesterol.

A more elaborated explanation is offered by Reyes and Leary. A low magnesium concentration will increase the release of catecholamines. Catecholamines activate adenylate cyclase, and therefore enhance the synthesis of cAMP from ATP. In addition, catecholamines inhibit insulin secretion (α -effect), resulting in an increased activity of adenylate cyclase (Reyes and Leary, 1983). Hypomagnesaemia inhibits adenylate cyclase directly, and indirectly decreases the rate of metabolism of the mononucleotides that control the enzyme activity. The net result is an increased level of cAMP, which increases the activity of the lipase cleaving the lipoprotein, and decreases the lipoprotein in the blood supply. Finally, cAMP activates phosphatase, which triggers glycogenolysis, and therefore lipogenesis is increased. Thiazides are direct activators of phosphatase. By direct action and through a loss of magnesium, therefore, thiazides result in increased lipoprotein levels. The net result is an increase in plasma lipids.

In the early 1960s, Haywood and Sylvester (1962) studied 35 patients in a 19-month, double-blind trial, examining the effects of magnesium chloride plus potassium chloride or placebo on the lipoprotein fractions. They found that the electrolytes, in a dose of 1 meq/kg/day, lowered the β - and α -lipoproteins by 10% over the placebo. In a similar study, Steiner (1963) showed that the β -fraction of the lipoprotein was lowered by magnesium replacement and rose to pretreatment values after supplementation was discontinued.

Chronic fatigue syndrome (CFS)

The CFS has been defined as fatigue that is medically unexplained, has lasted at least 6 months, and is associated with impaired physical and mental functioning. One of the most common symptoms of the syndrome is subjective impairment of sleep (Morris et al., 1993).

Many patients with the CFS also meet the criteria for major depressive disorder. About 60–70% of outpatients with major depressive disorder have a specific sleep abnormality of a shortened interval from the start of sleep to rapid eye movement sleep.

The effects of sleep loss on performance are similar to the complaints of patients with the CFS: increased subjective effort on exertion, slower subsequent recovery and reduced vigilance, attention span and cognitive performance.

Immunologic, virologic, and psychiatric hypotheses have been proposed for both the etiology and the chronicity of the disorder. Effective therapy has not yet been established, although six double-blind, placebo-controlled treatment trials have been reported (two assessing intravenous immunoglobulin and one each of acyclovir, vitamin B₁₂, magnesium, and essential fatty acid therapy). The potential for a positive outcome and continued benefit from these medical treatments may have been limited by associated psychiatric morbidity, which is common in patients with CFS (Lloyd et al., 1993).

More recently, it has been reported that patients with CFS have a low red cell magnesium level (Cox et al., 1991). Magnesium supplementation has therefore been suggested for this condition. In a recent trial, 15 patients with low magnesium levels received 1 g magnesium sulphate intramuscularly weekly for 6 weeks, while another 17 received a placebo injection. Twelve of the magnesium-treated patients claimed to have benefited from the treatment, while in the control group only 3 patients reported benefit. Red cell magnesium levels were normalized in all patients receiving the intramuscular magnesium, as compared with only one in the placebo group. Close to half of the patients receiving magnesium were free from fatigue symptoms at the end of the study, as determined by a health profile questionnaire.

However, several other authors have advised caution in the interpretation of the results of this trial, drawing attention to the fact that the magnesium level of red cells is not a good indicator of body magnesium and that a low red cell magnesium level is not a consistent observation in CFS patients. It is also hard to rationalize why a dose of less than 10% of the daily dietary intake should prove to be so effective. One possibility is that dietary magnesium is poorly bioavailable, or that CFS patients absorb the metal poorly from the intestinal tract. Further studies are obviously required to assess the potential usefulness of magnesium supplementation in CFS.

Indications and reasons for magnesium repletion in clinical practice

Evidence suggests that a magnesium deficiency is common in clinical practice. The prevalence of hypomagnesaemia in large city hospitals has been found to be approximately 10%, and as high as 65% in medical intensive care units (Wong et al., 1983).

The average American diet contains 200 to 350 mg/day of magnesium. Approximately 30–50% (100 to 150 mg/day) of this is absorbed, depending on the intake: the more magnesium ingested, the less efficient the absorption (Rude, 1989). As repletion continues, the body will absorb less and less, until more than 60% of a given dose is excreted.

A benefit of magnesium chloride is that it does not require preliminary chloride conversion in the stomach. Magnesium is absorbed most efficiently in the chloride form in the alkaline environment of the small intestine.

For ambulatory patients, oral magnesium supplements in the form of sulphate, lactate, hydroxide, chloride or glycerophosphate can be used. The percentage magnesium content (mmol/g salt) differs, depending on which salt form is used.

Oxide (bulk)	24.80
Hydroxide	17.00
Carbonate	10.50
Chloride	4.42
Acetate	4.66
Sulphate	4.06
Citrate	2.21

A recent survey of food consumption in the United Kingdom suggests that the average magnesium intake is about 320 and 240 mg per day for adult males and females, respectively. Studies on the magnesium balance of the human body indicate that a daily intake of 50 mg would be sufficient for adults if absorption of the metal were complete. Other researchers have suggested that an intake as low as 3 mg per day is sufficient to maintain a positive magnesium balance over the short term because the efficiency of the gastrointestinal absorption of magnesium increases when the dietary intake is reduced. (For Hungarian data, see "Epidemiologic studies", p. 162.)

Some important indications for oral magnesium supplementation

1. There are two types of resistant potassium depletion that can occur in the hypomagnesaemic patient: type A, in which there is a fall in serum magnesium levels with already low potassium concentrations, and type B, in which both intracellular potassium and magnesium levels fall, but there is no accompanying hypomagnesaemia or hypokalaemia. Type A is easily recognized and treated. Type B is difficult to detect, and hence the patient is often not treated.

2. Patients who are on cardiac glycosides (which decrease renal magnesium reabsorption) to lessen the toxic and arrhythmogenic side-effects.

3. Stress states with a high catecholamine level (magnesium blocks catecholamine release from adrenergic nerve endings and the adrenal medulla as a ganglion-blocking agent).

4. Treatment of acute myocardial infarction and secondary prevention (anti-arrhythmic and anti-ischaemic effects).

5. Adjuvant therapy of angina pectoris for the prevention of vasospastic episodes.

6. Treatment with diuretics (furosemide, ethacrinic acid and thiazides) and drugs causing renal loss of magnesium (mineralocorticoid, amphotericin B, calcitonin, carbenicillin disodium, cisplatin, gentamycin sulphate, growth hormone, ticarcillin, tobramycin and thyroxine). Diuretics with the exception of potassium-sparing agents (amiloride 5 mg, spironolactone 100 mg and triamterene 37.5 mg as a daily dose counteract the potassium and magnesium loss even during long-term diuretic or digitalis treatment) cause hypokalaemia with concomitant hypomagnesaemia, depending on the dosage and period of drug administration. The magnesium loss is also measurable in the skeletal muscle (Dyckner and Wester, 1984). Finland has reformulated its brand of table salt to include 10% magnesium with the standard sodium and potassium. In the U.S.A., salt substitutes have only recently received notice for their usefulness in hypertensive patients. In Hungary, "Redi" salt contains only 0.12% magnesium, but 44% potassium. Given the above data, the inclusion of magnesium as an essential part of salt substitutes seems strongly advisable.

7. Magnesium loss due to osmotic diuresis (excess alcohol intake, diabetes mellitus with large quantities of renal glucose loss, or precoma diabeticum). Adjuvant therapy in alcohol withdrawal syndrome.

8. Malabsorption, starvation.

9. Prevention of arteriosclerosis in high-risk populations (e.g. diabetes mellitus and hyperlipidaemia).

10. Strenuous sport and exercise (against muscle spasm, starvation with diuretics to appropriate weight).

11. Pregnancy (probably because of magnesium effects, the number of preterm labours decreases, and the weight of the neonates increases). Prevention of eclampsy in pregnant hypertension.

12. Hyperlipoproteinaemias with magnesium deficiency: a decrease in HDL cholesterol and an increase in circulating VLDL-apolipoprotein level occur, while the HDL-apolipoprotein level falls. As a consequence, the membrane fluidity, the conformation and the transport of ion channels change. Magnesium could decrease VLDL + LDL and possibly decrease total cholesterol.

13. Concomitant wasting of potassium and magnesium, as in the case of diuretic treatment: magnesium repletion is recommended in a ratio of 8 : 1 (K : Mg) in diuretic-treated patients and in hypertensive patients already on potassium supplements.

14. Intractable bronchial asthma, chronic respiratory failure following intravenous magnesium sulphate (calcium stores of sarcoplasmic reticulum of bronchi are greater than those of skeletal muscles) (Skobeloff et al., 1989).

15. Adjuvant therapy of hypertension (magnesium decreases peripheral vascular resistance).

16. In the treatment of several arrhythmias, magnesium is seldom effective ("torsades de pointes" ventricular tachycardia, ventricular arrhythmias induced by digitalis glycosides, multifocal atrial tachycardias) (Kiss and Fazekas, 1983; Kiss et al., 1989a, b).

17. Prevention of renal calculi containing calcium oxalate.

18. Magnesium-dependent refractory hypocalcaemia.

19. Vegetative dystonia, migraine, chronic cephalalgias, mitral valve prolapse and premenstrual syndrome (additive treatment).

20. Adjuvant therapy in aldosteronism and hyperthyroidism.

21. Based on epidemiologic studies in very soft-water areas (the water in a very hard-water area can contain up to 400 mg/dm³, whereas the level in a very soft-water area could be as low as 6 mg/dm³ of magnesium).

22. Postmenopausal osteoporosis (higher magnesium uptake because of the relative magnesium deficiency).

23. Chronic fatigue syndrome (low red cell magnesium).

If dietary considerations are ruled out, pharmacologic intervention should be considered. The hospitalized patient may be effectively replenished by magnesium sulphate 1.0 g (8.13 meq) for 5 days. For intramuscular injection, a 50% solution is used. For intravenous administration, a continuous infusion can be given throughout the day. Up to 100 meq/day for 5 days can be given to patients with a normal renal function. Rude et al. (1976) concluded that a 32–48 meq/day dose of magnesium will maintain a serum concentration of 2–2.5 mg/100 cm³ in most magnesium-deficient patients.

Magnesium as an infusion decreases renal potassium loss independently of whether it is administered as sulphate, chloride or lactate (Womersley, 1956). Rasmussen et al. (1986) and Kiss et al. (1986, 1992) report that different magnesium sulphate bolus intravenously daily for 5–10 days significantly increases the serum level of magnesium (Table 6.10) and it can be administered safely (Table 6.11; Kiss et al. 1986). The maximal renal tubular reabsorption capacity is stable, and thus the excess of magne-

Table 6.10. Mean serum magnesium concentration after intravenous administration of 42 mmol MgSO_4 (mmol/dm³)

Magnesium level Intervals of measurement	Patients with acute myocardial infarction (n = 20)		Control group (n = 10)	
	mean	range	mean	range
Before MgSO_4	0.88	0.81–1.00	0.79	0.64–1.04
10 min	1.20	1.04–1.39	1.10	0.81–1.30
30 min	1.52	0.96–2.50	0.90	0.77–1.17
1 hour	1.50	0.92–3.90	0.83	0.56–1.17
3 hours	1.08	0.85–1.40	0.95	0.77–1.08
6 hours	1.37	0.92–1.82	0.97	0.81–1.12

Table 6.11. Comparison of serum magnesium levels in two studied groups with acute myocardial infarction (mmol/dm³)

Patients	Kiss et al. (1986)* (n = 20)		Rasmussen et al. (1986)** (n = 54)	
	mean	range	mean	range
Before MgSO_4 administration	0.88	0.81–1.00	0.75	0.56–0.98
Day 2	1.21	1.00–1.40	1.25	0.77–2.27
Day 4	1.33	1.12–1.50	0.90	0.65–1.81

* Intravenous bolus injection of 42 mmol MgSO_4 daily.** 50 mmol on the first, 12 mmol on the second day as MgCl_2 infusion.

sium is readily excreted by the kidney. Magnesium infusions should not exceed 150 mg/minute in non-urgent situations. Boluses of 2 g of magnesium sulphate over 1 minute have been widely used without adverse sequelae (Arsenian, 1993).

Increased plasma magnesium concentrations are likely to occur when there is an increased intake, an impaired renal clearance ($< 30 \text{ cm}^3/\text{min}$), concurrent lithium administration, hepatitis or Addison's disease.

Treatment requires correction of the underlying cause and intravenous calcium supplementation to combat both the cardiac and electrolyte disturbances. When boluses of magnesium are given over a too short period of time, apnoea, hypotension or asystole may develop. The usual dose is 100–200 mg of elemental calcium (gluconate or chloride) infused over a 5–10 minute period ($1 \text{ g CaCl}_2 = 176 \text{ mg Ca}^{2+}$). Both peritoneal dialysis and haemodialysis are effective in removing plasma magnesium, but should be reserved for severe, refractory patients.

Thus, the only contraindications of magnesium supplementation are as follows: renal failure with anuria, significant exsiccrosis, renal calculi containing calcium, magnesium and ammonium phosphate, myasthenia gravis and AV-block.

Only 2 patients treated with intravenous magnesium sulphate because of preterm labour had a rapid and sudden onset of an urticarial eruption, which cleared when the magnesium sulphate was discontinued (Thorpe et al., 1989). Visual symptoms were common during intravenous magnesium sulphate tocolysis at 2.0–3.0 g/hr and again

1 to 4 days after cessation of therapy. Blurred vision was present in 12 of 13 patients, and diplopia was present in 10 of 13 patients. Findings included ptosis, accommodative and convergence insufficiency, and abnormal pupillary responsiveness to light and near. All patients were symptom-free and had normal examinations after magnesium sulphate was discontinued (Digre et al., 1990). Hypomagnesaemic hypocalcaemia rarely occurs in patients with tubulointerstitial nephropathies because of chronic renal magnesium wasting (Torralbo et al., 1993).

There is no evidence to show that modest supplementation of the diet with magnesium salts is harmful to patients with a normal renal function. There is, in fact, doubt about whether toxic levels of magnesium can be achieved by oral ingestion in such patients. Doses higher than a few grams lead to catharsis. This effect is, of course, the basis of the use of magnesium compounds as laxatives. The medical literature includes a number of reports of apparently idiopathic diarrhoea which were subsequently traced to surreptitious abuse of magnesium compounds. Magnesium, being a divalent cation, will complex with most tetracyclines. This could possibly lead to antibiotic treatment failure, particularly in acne, where small doses are used. Concurrent administration must therefore be avoided. Reduced absorption of the quinolone antibiotics is also likely and the same precaution applies (Gilligan et al., 1992).

References to Chapter 6

6.1. Absorption and malabsorption of magnesium

- Achilles, W., Scheffel, M. (1983): Measurement of ionized Ca and Mg in human whole blood by ion exchange. *Magnesium-Bull.* **5**, 2, 69.
- Ahmad, S., Cassias, E., Kenny, M. (1984): Three years of Mg-free dialysis: relationship between Mg, Ca and n-PTH. *Kidney Intern.* **25**, 1, 138.
- Aikawa, J. K. (1978): Biochemistry and physiology of Mg. *Wld. Rev. Nutr. Diet.* **28**, 112.
- Arsura, E. L., Gorfein, P., Guadagnino, V., Lipner, H. J., Lichstein, E. (1984): Plasma and erythrocyte Mg levels in coronary artery disease. *Fed. Proc.* **43**, 4, 619.
- Augusti, Y., Rayssiguier, Y., Larvor, P., Durlach, J. (1973): Carence en Mg chez le rat et variations de certains paramètres protéiques sériques. *C. R. Soc. Biol.* **167**, 1, 1804.
- Avakian, E. V., Bricca, L., Colburn, R. W., Horváth, S. M., Evonuk, E. (1984): Effects of dietary Mg deficiency and chronic exercise training on adrenal catecholamine concentration. *Fed. Proc.* **43**, 4, 801.
- Booth, C. C., Babouris, N., Hanna, S., MacIntyre, I. (1963): VII Incidence of hypomagnesemia in intestinal malabsorption. *Brit. Med. J.* **2**, 5350, 141.
- Borkenstein, M., Dambacher, A. (1981): Transitorische Hypomagnesemie und Hypoparathyreodismus bei einem 18 Monate alten Kind mit akuter Enteritis. *Magnesium-Bull.* **2**, 3, 159.
- Brown, E. M., Thatcher, J. G., Wason, E. J., Leombruno, R. (1984): Extracellular Ca potentiates the inhibitory effects of Mg on parathyroid function in dispersed parathyroid cells. *Metabolism* **33**, 2, 171.
- Bueno, I., Fioramonti, E., Gueux, E., Rayssiguier, Y. (1980): Gastro-intestinal hypomotility in Mg deficient sheep. *Can. J. Anim. Sci.* **60**, 293.

- Caddell, J. L., Calhoun, N. R., Howard, M. P., Patteson, K., Smith, J. C. (1980): Parenteral Mg load testing in weanling and young adult rats using ^{28}Mg . *Fed. Proc.* **39**, 3, 1043.
- Cohen, L., Laor, A., Kitzes, R. (1983): Bone Mg crystallinity index and state of body magnesium in subjects with senile osteoporosis maturity onset diabetes and women treated with contraceptive preparations. *Magnesium* **2**, 2, 70.
- Cohen, L., Laor, A., Kitzes, R. (1983): Mg malabsorption in post menopausal osteoporosis. *Magnesium* **2**, 3, 139.
- Devone, J., Ryan, M. P. (1983): Aldosterone and renal Mg excretion: an acute clearance study in adrenalectomized rats. *Br. J. Pharmacol.* **80**, Supp. 695P.
- Dunn, M. J., Walser, M. (1966): Mg depletion in normal men. *Metabolism* **15**, 10, 884.
- Durlach, J. (1961): Traitement pratique de la spasmophilie constitutionnelle idiopathique. *Vie Médicale* **42**, 8, 1067.
- Durlach, J. (1963): Tetanie durch Magnesiummangel. Konstitutionelle idiopathische Spasmophilie. *Münchener medizinische Wochenschrift* **104**, 1, 57.
- Durlach, J. (1969): Traitement des tétanies de l'hypoparathyroïdisme et de la spasmophilie. *Encyclopédie Médico-chirurgicale* 25260 C10, 1.
- Ebel, H., Gunther, T. (1980): Mg metabolism: a review. *J. Clin. Chem. Clin. Biochem.* **18**, 257.
- Edmondson, H. A., Berne, C. J., Homann, R. E., Wertman, M. (1952): Ca, Mg, K and amylase disturbances in acute pancreatitis. *Am. J. Med.* **12**, 1, 34.
- Eisinger, J. (1983): Spasmophilie: définition et traitement. *Revue Médecine Fonctionnelle* **16**, 135.
- Elin, R. J., Hossein, J. M. (1984): Mg content of lymphocytes from cell cultures. *Fed. Proc.* **43**, 4, 670.
- Elin, R. J., Johnson, E. (1983): A method for the determination of the Mg content of blood mononuclear cells. *Fed. Proc.* **42**, 5, 1452.
- Fletcher, R. F., Henley, A. A., Sammons, H. G., Squire, J. R. (1960): A case of Mg deficiency following massive intestinal resection. *Lancet* **1**, 7123, 522.
- Foert, P., Lifschitz, F., Noto, R. A., Ginsberg, L. J. (1980): Magnesium deficiency in patients with insulin dependent diabetes mellitus. *Prog. Clin. Biol. Res.* **61**, 181.
- Goldman, A. S., Fossan, D. D., VanBaird, E. E. (1962): Mg deficiency in coeliac disease. *Pediat.* **29**, 8, 948.
- Graham, D. Y. (1982): Pancreatic enzyme replacement. The effect of antacids or cimetidine. *Digestive Diseases Sciences* **27**, 6, 485.
- Graham, D. Y., Sackman, J. W. (1982): Mechanism of increase in steatorrhea with Ca and Mg in exocrine pancreatic insufficiency. An animal model. *Gastroenterology* **83**, 3, 638.
- Graham, L. A., Caesar, J. J., Burgen, A. S. V. (1960): Gastrointestinal absorption and excretion of Mg in man. *Metabolism* **9**, 5, 646.
- Grünzig, G., Lücker, P. W., Wetzelsberger, N., Witzmann, H. K. (1983): Determination of the therapeutic utilization of Mg and K based on renal elimination. *Magnesium* **2**, 3, 144.
- Günther, T., Vormann, J., Förster, R. (1984): Regulation of intracellular Mg by Mg ion efflux. *Biochem. Bioph. Res. Comm.* **119**, 1, 124.
- Haddad, Z. (1982): Effects of Mg rich drinking water in bronchial asthma. *Ann. Allergy* **48**, 4, 259.
- Hanna, S., Harrison, M., MacIntyre, I., Fraser, R. (1960): The syndrome of Mg deficiency in man. *Lancet* **2**, 7143, 172.
- Harris, I., Wilkinson, A. W. (1971): Mg depletion in children. *Lancet* **2**, 7727, 735.
- Hessov, I., Berg, V., Nepper-Holm, C., King, R. F. G. J. (1982): Treatment of Mg deficiency after intestinal bypass for obesity. *Ann. Nutr. Metab.* **26**, 1, 63.
- Hessov, I., Hasselbold, C., Fasth, S., Hulten, L. (1983): Mg deficiency after ileal resection for Crohn disease. *Scand. J. Gastroenterol.* **18**, 5, 643.
- Hodgkinson, A., Marshall, D. H., Nordin, B. E. C. (1979): Vitamin D and magnesium absorption in man. *Clin. Sci.* **57**, 2, 121.

- Holtmeier, H. J. (1968): *Das primäre Magnesiummangelsyndrom. Ernährungswissenschaften*. G. Thieme Verlag, Stuttgart, 111.
- Homeida, M. G., Walters, G., Staddon, G. E., Read, A. E. (1973): Effects of magnesium therapy on steatorrhea in a patient with intestinal resection. *Nig. Med. J.* **9**, 2, 265.
- Lee, C. H., Kaplan, B. L., Sugimoto, J., Health, H. (1980): A portal factor influences serum Ca homeostasis. *Ann. Surg.* **192**, 4, 459.
- Levine, B. S., Brautbar, N., Walline, M. W., Lee, D. N. B., Coburn, J. W. (1980): Effect of vitamin D and diet magnesium on Mg metabolism. *Am. J. Physiol.* **239**, 4, E515.
- Levine, B. S., Walling, M. W., Coburn, J. W. (1979): Effect of 1-25(OH)₂-vitamin D on Mg metabolism. *Kidney Int.* **16**, 6, 867.
- MacHale, M., Kies, C., Fox, H. M. (1979): Ca and Mg nutritional status of adolescent humans fed cellulose or hemicellulose supplements. *J. Food Sci.* **44**, 5, 1412.
- MacIntyre, I., Robinson, C. J. (1964): Mg and the gut: experimental and clinical observations. *Ann. N. Y. Acad. Sci.* **162**, 2, 865.
- Mosekilde, L., Melsen, P., Hesse, I., Christensen, M. S., Luald, B. J., Lund, B. I., Sorensen, O. H. (1980): Low levels of 1-25(OH) D and histometric evidence of osteomalacia after jejunioileal bypass for obesity. *Gut* **21**, 7, 624.
- Mountokalakis, T. D. (1983): Diuretic induced Mg deficiency. *Magnesium* **2**, 2, 57.
- Mountokalakis, T. D., Singhellakis, P. N., Alevisaki, C. C., Caramanakis, E., Ikkos, D. G. (1976): Absorption intestinale du Mg chez des malades en insuffisance renale chronique. *Rev. Franç. Endocrinologie Clin.* **17**, 3, 229.
- Moussavian, S. N., Nichas, C. A. (1979): Vitamin B12, Ca and Mg administration following jejuno-ileal bypass. *Gastroenterol.* **70**, 5/2, 1207.
- Nath, K., Sikka, K. K., Govil, M. K. (1974): Serum Mg in diabetes mellitus. *J. Diab. Ass. India* **14**, 2, 49.
- Nicar, M. J. (1981): The evolution and use of an oral magnesium tolerance test. *Diss. Abstr.* **42**, 3, 954B.
- Nicar, M. J., Pak, C. Y. C. (1982): Oral Mg load test for the assessment of intestinal Mg absorption. *Mineral and Electrolyte Metabolism* **8**, 1, 44.
- Nichini, F., Tansy, M. F., Kendall, F. M. (1973): Serum Mg fall in radiation induced gastrointestinal symptomatology. *Radiology* **108**, 2, 413.
- Paschen, K., Bachem, M. G., Strobel, B. (1981): Magnesiumstoffwechsel beim Diabetes Mellitus. *Magnesium-Bull.* **3**, 1a, 307.
- Paunier, L. (1979): Magnesiummalabsorption. *Ergeb. Inn. Med. Kinderheilk.* **42**, 113.
- Paunier, L. (1980): Troubles du métabolisme du Mg chez le nouveau-né et le nourrisson. *Med. et Nutr.* **16**, 1, 31.
- Peerenboom, H., Vormann, S., Keck, E., Stromeyer, G. (1980): Intestinale Absorption von Mg I. Messung des Mg-Transports im Jejunum des Menschen. *Magnesium-Bull.* **2**, 2, 121.
- Rude, R. K. (1989): Physiology of magnesium metabolism and the important role of magnesium in potassium deficiency. *Am. J. Cardiol.* **63**, 31G.
- Roth, P., Werner, E. (1979): Intestinal absorption of Mg in man. *J. Appl. Rad. Isot.* **30**, 523.
- Schmulen, A. C., Lernan, M., Bak, C. Y. C., Zerwekh, J., Morawski, S., Fordtran, J. S., Vergne-Martini, P. (1980): Effect of 1.25(OH)₂D₃ on jejunal absorption of Mg in patients with chronic renal disease. *Am. J. Physiol.* **238**, 4, G349.
- Seeling, M. S. (1981): Magnesium requirements in human nutrition. *Magnesium-Bull.* **3**, 1a, 26.
- Spencer, H., Lesniak, M., Gatz, C. A., Osis, D., Lender, M. (1980): Mg absorption and metabolism in patients with renal failure and patients with normal renal function. *Gastroenterol.* **79**, 1, 26.
- Tansy, M. F., Kendall, F. M. (1981): Mg and the gastrointestinal tract. *Magnesium-Bull.* **3**, 1a, 55.

- Tansy, M. F., Landin, W. E., Salkin, L. (1980): Alteration of gastrointestinal function in the Mg deficient rat. In: Cantin, M., Seeling, M. S.: *Magnesium in Health and Disease*. Spectrum Press, New York – London, 137.
- Tansy, M. F., Nichini, F. M., Baker, H. W., Chyzyanowski, J. (1971): Association of low serum Mg concentration with severity of gastro-intestinal symptomatology in the irradiated patient. *J. Surg. Res.* **11**, 2, 213.
- Teebi, A. S. (1983): Primary hypomagnesemia, an X-born allele. *Lancet*, I, March **26**, 701.
- Thoren, L. (1963): Magnesium deficiency in gastro-intestinal fluid loss. *Acta Clin. Scand.* **14**, Suppl. 306, 1.

6.2. Recommended magnesium intake and magnesium in human nutrition

- Bíró, Gy. et al. (1987): The epidemiology of nutritional diseases. IV. Study of the nutrition, state of nourishment and level of supply of some nutrients in 4 counties of Hungary. *Egészségtudomány* **31**, 365. (In Hung.)
- Bíró, Gy. (1992): *First Hungarian Representative Nutrition Survey (1985–1988) Results*. Vol. 1. Private edition, Budapest.
- Caddel, J. (1980): Clinical signs of magnesium deficiency (Letter to the Editor), *Nutr. Rev.* **38**, 100.
- Diet and Health (1989): *Implications for Reducing Chronic Disease Risk, Minerals*. Ntl. Acad. Press, Washington, D. C., 347.
- Durlach, J. (1989): Recommended dietary amounts of magnesium: Mg RDA, *Magnesium Research* **2**, 195.
- Elin, R. J. (1988): Magnesium metabolism in health and disease. *Dis. Mon.* **34**, 161.
- Frandsen, N. J., Pedersen, F. (1992): Magnesium and ischemic heart disease. *Ugeskr. Laeger.* **154**, 188.
- Garland, H. O. (1992): New experimental data on the relationship between diabetes mellitus and magnesium. *Magnesium Research* **5**, 193.
- Goto, S. (1986): Magnesium intake and its balance in Japanese. *Japanese J. Nutr.* **44**, 61.
- Greger, J. L., Baier, M. J. (1983): Effect of dietary aluminium of mineral metabolism of adult males. *Am. J. Clin. Nutr.* **38**, 411.
- Greger, J. L., Gruner, S. M., Ethyre, G. M., Adbernathy, R. P., Stickles, V. (1979): Dietary intake and nutritional status in regard to magnesium of adolescent females. *Nutr. Reports Int.* **20**, 235.
- Gums, J. G. (1987): Clinical significance of magnesium: a review. *Drug Intell. Clin. Pharm.* **21**, 240.
- Harlan, W. R., Hull, A. L., Schmouder, R., Landis, J. R., Thompson, F. E., Larkin, F. A. (1984): Blood pressure and nutrition in adults. The National Health and Nutrition Examination Survey. *Am. J. Epidemiol.* **120**, 17.
- ILSI (International Life Science Institute) European Branch (1990): Recommended daily amounts of vitamins and minerals in Europe. *Nutr. Abstr. Rev.* **60**, 827.
- Joffres, M. R., Reed, D. M., Yano, K. (1987): Relationship of magnesium intake and other dietary factors to blood pressure: the Honolulu heart study. *Am. J. Clin. Nutr.* **45**, 469.
- Kesteloot, H. (1984a): Epidemiological studies on the relationship between sodium, potassium, calcium, and magnesium and arterial blood pressure. *J. Clin. Cardiovasc. Pharmacol.* **6**, S192.
- Kesteloot, H. (1984b): Urinary cations and blood pressure — population studies. *Ann. Clin. Res.* **16** Suppl. **34**, 72.

- Kesteloot, H., Joossens, J. V. (1988): Relationship of dietary sodium, potassium, calcium, and magnesium with blood pressure. Belgian Interuniversity Research on Nutrition and Health. *Hypertension* 12, 594.
- Kornitzer, M., Bara, L. (1989): Clinical and antropometric data, blood chemistry and nutritional patterns in the Belgian population according to age and sex. *Acta Cardiol.* 44, 101.
- Lakshmanan, F. L., Rao, R. B., Kim, W. W., Kelsay, J. L. (1984): Magnesium intakes balances, and blood levels of adults consuming self-selected diets. *Am. J. Clin. Nutr.* 40, 1380.
- LST Levnedsmiddelstyrelsen Ernæringsenheden (1985): Danskernes Kost Vaner.
- Lewis, J., Buss, D. K. (1988): Trace nutrients. 5. Minerals and vitamins in the British household food supply. *Brit. J. Nutr.* 60, 412.
- Lichton, I. J. (1989): Dietary intake levels and requirements of Mg and Ca for different segments of the U. S. population. *Magnesium* 8, 117.
- Motoyama, T., Sano, H., Fukuzaki, H. (1989): Oral magnesium supplementation in patients with essential hypertension. *Hypertension* 13, 227.
- Neri, L. C., Johansen, H. L. (1978): Water hardness and cardiovascular mortality. *Ann. N. Y. Acad. Sci.* 304, 203.
- Nowson, C. A., Morgan, T. O. (1989): Magnesium supplementation in mild hypertensive patients on a moderately low sodium diet. *Clin. Exp. Pharmacol. Physiol.* 16, 299.
- Rude, R., Manoogian, C., Ehrlich, L., De Russo, P., Ryzen, E., Nadler, J. (1989): Mechanisms of blood pressure regulation by magnesium in man. *Magnesium* 8, 266.
- Ryzen, E. (1989): Magnesium homeostasis in critically ill patients. *Magnesium* 8, 201.
- Sangal, A. K., Beevers, D. G. (1982): Serum calcium and blood pressure. *Lancet* 2, 493.
- Schroeder, H. A. (1960): Relation between mortality from cardiovascular disease and treated water supplies: variations in states and 163 largest municipalities of the United States. *J. Am. Med. Assoc.* 172, 1902.
- Schwartz, R., Apgar, B. J., Wien, E. M. (1986): Apparent absorption and relation of Ca, Cu, Mg, Mn, and Zn from diet containing bran. *Am. J. Clin. Nutr.* 43, 444.
- Schwartz, R., Spencer, H., Welsh, J. J. (1984): Magnesium absorption in human subjects from leafy vegetables, intrinsically labeled with stable ^{26}Mg . *Am. J. Clin. Nutr.* 39, 571.
- Shils, M. E. (1988): Magnesium in health and disease. *Ann. Rev. Nutr.* 8, 429.
- Simopoulos, A. P. (ed.) (1987): Diet and health: scientific concepts and principles. *Am. J. Clin. Nutr.* 45, 1043.
- Singh, R. B. (1990): Effect of dietary magnesium supplementation in the prevention of coronary heart disease and sudden cardiac death. *Magnes. Trace Elem.* 9, 143.
- Singh, A., Day, B. A., De Bolt, J. E., Trostmann, U. H., Bernier, L. L., Deuster, P. A. (1989): Magnesium, zinc, and copper status of US Navy SEAL trainees. *Am. J. Clin. Nutr.* 49, 695.
- Singh, R.B., Rastogi, S. S., Mehta, P. J., Cameron, E. A. (1989): Magnesium metabolism in essential hypertension. *Acta Cardiol.* 44, 313.
- Thulin, T., Abdulla, M., Dencker, I., Jagerstad, M., Melander, A., Schersten, N., Akesson, B. (1980): Comparison of energy and nutrient intakes in women with high and low blood pressure levels. *Acta Med. Scand.* 208, 367.
- Vaessen, H. A. M. G., Kamp, C. G. van de (1986): Calcium, magnesium, lithium and rubidium in 24-h diets of adults. *Voeding* 47, 224.
- Wester, P. O. (1987): Magnesium. *Am. J. Clin. Nutr.* 45, 1305.
- Whang, R., Oei, T. O., Aikawa, J. J., Watanabe, A., Vannatta, J., Fryer, A., Nakanich, M. (1984): Predictors of clinical hypomagnesemia: hypokalemia, hypophosphatemia, hyponatremia, and hypocalcemia. *Arch. Intern. Med.* 144, 1794.
- Whelton, P. K., Klag, M. J. (1989): Magnesium and blood pressure: review of the epidemiologic and clinical trial experience. *Am. J. Cardiol.* 63, 26G.
- Wong, E. T., Rude, R. K., Singer, F. R., Shaw, S. T. (1983): A high prevalence of hypomagnesemia in hospitalized patients. *Am. J. Clin. Pathol.* 79, 348.

6.3. Magnesium deficiency syndrome

- Aikawa, J. K. (1981): *Magnesium: Its Biologic Significance*. Boca Raton, Fla, CRC Press Inc.
- Aikawa, J. K., Gordon, G. S., Rhoades, E. L. (1960): Magnesium metabolism in human beings: Studies with ^{28}Mg . *J. Appl. Physiol.* **15**, 503.
- Albert, D. B., Morita, Y., Iseri, L. (1958): Serum magnesium and plasma sodium levels in essential vascular hypertension. *Circulation* **17**, 761.
- Altura, B. M., Altura, B. T. (1984): Magnesium electrolyte transport and coronary vascular tone. *Drugs* **28** (Suppl. I), 120.
- Arsenian, M. A. (1993): Magnesium and cardiovascular disease. *Progress in Cardiovascular Diseases* **35**, 271.
- Baehler, R. W., Work, J., Kotchen, T. A., McMorrow, G., Guthrie, G. (1980): Studies in the pathogenesis of Bartter's syndrome. *Am. J. Med.* **69**, 933.
- Bajusz, E., Lossnitzer, K. (1968): A new disease model of chronic congestive heart failure: Studies on its pathogenesis. *Trans. N.Y. Acad. Sci.* (Ser. II) **30**, 93.
- Berkelhammer, C., Bear, R. A. (1985): A clinical approach to common electrolyte problems: hypomagnesemia. *Can. Med. Assoc. J.* **132**, 360.
- Bíró, G. (1990): Nutrition and cardiovascular risk: the Hungarian experience. *Acta Cardiologica* **45**, 3.
- Bloom, S. (1985): Coronary arterial lesions in Mg-deficient hamsters. *Magnesium* **4**, 82.
- Boezoboc, PH., Dexgere, H., Boccaccio, F., Christoforer, B. (1989): Coma hypomagnésémique, hypocalcémique après carboplatine. *Presse Méd.* **18**, 1343.
- Boyd, J. C., Bruns, D. E., Will, M. R. (1983): Frequency of hypomagnesemia in hypokalemic states. *Clin. Chem.* **29**, 178.
- Braun, W. E., Ronan, J. A., Schachter, P., Gardin, J., Isner, J., Greeck, D. (1977): HLA antigens in mitral valve prolapse. *Transplant. Proc.* **9**, 1869.
- Brenton, D. P., Gordon, T. E. (1984): Fluid and electrolyte disorders: magnesium. *Br. J. Hosp. Med.* **32**, 60.
- Chang, C., Bloom, S. (1985): Interrelationship of dietary Mg intake and electrolyte homeostasis in hamsters: I. Severe Mg deficiency, electrolyte homeostasis, and myocardial necrosis. *J. Am. Coll. Nutr.* **4**, 173.
- Chang, C., Varghese, P. J., Downey, J., Bloom, S. (1985): Magnesium deficiency and myocardial infarct size in the dog. *JACC* **5**, 280.
- Cohen, L., Kitzes, R. (1983): Magnesium sulfate and digitalis-toxic arrhythmias. *JAMA* **249**, 2808.
- Cox, I. M., Campbell, M. J., Dowson, D. (1991): Red blood cell magnesium and chronic fatigue syndrome. *Lancet* **337**, 757.
- Darlu, P., Rao, D. C., Henrotte, J. G., Lalouel, J. M. (1983): Genetic regulation of plasma and red blood cell magnesium concentrations in man. *Am. J. Hum. Genet.* **34**, 874.
- Davis, W. H., Leary, W., Reyes, A. J., Olhaberry, J. V. (1984): Monotherapy with magnesium increases abnormally low high density lipoprotein cholesterol: a clinical assay. *Curr. Ther. Res.* **36**, 341.
- DeCarli, C., Sprouse, G., LaRosa, J. C. (1986): Serum magnesium levels in symptomatic atrial fibrillation and their relation to rhythm control by intravenous digoxin. *Am. J. Cardiol.* **57**, 956.
- Digre, K. B., Varner, M. W., Schiffman, J. S. (1990): Neuroophthalmologic effects of intravenous magnesium sulfate. *Am. J. Obstet. Gynecol.* **163**, 1848.
- Dudin, K. I., Teebi, A. S. (1987): Primary hypomagnesaemia. A case report and literature review. *Eur. J. Pediatr.* **146**, 303.

- Durlach, J. (1988): II: Primary magnesium deficits. III: Secondary magnesium deficits. In: *Magnesium in Clinical Practice*. John Libbey Company Ltd., London 61.
- Durlach, J., Durlach, V. (1984): Speculations on hormonal controls of magnesium homeostasis: A hypothesis. *Magnesium* 3, 109.
- Durlach, J., Rayssiguier, Y. (1983): Magnésium et glucides. II. Données cliniques et thérapeutiques. *Magnésium* 2, 4/6, 192.
- Dyckner, T., Hallbert, D., Hultman, E., Wester, P. O. (1982): Magnesium deficiency following jejuno-ileal bypass operations for obesity. *J. Am. Coll. Nutr.* 1, 239.
- Dyckner, T., Wester, P. O. (1979): Ventricular extrasystoles and intracellular electrolytes before and after potassium and magnesium infusions in patients on diuretic treatment. *Am. Heart J.* 97, 12.
- Dyckner, T., Wester, P. O. (1981): Effects of magnesium infusions in diuretic induced hyponatremia. *Lancet* 1, 585.
- Dyckner, T., Wester, P. O. (1982): Magnesium deficiency-guidelines for diagnosis and substitution therapy. *Acta Med. Scand.* (Suppl.) 661, 37.
- Dyckner, T., Wester, P. O. (1983): Effect of magnesium on blood pressure. *Br. Med. J.* 186, 1847.
- Dyckner, T., Wester, P. O. (1984): Intracellular magnesium loss after diuretic administration. *Drugs* 28 (Suppl. 1) 161.
- Edmondson, R. P., Thomas, R. D., Patrick, J., Hilton, P. J., Jones, N. F. (1974): Leukocyte electrolytes in cardiac and non-cardiac patients receiving diuretics. *Lancet* 1, 12.
- Elin, R. J. (1988): Magnesium metabolism in health and disease. *Dis. Mon.* 34/41, 163.
- Evans, R. A., Carter, J. N., George, C. R. P., Walls, R. S., Newland, C. N., McDonnell, G. D., Laurence, J. R. (1981): The congenital magnesium losing kidney. *Q. J. Med.* 197, 39.
- Fabiato, A., Fabiato, F. (1975): Effects of magnesium on contractive activation of skinned cardiac cells. *J. Physiol. Lond.* 249, 497.
- Flink, E. B., Brick, E. J., Shane, S. R. (1981): Alterations of long-chain free fatty acid and magnesium concentration in acute myocardial infarction. *Arch. Intern. Med.* 141, 441.
- Flink E. B. (1986): Magnesium deficiency in alcoholism. *Clin. Exp. Res.* 10, 590.
- Flink, E. B., Shane, S. R., Scobbo, R. R., Blehschmidt, N. G., McDowell, P. (1979): Relationship of free fatty acids and magnesium in ethanol withdrawal in dogs. *Metabolism* 28, 858.
- Flink, E. B., Stutzman, F. L., Anderson, A. R., Konig, T., Fraser, R. (1954): Magnesium deficiency after prolonged parenteral fluid administration and after chronic alcoholism complicated by delirium tremens. *J. Lab. Clin. Med.* 43, 956.
- Francis, G. S. (1985): Neurohumoral mechanisms involved in congestive heart failure. *Am. J. Cardiol.* 55, 15A.
- Galland, L. D., Baker, S. M., McLellan, R. K. (1986): Magnesium deficiency in the pathogenesis of mitral valve prolapse. *Magnesium* 5, 165.
- Gertz, S. D., Wajnberg, R. S., Kurgan, A., Uretzky, G. (1987): Effect of magnesium sulfate on thrombus formation following partial arterial constriction: implications for coronary vasospasm. *Magnesium* 6, 225.
- Gilligan, C., Li Wan Po, A. (1992): Magnesium: Therapeutic and dietary use. *Pharmaceut. J.* January, 81.
- Gitelman, H. J., Graham, J. B., Welt, G. (1969): A familiar disorder characterized by hypokalemia and hypomagnesemia. *Ann. N.Y. Acad. Sci.* 162, 2, 856.
- Glauser, S. C., Bello, C. T., Glauser, E. M. (1976): Blood-cadmium levels in normotensive and untreated hypertensive humans. *Lancet* 1, 717.
- Goto, K., Yasue, H., Okumura, K., Matsuyama, K., Kugiyama, K., Miyagi, H., Higashi, T. (1990): Magnesium deficiency by intravenous loading test in variant angina pectoris. *Am. J. Cardiol.* 65, 709.

- Gullner, J. G., Gill, J. R. Jr., Bartter, F. C. (1981): Correction of hypokalemia by magnesium repletion in familiar hypokalemic alkalosis with tubulopathy. *Am. J. Med.* **71**, 578.
- Gums, J. G. (1987): Clinical significance of magnesium: A review. *Drug Intell. Clin. Pharm.* **21**, 240.
- Haddy, F. J., Scott, J. B., Emerson, T. E., Overbeck, H. W., Dougherty, R. M. (1969): Effect of generalized changes in plasma electrolyte concentrations and osmolarity on blood pressure in the anesthetized dog. *Circ. Res.* **25**, 59.
- Haywood, J., Sylvester, R. (1962): Effect of oral magnesium and potassium on serum lipids. *Clin. Med.* **10**, 87.
- Heggtveit, H. A., Herman, L., Mishra, R. K. (1964): Cardiac necrosis and calcification in experimental magnesium deficiency: A light and electron microscope study. *Am. J. Pathol.* **45**, 757.
- Heggtveit, H. A., Tanser, P., Hunt, B. J. (1969): Magnesium content of normal and ischemic human hearts. *Seventh International Congress of Clinical Pathology*. Montreal, Canada, 53.
- Henrotte, J. G. (1980): The variability of human red blood cell magnesium levels according to HLS groups. *Tissue Antigens* **15**, 419.
- Horner, S. M. (1992): Efficacy of intravenous magnesium in acute myocardial infarction in reducing arrhythmias and mortality. Meta-analysis of magnesium in acute myocardial infarction. *Circulation* **86**, 774.
- Horton, R., Biglieri, E. G. (1962): Effect of aldosterone on the metabolism of magnesium. *J. Clin. Endocrinol. Metab.* **22**, 1187.
- Hurley, L. S., Crosens, G., Theriault, L. L. (1976): Tetratogenic effects of magnesium deficiency in rats. *J. Nutr.* **106**, 1254.
- Iseri, L. T., Freed, J., Bures, A. R. (1975): Magnesium deficiency and cardiac disorders. *Am. J. Med.* **58**, 837.
- Iseri, L. T., French, J. H. (1984): Magnesium: nature's physiologic calcium blocker. *Am. Heart J.* **108**, 188.
- Itokawa, Y., Inoue, K., Natori, Y., Okazaki, K., Fujiwara, M. (1972): Effect of thiamine on growth tissue magnesium and thiamine levels and on transketolase in magnesium deficient rats. *J. Nutr. Sci. Vitaminol.* **18**, 159.
- Kalbfleisch, J. M., Linderman, R. D., Ginn, H. E., Smith, W. O. (1963): Effects of ethanol administration on urinary excretion of magnesium and other electrolytes in alcoholic and normal subjects. *J. Clin. Invest.* **42**, 1471.
- Karppanen, H. (1981): Epidemiological studies on the relationship between magnesium intake and cardiovascular diseases. *Artery* **9**, 190.
- Kiss, Z., Fazekas, T. (1979): Cardiac arrhythmias in barium poisoning. *Magyar Belorv. Arch.* **32**, 297. (In Hung.)
- Kiss, Z., Barna, M., Gáspár, A. (1989): Efficacy of intravenous $MgSO_4$ in the treatment of paroxysmal supraventricular tachycardias. *Magnesium Research* **2**, 228.
- Kiss, Z., Bárdos, J., Domokos, M., Tóth, M., Sepp, J. (1986): The antiarrhythmic effect of intravenous $MgSO_4$ in acute myocardial infarction. *31st Congress of the Hungarian Society of Internal Physicians*, Budapest, November 1986. (In Hung.)
- Kiss, Z., Bárdos, J., Domokos, M., Tóth, M., Sepp, J. (1992): Beneficial effect of intravenous magnesium sulfate in acute myocardial infarction. *Magnesium Research* **6**, 5 (3), 242.
- Kiss, Z., Fazekas, T. (1983): Organophosphates and torsade de pointes ventricular tachycardia. *J. Royal Soc. Med.* **76**, 984.
- Kiss, Z., Mérai, S., Szekeres, E., Nagypál, E. (1989): Prinzmetal's angina during glucocorticoid treatment. *16th Int. Congr. on Electrocardiology*. Budapest, 4-6 Sept., 1989. Abstracts No 36.

- Kopp, S. J., Fischer, V. W., Erlanger, M., Perry, E. F., Perry, H. M. (1978): Electrocardiographic, biochemical and morphological effects of chronic low level cadmium feeding on the rat heart. *Proc. Soc. Exp. Biol. Med.* **159**, 339.
- Lehr, D. (1966): About the pathogenesis of perivascular myocardial necrosis caused by sympathomimetic amines. Quoted by M. Seelig, ref 44, 197; In: Harders, H. (ed.): *Proceedings of the Fourth European Conference on Microcirculation*, Cambridge. S. Karger, Basel - New York, 355.
- Leicht, E., Biró, G., Keck, E., Langer, H.-J. (1990): Die Hypomagnesaemie-bedingte Hypocalcinaemie: Funktioneller Hypoparathyreodismus, Parahormon- und Vitamin-D-Resistenz. *Klin. Wochenschr.* **68**, 678.
- Lim, P., Jacob, E. (1972): Magnesium deficiency in patients on long-term diuretic therapy for heart failure. *Br. Med. J.* **3**, 620.
- Lipner, A. (1977): Symptomatic magnesium deficiency after small-intestinal bypass for obesity. *Br. Med. J.* **1**, 148.
- Lloyd, A. R., Hickie, I., Brockman, A., Hickie, C., Wilson, A., Dwyer, J., Wakefield, D. (1993): Immunologic and psychologic therapy for patients with chronic fatigue syndrome: A double-blind, placebo-controlled trial. *Am. J. Med.* **94**, 197.
- Lorraine, R. B., Fredrickson, J. H., Lombardi, V. P. (1989): Effect of hypomagnesemia and exercise on slowly exchanging pools of magnesium. *Metabolism* **38**, 797.
- Lowenstein, F. W., Santon, M. F. (1986): Serum magnesium levels in the United States: 1971-1974. *J. Am. Cell. Nutr.* **5**, 399.
- Manthey, F., Gelder, C. M., Schon, F. E. G. (1986): Isolated hypomagnesemia presenting as focal seizures in diabetes mellitus. *Br. Med. J.* **293**, 1409.
- Manthey, J., Stoepper, M., Morgenstern, W., Nussel, E., Opherk, V., Weintraut, A., Wesch, H., Kübler, W. (1981): Magnesium and trace metals: Risk factors for coronary heart disease? Associations between blood levels and angiographic findings. *Circulation* **64**, 722.
- Mather, H. M., Nisbet, J. A., Burton, G. H., Poston, G. I., Bland, J. M., Barley, P. A., Pilkington, T. R. E. (1979): Hypomagnesaemia in diabetes. *Clin. Chim. Acta* **95**, 235.
- McNeill, D. A. (1983): Effect of magnesium deficiency in the rat on renal glutaminase and three key gluconeogenic enzymes. *Nutr. Reports Internat.* **27**, 1169.
- Moneret-Vautrin, D. A., Gazel, P., Wayoff, M., Lacoste, J., Pinze, L., Leduc, P. (1980): Profils cliniques différentiels des rhinites allergiques, rhinites vasomotrices non allergiques et polyposes nasales. *Méd. et Hyg.* **38**, 1361, 119.
- Moore, L. A., Hallerman, E. T., Shol, L. B. (1938): Cardiovascular and other lesions in calves fed diet low in magnesium. *Arch. Pathol.* **26**, 820.
- Morriss, R., Sharpe, M., Sharpley, A. L., Cowen, P. J., Hawton, K., Morris, J. (1993): Abnormalities of sleep in patients with the chronic fatigue syndrome. *Br. Med. J.* **306**, 1161.
- Murphy, E., Steenbergen, C., Levy, L. A., Raju, B., London, R. E. (1989): Cytosolic free magnesium levels in ischemic rat heart. *J. Biol. Chem.* **264**, 5622.
- Ott, P., Fenster, P. (1992): Should magnesium be part of the routine therapy for acute myocardial infarction? *Am. Heart J.* **124**, 1113.
- Petersen, B., Schroll, M., Christiansen, C., Transbol, I. (1977): Serum and erythrocyte magnesium in normal elderly Danish people. *Acta Med. Scand.* **201**, 31.
- Rasmussen, H. S., Aurup, P., Hojberg, S., Jensen, E. K., McNair, P. (1986): Magnesium and acute myocardial infarction: transient myocardial ischemia not induced by renal magnesium loss in patients with acute myocardial infarction. *Arch. Intern. Med.* **146**, 872.
- Rasmussen, H. S., McNaair, P., Norregard, P., Backer, V., Lindeneg, O., Balslev, S. (1986): Intravenous magnesium in acute myocardial infarction. *Lancet* **1**, 234.
- Rayssiguier, Y. (1986): Magnesium, lipids and vascular diseases. *Magnesium* **5**, 182.
- Rayssiguier, Y., Gueux, E., Weiser, D. (1981): Effect of magnesium deficiency on lipid metabolism in rats fed a high carbohydrate diet. *J. Nutr.* **111**, 1876.

- Reinhart, R. A. (1988): Magnesium metabolism: A review with special reference to the relationship between intracellular content and serum levels. *Arch. Intern. Med.* **148**, 2415.
- Resnick, L. M., Gupta, R. K., Laragh, J. H. (1984): Intracellular free magnesium in erythrocytes of essential hypertension: relation to blood pressure and serum divalent cations. *Proc. Natl. Acad. Sci. USA* **81**, 6511.
- Reyes, A. J., Leary, W. P. (1983): Diuretic therapy, magnesium deficiency and lipid metabolism. *South Afr. Med. J.* **64**, 355.
- Rigó, J., Szelényi, I. (1969): The role of magnesium in the pathology of circulation. In: Fischer, A., Káldor, A. (eds): *Current Problems of Medical Sciences*. Vol. 1. Medicina, Budapest, 63. (In Hung.)
- Rinner, M. D., Laar, L. S., Kromhout, D. (1989): Serum, sodium, potassium, calcium and magnesium and blood pressure in a Dutch population. *J. Hypertension* **7**, 977.
- Rude, R. K. (1989): Physiology of magnesium metabolism and the important role of magnesium in potassium deficiency. *Am. J. Cardiol.* **63**, 316.
- Rude, R. K., Oldham, S. B., Singer, F. R. (1976): Functional hypoparathyroidism and parathyroid hormone and organ resistance in human magnesium deficiency. *Clin. Endocrinol.* **5**, 209.
- Ryan, M. F., Ryan, M. P. (1979): Lymphocyte electrolyte alterations during magnesium deficiency in the rat. *Ir. J. Med. Sci.* **148**, 108.
- Ryzen, E., Elbaum, N., Singer, F. R., Rude, R. K. (1985): Parenteral magnesium tolerance testing in the evaluation of magnesium deficiency. *Magnesium* **4**, 137.
- Ryzen, E., Elkayam, U., Rude, R. K. (1986): Low blood mononuclear cell magnesium in intensive cardiac care unit patients. *Am. Heart J.* **111**, 475.
- Seelig, M. S. (1980): *Magnesium Deficiency in the Pathologies of Disease*. Plenum Medical Book Co, New York - London, 185.
- Seelig, M. (1989): Cardiovascular consequences of magnesium deficiency and loss: Pathogenesis, prevalence and manifestation — magnesium and chloride loss in refractory potassium repletion. *Am. J. Cardiol.* **63**, 4G.
- Seelig, M. S., Haddy, F. J. (1980): Magnesium and the arteries: I. Effects of magnesium deficiency on arteries and on the retention of sodium, potassium and calcium. In: Cantin, M., Seelig, M. S. (eds): *Magnesium in Health and Disease*. SP Medical and Scientific Books, New York, 605.
- Seller, R. H. (1971): The role of magnesium in digitalis toxicity. *Am. Heart J.* **82**, 551.
- Seller, R. H., Cangiano, J., Kwan, K. E., Mendelssohn, S., Brest, A., N., Schwartz, C. (1970): Digitalis toxicity and hypomagnesemia. *Am. Heart J.* **79**, 57.
- Sheehan, J., White, A. (1982): Diuretic-associated hypomagnesemia. *N. Engl. J. Med.* **285**, 1157.
- Shils, M. E. (1969): Experimental human magnesium depletion. *Medicine* **48**, 61.
- Silver, B. B., Sordahl, L. A. (1980): Magnesium modulation in calcium uptake in cardiac mitochondria: An ultrasound study. In: Cantin, M., Seelig, M. S. (eds): *Magnesium in Health and Disease*. SP Medical and Scientific Books, New York.
- Skobeloff, E. M., Spivey, W. H., McNamara, R. M., Greenspon, L. (1989): Intravenous magnesium sulfate for the treatment of acute asthma in the emergency department. *JAMA* **262**, 1210.
- Skyberg, D., Stromme, J. H., Nesbakken, R., Harnaes, K. (1968): Neonatal hypomagnesemia with selective malabsorption of magnesium: a clinical entity. *Scand. J. Clin., Lab. Invest.* **21**, 355.
- Steiner, A. J. (1963): Lipid-lowering by magnesium — a trace element. *J. Appl. Nutr.* **16**, 125.
- Suh, S. M., Tashjian, A. H., Matsuo, N., Parkinson, D. K., Fraser, D. (1973): Pathogenesis of hypocalcaemia in primary hypomagnesaemia. *J. Clin. Invest.* **52**, 153.

- Szelényi, Y., Rigó, R., Ahmen, B. O., Sós, J. (1967): The role of magnesium in blood coagulation. *Thromb. Diath. Hemorrh.* **18**, 626.
- Thögersen, A. M., Johnson, O., Wester, P. O. (1993): Effect of magnesium infusion on thrombolytic and non-thrombolytic treated patients with acute myocardial infarction. *Intern. J. Cardiol.* **39**, 13.
- Thorp, J. M., Katz, V. L., Campbell, D., Cefalo, R. C. (1989): Hypersensitivity to magnesium sulfate. *Am. J. Obstet. Gynecol.* **161**, 889.
- Torralbo, A., Portoles, J., Perez, A-J. P., Barrientos, A. (1993): Hypomagnesaemic hypocalcaemia in chronic renal failure. *Am. J. Kidney Dis.* **21**, 167.
- Turlapaty, P. D. M. V., Altura, B. M. (1980): Magnesium deficiency produces spasm of coronary arteries: Relationship to etiology of sudden death in ischemic heart disease. *Science* **208**, 198.
- Wester, P. O., Dyckner, T. (1981): Diuretic treatment and magnesium losses. *Acta Med. Scand.* (Suppl.) **647**, 145.
- Whang, R. (1987): Magnesium deficiency: Pathogenesis, prevalence, and clinical implications. *Am. J. Cardiol.* **82** (Suppl. 3A), 24.
- Whang, R., Aikawa, J. K., Oei, T. O., Hamiter, T. (1980): Routine serum magnesium determination: an unrecognized need. In: Cantin, M., Seelig, M. S. (eds): *Magnesium in Health and Disease*. SP Medical and Scientific Books, New York, 1.
- Whang, R., Flink, E. B., Dyckner, T., Wester, P. O., Aikawa, J. K., Ryan, M. P. (1985): Magnesium depletion as a cause of refractory potassium repletion. *Arch. Intern. Med.* **145**, 1686.
- Whang, R., Welt, L. G. (1963): Observations in experimental magnesium depletion. *J. Clin. Invest.* **42**, 305.
- Widdowson, E. M., McCance, R. A., Spray, C. M. (1951): The chemical composition of the human body. *Clin. Sci.* **10**, 113.
- Windholz, M. (ed.) (1983): *The Merck Index: An Encyclopedia of Chemicals, Drugs and Biologicals*. 10th ed. Merck Co. Inc., Rahway - New York, 5474.
- Winter, R. J., Harris, C. J., Phillips, L. S., Green, O. C. (1979): Diabetic ketoacidosis. Induction of hypocalcaemia and hypomagnesaemia by phosphate therapy. *Am. J. Med.* **67**, 897.
- Womersley, R. A. (1956): Studies on the renal excretion of magnesium and other electrolytes. *Clin. Sci.* **15**, 465.
- Wong, E. T., Rude, R. K., Singer, F. R., Shaw, S. T. (1983): A high prevalence of hypomagnesemia and hypermagnesemia in hospitalized patients. *Am. J. Clin. Pathol.* **79**, 348.
- Zieve, L. (1969): Influence of magnesium deficiency on the utilization of thiamine. *Ann. N.Y. Acad. Sci.* **162**, 732.

7. Pathophysiological and clinical aspects of magnesium

7.1. The cardiovasoprotective effect of magnesium supplementation

The homeostasis of magnesium

Magnesium is a ubiquitous element in the organism. It is to be found in the tissues and erythrocytes and also in the extra- and intracellular spaces. Some of the magnesium is protein-bound. Walker and Walker (1936) concluded that 50% of the magnesium content of the plasma is in the free ionic form, 32% is protein-bound, while 3% is found in MgHPO_3 and 4% in magnesium citrate. The remaining 6% is bound in complexes. The magnesium content of the serum is $0.7\text{--}1\text{ mmol/dm}^3$, as determined by atomic absorption. A more reliable indicator of the magnesium supply than the serum content is the intracellular magnesium content determined in the erythrocytes or lymphocytes. The magnesium content of the erythrocytes is 2–3 times higher than that of the serum. Another good indicator, under certain conditions, is the amount excreted in the 24-hour urine.

The magnesium level of the serum may be influenced by several factors. It is reduced in the event of increased urination, as a consequence of alcohol consumption, in pregnancy, in aldosteronism, atherosclerosis, diabetes mellitus and numerous other diseases. In the above cases, therefore, the magnesium requirements of the organism are increased.

The daily magnesium intake of grown-ups on a mixed diet is between 200 mg and 400 mg. Because of the alimentary habits in Hungary, the magnesium intake of the Hungarian population is low. Bíró (1990), reported that the daily magnesium consumption of Hungarian women is 210 mg, while that of men is 270 mg, instead of the optimal 300–400 mg. According to Durlach (1989a), publishing the RDA recommendations of the International Life Sciences Institute (1989) (ILSI) with respect to magnesium, the suggested requirement is 6 mg/kg/day. In consequence of the numerous interrelationships between calcium and magnesium in the intermediate metabolism, a ratio of 2:1 was proposed for their intake. With regard to the nutritional traditions, in Hungary, an actual ratio of between 3:1 and 4:1 is probably common. The observations point to a marginal hypomagnesaemia.

The homeostasis of magnesium is influenced considerably by functional changes in some organs of the endocrine system. Hypomagnesaemia has been observed in primary hyperparathyroidism. Parathyroid hormone increases the amount of urinary magnesium. Hypomagnesaemia has been also encountered in aldosteronism.

Vitale et al. (1957a) found that large amounts of magnesium could prevent the thyroxine-induced inhibition of oxidative phosphorylation of the mitochondria in the rat heart. Szélenyi et al. (1957) observed that in hypothyroidism the serum magne-

sium level is elevated, the amount of magnesium excreted by the kidneys is increased, and the magnesium contents of the cardiac and skeletal muscles are decreased.

There is also a close connection between the magnesium homeostasis and the metabolism of nutrients. A magnesium deficiency may have a deleterious effect on the protein anabolism. Animals kept on a high protein content diet deficient in magnesium developed less well than those receiving less protein but more magnesium. Colby and Frye (1951) drew attention to the fact that the development of a magnesium deficiency should be considered in cases of increased protein consumption.

Magnesium plays an important role in the carbohydrate metabolism. It is an essential enzyme-activating factor at several points during glycolysis and the Szent-Györgyi-Krebs cycle. The activity of hexokinase, which promotes the formation of glycose-6-phosphate, depends on the magnesium ion. The enzymes phosphofructokinase, phosphoglyceric acid kinase, pyruvic acid kinase, enolase, pyruvate kinase, pyruvate decarboxylase and isocitrate dehydrogenase are also activated by magnesium. Furthermore, magnesium participates in the activation of lactic acid dehydrogenase and succinic acid dehydrogenase.

Accordingly, a magnesium deficiency may inhibit glycolysis and the Szent-Györgyi-Krebs cycle at several points, thereby influencing the intermediate carbohydrate metabolism. It is noteworthy that an excess sugar intake may cause an increased magnesium excretion. An increased sugar consumption and a marginal magnesium intake may therefore result in a magnesium deficiency. Under experimental conditions, a low magnesium consumption and a high sugar consumption increase the levels of LDL and VLDL, and reduce that of HDL (Seelig, 1989).

The connections between magnesium and the lipid metabolism have been extensively studied (Rigó, J. Jr. et al., 1987). Bersohn and Oelofse (1957) found higher levels of magnesium and lower levels of cholesterol in the serum of Bantus than in that of Europeans. Experimentally, magnesium inhibited the apposition of lipids induced in the aorta by an atherogenic diet. On the other hand, cholesterol and cholic acid, as additives in the diet of rats, decreased the serum magnesium level. In dogs, cholesterol consumption resulted in a higher increase in the cholesterol level if it was combined with magnesium deprivation than when there was an adequate magnesium intake (Vitale et al., 1957b, c; Bunce et al., 1962). High lipid consumption and low magnesium intake facilitate the development of cardiovascular diseases. The alimentary habits in Hungary (the excessive consumption of 140 g fat and 100 g sugar, and the low intake of daily 250 mg magnesium) are risk factors of ischaemic cardiac diseases.

The metabolism of magnesium is connected with those of other minerals in the organism. Its relationship with calcium has been the most extensively studied and is best known. Alcock and McIntyre (1962) found that a decreased calcium intake led to an improved magnesium absorption. Hänze (1960) demonstrated that the calcium excretion is doubled in the first 2–3 hours following magnesium administration. In the mineral metabolism, the antagonism of calcium and magnesium is an important factor. A high calcium/magnesium ratio is a risk factor in the development of cardiovascular diseases.

There is also a metabolic antagonism between magnesium and phosphate ions. The effects of a magnesium deficiency are more pronounced if it is accompanied by high calcium and phosphate intakes. In the cardiopathogenic diet, the consequences

of the magnesium deficiency are exacerbated by the administration of calcium and phosphate.

As concerns the potassium metabolism, McIntyre and Davidson (1958) reported that, in rats kept in a magnesium-deficient state, the potassium content of the muscles decreases together with the magnesium content. Similar changes were found in the muscular tissue of animals kept on a cardiopathogenic diet (Rigó et al., 1961). Thus, magnesium and potassium deficiencies are considered to be risk factors in cardiovascular alterations.

Osten (1955) studied the relation of magnesium and vitamin E, and observed that the peripheral blood flow is favourably influenced by vitamin E. This effect was more pronounced if magnesium was administered at the same time. On the other hand, the administration of the magnesium-antagonist calcium diminished the therapeutic effects of vitamin E. Simon et al. (1963) found vitamin E to have a protective effect against the deleterious effects of the cardiovasopathogenic diet on the cardiac muscles. Vitamin A proved to have the same effect in dwarf pigs kept on the cardiovasopathogenic diet.

Vitamin D is one of the components of the experimental cardiovasopathogenic diets. It brings about a reduction of the serum magnesium level and the increased apposition of collagen and calcium in the aorta of experimental animals. The effects of vitamin D may be prevented by magnesium.

Aikawa (1960) reported that the cardiac muscles absorb more magnesium in the presence of pyridoxine. On the other hand, in a vitamin B₆ deficiency, the magnesium contents of the serum and the tissues decrease. Following the administration of pyridoxine, the serum magnesium level increases. Thus, vitamin B₆ plays a role in intracellular magnesium accumulation (Szelényi et al., 1969a).

The excess consumption of protein, fat or sugar increases the magnesium requirements of the organism. A marginal or low magnesium intake may result in a relative deficiency, which is a risk factor of cardiovascular diseases. This risk is increased by a diet rich in calcium, sodium and phosphate and poor in magnesium and potassium. The cardiovascular alterations are also aggravated by vitamin D, whereas a diet rich in vitamin E, A and B₆ has a mitigating effect on them.

The effects of magnesium supplementation in experimental hypertension; the "antistress" electrolyte

The environment influences the processes of the organism through the substances absorbed in the intestinal tract, and also through stimuli, i.e. via the nervous system. Both types of factors play important roles in the development of hypertension. Numerous authors have studied the effects of the various alimentary components on the development of hypertension. Such studies revealed the connections between hypertension and the magnesium metabolism. Albert et al. (1958) observed that the serum magnesium levels of patients with essential hypertension are lower than those of healthy controls. Haury and Cantarov (1942) found the serum magnesium level to be decreased in diseases accompanied by vasospasm. In experimental hypertension therefore, studies concerning magnesium supplementation are of special interest.

As an additive in the diet of rats, vitamin D proves to be a cardiovasopathogenic factor. It results in increased magnesium secretion, a decreased serum magnesium level (Seelig, 1989) and an elevated blood pressure in the animals. The hypertension is partly of vascular, and partly of renal origin. Supplementation of the diet of the animals with magnesium chloride prevents this hypertension (Rigó and Szelényi, 1963).

Magnesium chloride supplementation likewise exerts a protective effect in the hypertension induced by the cardiovasopathogenic diet of Sós, with which the cholesterol, vitamin D and mineral contents are modified. The essentials of the diet are the deficiency of magnesium and potassium and the excess of calcium, sodium and phosphate. While the daily magnesium intake of animals kept on a normal diet is 16 mg, that of animals on the cardiovasopathogenic diet is only 6 mg. In magnesium supplementation, the daily dose is increased 5-fold, i.e. 80 mg is added to the diet in the form of magnesium chloride (Rigó and Szelényi, 1963), magnesium citrate (Rigó and Szelényi, 1964), magnesium aspartate (Sós et al., 1964a) or magnesium orotate (Szelényi et al., 1970).

Magnesium supplementation may also exhibit a favourable effect in existing experimental hypertension. Thus, hypertension induced by vitamin D loading or a cardiovasopathogenic diet is eliminated by a magnesium-rich diet during 2–3 weeks (Rigó, 1971).

Hypertension is often induced when the nervous system is overloaded. Frequently recurring or lasting stimuli play an important role in the development of essential hypertension. It was first reported by Mills (1959) that stressors may induce or aggravate hypertension. In consequence of the increased amounts of catecholamines and corticosteroids, the magnesium contents of the serum and the tissues decreases, while the excretion of magnesium increases (Ising, 1981). Further, a magnesium deficiency enhances the sensitivity of the organism to stress-inducing effects (Durlach, 1989b; Kubena and Durlach, 1990). Experiments have also drawn attention to the fact that the catecholamine production induced by noise is higher in animals fed on a diet poor in magnesium than in animals kept on a normal diet. Lehr (1981) reported that a magnesium deficiency combined with stress-inducing effects is followed not only by changes in the electrolyte content of the cardiac muscles, but also by a 90%-increase in the hydroxyproline content. Fischer and Fischer (1981) pointed out that the stress induced by adrenaline and cold results in increased amounts of long-chain fatty acids and a decreased serum magnesium level. Reinhart (1988) is of the opinion that catecholamine-induced lipolysis gives rises to an intracellular accumulation of free fatty acids, which leads to the precipitation of magnesium.

In experimental animals, the protective action of magnesium supplementation against the hypertensive effects of stressors may be followed. The blood pressure of animals exposed to noise and light stimulation is elevated considerably by the end of the 6th week. Magnesium supplementation prevents the effects of such stressors, the blood pressure of animals receiving additional magnesium remaining normal even after 6 weeks. This protective effect of magnesium supplementation may also be observed if stress-inducing stimuli are applied to animals kept on a cardiovasopathogenic diet. This combination of stress and such a diet result in the most pronounced blood pressure elevations. Supplementation of the diet with magnesium chloride provides protection against both the alimentary and the neurogenic effects (Rigó and Szelényi,

1963). Antihypertensive protection is similarly achieved if the dietary magnesium is supplemented by administration of Viróma, a syrup containing 500 mg/100 cm³ magnesium in the form of magnesium citrate (Herbária, Budapest).

The enhancement of catecholamine secretion by cold-provoked stress leads to an elevation of the blood pressure in experimental animals.

When animals sensitized with a cardiovasopathogenic diet are kept at 4 °C for 30 min their blood pressure increases significantly. If the animals are fed with the cardiovasopathogenic diet supplemented with the magnesium-rich Viróma syrup, the blood pressure elevation induced by the cold pressor reflex fails to develop. Supplementation with magnesium chloride has the same effect (Gáti et al., 1964). Porta et al. (1989) found that the hypersecretion of adrenaline and the drastic decrease induced by stress in the amount of glycogen in the liver can be prevented by administration of large amounts of magnesium aspartate hydrochloride.

Székács et al. (1969) reported a decreased sensitivity of rats to renin following magnesium supplementation. Investigation of the renin-angiotensin system reveals that the decreased sensitivity to adrenaline may be explained by the decreased sensitivity of the animals to angiotensin. As concerns the point of attack of angiotensin, it seems that magnesium decreases the sensitivity of the vessel walls to pressor substances. The studies by Szelényi et al. (1969b) also prove the direct effect of magnesium on the vessel wall. The magnesium ion brings about a relaxation of the smooth muscles in the arterioles and the active dilatation of the vessels, and magnesium aspartate or magnesium sulphate increases the blood flow in isolated vessel or heart preparations.

The effects of magnesium on experimental vascular changes; the "calcium antagonist" electrolyte

Lehr (1981) demonstrated that a combination of stress and magnesium deficiency does not only result in electrolyte changes in the myocardium but it considerably elevates its hydroxyproline content as well. Levence and Poole (1962), concluded that almost the total amount of hydroxyproline found in the intimal layer originates from collagen, and changes in hydroxyproline content may therefore be considered to reflect changes in collagen content. Verzár (1963) reported that the collagen bonds, studied by means of thermal contraction, become stronger in parallel with advancing age. Similar changes may be observed in the aorta of albino rats. In old animals, the total contents of hydroxyproline and of collagen containing ester bonds increase, while the amount of labile collagen containing H-bonds decreases (Rigó, 1965). The cross-links may be decomposed by heat, and the resulting tension may be measured in g with a tensiometer.

If the diet of rats contains 20 mg/kg vitamin D₂, the tension produced during thermal contraction increases significantly as a consequence of the increased level of calcium and the decreased level of magnesium in the wall of the aorta.

Magnesium supplementation prevents the effects of calciferol during thermal contraction, i. e. it exerts a protective effect against the accumulation and ageing of collagen in the vessel wall (Rigó 1965).

Magnesium supplementation has a favourable effect not only on the collagen content, but also on the calcium content of the aorta of experimental animals receiving vitamin D or kept on the cardiovascular pathogenic diet. The calcium content of the aorta is increased by the cardiovascular pathogenic diet. This increase may be prevented by supplementation with magnesium chloride.

Study of the ratio of the vessel wall thickness and the lumen-diameter confirms the favourable effect of magnesium supplementation on the coronary vessels. While the vessel wall thickness/lumen diameter ratio is 2.2 in the coronaries of the control group, in animals kept on the cardiovascular pathogenic diet it is 5.2, indicating thickening of the vessel wall and/or narrowing of the lumen. If the cardiovascular pathogenic diet is supplemented with magnesium, the ratio remains at 2.1, as in the control group (Rigó, 1971).

Of the experimentally induced vascular changes, the severe alterations in the kidneys of animals kept on a diet poor in magnesium deserve special attention. McIntyre and Davidson (1958) emphasized the renal calcification in magnesium-deficient rats. Hess et al. (1959) reported the development of intracellular calcification and tubular necrosis after 9 days in animals on a diet poor in magnesium. A blood pressure elevation also appears after 9–10 days. The cardiovascular pathogenic diet results in impaired renal functions, and glomerular and tubular alterations. Necrosis may be observed in the glomeruli in some cases, with calcification in the majority of cases. Degenerative alterations and severe calcification occur in the tubuli. These alterations create a possible route for the development of hypertension induced by the cardiovascular pathogenic diet, but this may be prevented by magnesium supplementation (Rigó and Sós, 1963).

The effects of magnesium on experimentally induced alterations of the myocardium.

The "potassium-protecting" electrolyte

There is a bidirectional relationship between myocardial changes and the mineral metabolism. As insufficient intake of magnesium and potassium results in an impairment of the myocardium, and myocardial alterations cause disturbances in the mineral metabolism. Vitale et al. (1957b) and McIntyre and Davidson (1958) induced a myocardial impairment by administering magnesium-deficient diets, while Mori and Duruisseau (1960), Kaltenbach (1961) and Russel et al. (1961) reported on electrolytic disturbances in the myocardium following myocardial alterations.

A cardiovascular pathogenic diet results in decreased magnesium and potassium contents, and in increased sodium and calcium contents in the myocardium of rats (Rigó et al., 1961), cocks (Sós et al., 1964b) and dogs (Sós et al., 1964a).

Similar alterations may be observed in the myocardium of dogs after ligation of a coronary branch (Rigó et al., 1966a). In the infarction zone, the potassium and magnesium contents are decreased, while the calcium and sodium levels are increased. Dennis and Moore (1938) found an increased concentration in the vein in the ischaemic area, while histological analysis revealed a decreased myocardial potassium content. The primary cause was considered by Nickerson et al. (1961), to be the potassium deficiency and by Mori and Duruisseau (1960) to be the magnesium deficiency. Magnesium supplementation prevents the electrolyte changes induced by the cardiovaso-

pathogenic diet. It is an important finding that, despite the insufficient potassium intake, the potassium level of the myocardium of animals kept on a magnesium-supplemented cardiovasopathogenic diet is not decreased (Rigó et al., 1963). If the Straub frog heart preparation is examined with regard to the potassium content of the Boyle-Conway perfusion solution as a function of the magnesium concentration it is found that a 5-fold increase of magnesium concentration is followed within 15 minutes by a significant decrease in the potassium content as compared with the control level. This indicates that in a magnesium-rich milieu the myocardial intake of magnesium ion is increased or its release is slowed down (Rigó et al., 1963). If the intake and release of ^{42}K are determined in animals kept on a magnesium-rich diet for 3 weeks, in the first hour no essential difference can be observed as compared with the controls; in the third hour, however, the myocardial potassium content of the animals on the magnesium-rich diet is significantly higher than that of the controls on the normal diet. This means that the potassium release of the myocardium is moderated, i. e. magnesium has a potassium-protecting role.

The above studies explain the cardioprotective anti-infarction effect of magnesium supplementation. The mechanism of this effect has been examined by Selye (1958), Bajusz and Selye (1960) and others. Vitale et al. (1957a) found that a magnesium deficiency is followed within days by considerable mitochondrial changes in the myocardium. McIntyre and Davidson (1958) discovered that the mitochondria are the organelles responsible for the electrolyte transport of the cells, and that the decrease in the potassium level is induced by the magnesium deficiency. Seelig (1989) is of the opinion that potassium repletion should be supplemented with magnesium chloride.

The reductions in the magnesium and potassium levels and the accumulation of sodium and calcium in the cells of the myocardium are closely related with the decreased contents of creatine phosphate, ATP and glycogen, as a consequence of which the energy production is impaired. The presence of magnesium in the process of oxidative phosphorylation is indispensable. The intracellular magnesium forms a complex with ATP, which is the substrate in many enzyme reactions. The rates of the ATP-dependent reactions increase in parallel with increasing concentration of magnesium until a maximum is reached. The catalytic activity of magnesium is based on the presence of the complex MgATP . Its absence is reflected in myocardial ischaemia. The impairment of the cells of the myocardium is further intensified by mitochondrial calcium accumulation (Lehr, 1981). This effect was observed by Janke et al. (1975) in myocardial necrosis induced by isoproterenol: besides a reduced magnesium content, an increase in calcium content and decreases in ATP and creatine phosphate content occurred. Increased plasma levels of magnesium, potassium or hydrogen proved to exert protective effects against necrosis and calcium accumulation. Fazekas et al. (1985) similarly reported on mitochondrial calcification in infarctoid cardiomyopathy induced by isoproterenol. Electron-microscopic examinations revealed that in infarctoid cardiopathies the mitochondria become swollen, and calcium-containing electron-dense granulates appear in their matrix as a consequence of the intracellular calcium accumulation. In this mechanism, a role is played by the isoproterenol-activated calcium-dependent ATPase activation, which entails a reduction of ATP, an increased intracellular influx of calcium and a decreased magnesium content. Magnesium supplementation exerts its protective effect by inhibiting the influx of calcium.

The magnesium supply also determines the activity of the sodium-potassium pump, which directly influences the exchange of the sodium and potassium ions, the intracellular potassium content and the ratio of the extra- and intracellular potassium contents (Fischer and Giroux, 1987; Skou, 1988). These metabolic changes are characteristic of the ischaemic myocardium. By comparing the pre- and postischaemic effects of magnesium supplementation, Hara et al. (1990) established that large doses of magnesium have a favourable influence on the postischaemic heart by mitigating both the functional and the above-mentioned metabolic disturbances.

The severity of infarctoid myocardial impairments may be enhanced by applying neurogenic stress in addition to the cardiovascular pathogenic diet, or by increasing the fat content of the diet. Magnesium supplementation mitigates the myocardial lesions aggravated either by neurogenic stress or by a fat load.

As regards the cardiovascular pathogenic diet, which is poor in magnesium and potassium, rich in calcium, sodium and phosphate, and contains vitamin D and cholesterol, the enhanced lipolysis caused by the stress-induced increase in catecholamine production, and also the clotting disturbances appearing after a fat load, explain the further deterioration of the myocardial metabolism and the perpetuation of the infarctoid changes.

Magnesium supplementation leads to a moderation of the biochemical disturbances and to mitigation of the infarctoid impairment of the myocardium.

The effects of magnesium implementation on blood coagulation.

The physiological antithrombotic electrolyte

It has been reported that magnesium supplementation may be effectively used in the prevention of thrombosis. Anstall et al. (1959) found that magnesium lengthened the clotting time. Schnitzler (1957) pointed out that magnesium has a stabilizing effect on the thrombocytes.

Magnesium facilitates fibrinolysis. After magnesium administration severe thrombosis was not encountered and superficial thrombophlebitides occurred less frequently. Magnesium supplementation decreases increased platelet aggregation (Hackethal, 1949).

Blood clotting is increased by excess amounts of fat. Diets with a low magnesium content and a high fat content result in shortening of both the clotting time and the prothrombin time. If the diet is supplemented with magnesium, no changes are found either in the clotting time or in the prothrombin time as compared with the control values (Rigó et al., 1966b). The intravenous application of magnesium sulphate increases the clotting time and shortens the utilization of prothrombin in dogs. Butter loading via a probe results in a shortening of the clotting time and in an enhanced prothrombin utilization. The intravenous administration of magnesium sulphate prevents the changes caused by the butter load in the clotting time and prothrombin utilization (Rigó and Szelényi, 1967; Szelényi et al., 1967). The anticoagulant effect of magnesium supplementation is corroborated by the clinical observation that the

daily intake of 500 mg magnesium in the form of Viróma syrup, similarly to other anticoagulant treatments, decreases the capillary resistance considerably in elderly atherosclerotic patients (Rigó et al., 1971).

All the above studies and observations point to the favourable effects of magnesium supplementation in diseases involving an increased coagulability.

The cardiovasoprotective electrolyte

Experimental studies unambiguously support the importance of magnesium supplementation in cardiovascular diseases. In this regard, both quantitative and qualitative aspects deserve attention (Durlach et al., 1989). With respect to dietetic therapy, the quantitative requirement may be covered mainly by magnesium-rich vegetable nutriment, and primarily by cereals and oilseeds. The magnesium contents of such nutrients are listed in *Table 7.1*.

It deserves special attention that in the developed industrial countries the dietary fibre and magnesium consumption of the population has decreased in parallel with the decrease in consumption of cereals (Rigó et al., 1986). It is therefore advisable to consume wholemeal bread or rye-bread, which are rich in dietary fibre and magnesium.

As concerns the qualitative aspect, the utilization of the consumed magnesium is crucial. Magnesium absorption is known to be influenced by the phytic acid and calcium contents of cereals, and primarily bran.

Marier (1981) and Durlach et al. (1989) state that the consumption of magnesium-rich, hard water is ideal for magnesium supplementation. Drinking water containing 30 mg/dm³ magnesium is suitable for this purpose. Cooking with soft water leads to a considerable magnesium loss from the food. The magnesium content of the drinking water obtained from the River Danube is low, at 10 mg/dm³.

In Hungary, the domestic magnesium-enriched syrups Viróma and Diviróma are popular. Both contain 500 mg/100 cm³ magnesium in the form of magnesium citrate.

The literature data emphasize the favourable effects of magnesium supplementation in cardiovascular diseases. Morton et al. (1981) reported on the beneficial influence of magnesium sulphate infusion administered in the first 36 hours of myocardial

Table 7.1. Nutrients rich in magnesium

Nutrient	Magnesium content (mg/100 g)	Nutrient	Magnesium content (mg/100 g)
Pumpkin seeds	970	Beans	217
Sunflower seeds	620	Lentils	134
Wheat bran	500	Peas	126
Viróma syrup	500	"Bakony" whole bread	122
Almonds	360	Corn flour	120
Extruded soy flour	290	Ground peas	120
Walnuts	256	Oatmeal	110
Wheat germ	230	Rye bread	74

infarction. This influence of magnesium is due to its enzyme-activating role in the regulation of intracellular, mainly mitochondrial processes and in the production of ATP. It is also indisputable that magnesium is required for the contraction and relaxation of the myofibrils. The importance of magnesium supplementation is further demonstrated by studies which unambiguously reveal the reduction in the myocardial magnesium content in myocardial infarction. The significance of supplementation is underlined by the potassium-protecting, calcium-antagonist, antithrombotic effects of magnesium, its mitigating influence in stress and its role in the lipid metabolism. Its favourable effect in arrhythmias forms the topic of the following section.

The experimental results draw attention to the fact that, by virtue of its versatility in the prevention and treatment of multicausal cardiovascular diseases, magnesium supplementation is advantageous both as a medicament and as dietetic therapy.

7.2. Cardiac electrophysiology and clinical use of magnesium

After potassium, the naturally ubiquitous magnesium is the second most abundant intracellular cation in the human organism. Magnesium catalyses/activates more than 300 enzymatic reactions as a metallocoenzyme (Garfinkel et al., 1987; Gums, 1987; White and Hartzell, 1989; Seelig et al., 1989; Iseri et al., 1992). A human body weighing 70 kg contains about 24 g magnesium, 99% of which is located intracellularly (Gums, 1987). Investigations with the radioactive isotope ^{28}Mg have revealed that 98% of the magnesium in the myocardium is present in readily exchangeable form, which provides an explanation for the sensitivity of the metabolism and electrical activity of the myocardium to a magnesium deficiency or hypomagnesaemia (Ghani and Rebah, 1977; Gums, 1987). Knowledge of the ionic intracellular magnesium concentration, $[\text{Mg}^{2+}]$, of the mammalian myocardium was hampered for years by methodological difficulties, but it is now known (primarily from ^{31}P -NMR studies) that it is in the submillimolar range, varying between 0.3 and 0.8 mmol/dm³, and usually around 0.5–0.6 mmol/dm³ (White and Hartzell, 1989). Intracellular compartmentalization may also be observed: 60% of the magnesium is situated in the cytosol, and 38% in the mitochondria. A considerable proportion of the magnesium in the myocardial cells is bound to high-energy phosphates (ATP, creatine phosphate) and also to membrane phospholipids, organic acids and proteins, forming organometallic complexes, and thus the concentration of the *free* ion Mg^{2+} is relatively low, at around 0.2 mmol/dm³ (Garfinkel et al., 1986; Gums, 1987; Iseri et al., 1992). Changes in this very low intracellular concentration can lead to major effects on the functioning of the ion channels and the second messenger systems of cardiac cells. Magnesium is therefore regarded as an important regulator/modulator of the heart cell function (Matsuda et al., 1987; Rude, 1989; Reinhart, 1991). A fundamental role is played in the maintenance of the Na^+ and K^+ gradients of the cardiac cell membrane (extracellular/intracellular concentrations in mmol/dm³: sodium 145/10, potassium 4.5/140) by the $(\text{Na}^+, \text{K}^+)\text{-ATPase}$ system. For normal functioning, this sarcolemmal enzyme requires magnesium, though the same can be said for all biochemical processes utilizing ATP

(Garfinkel et al., 1986). The ATP-Mg binding facilitates the enzyme-substrate coupling, and also the splitting-off of the terminal PO_4 group of the high-energy phosphate compound, which is the energetic basis of biocatalytic reactions. The Ca^{2+} gradient of the heart cell is maintained partially by the magnesium-dependent Ca^{2+} -ATPase system. Besides $(\text{Na}^+, \text{K}^+)\text{-ATPase}$ and $\text{Ca}^{2+}\text{-ATPase}$, magnesium is indispensable for the functioning of numerous other important myocardial enzymes, such as glycolytic enzymes (e.g. hexokinase, enolase and pyruvate kinase), protein kinases, GTPase, and adenyl and guanyl cyclases. An increasing body of evidence demonstrates that $[\text{Mg}^{2+}]_i$ modulates the permeability of the cation channels of the sarcolemma (see later), and can thereby exert a fundamental influence, probably in the same way as exogenous magnesium administration (for therapeutic purposes) on the metabolic and electrical functions of the myocardium (Shine 1979; Matsuda et al., 1987; Zwerling 1987; Kaseda et al., 1989; Krause and Rozanski, 1991; Zipes 1991; du Troit and Opie, 1992).

On the above basis, it can readily be understood that a manifest hypomagnesaemia or latent magnesium deficiency enhances the "electrical instability" of the atrial and ventricular myocardium and its tendency to arrhythmias (Ramee et al., 1985; DeCarli et al., 1986; Rasmussen et al., 1986; Sjögren et al., 1989; Katholi et al., 1990; Reinhardt et al., 1991; Whang et al., 1992). It was reported by Chipperfield and Chipperfield in 1973 that a subnormal magnesium concentration was present in the myocardium of subjects undergoing sudden arrhythmic cardiac death (SCD) (Chipperfield and Chipperfield, 1973). In connection with myocardial ischaemia or infarction induced by coronary artery occlusion, it further emerged that the affected myocardial region loses not only potassium, but also magnesium (Dubey and Solomon, 1989; Fazekas and Szerdahelyi, 1989). Recent preliminary data, however, suggest a 3-fold increase in intracellular magnesium level during global ischaemia (Steenbergen et al. 1989). Whatever is the case, after hospitalization approximately 30% of patients with acute myocardial infarction (MI) have hypomagnesaemia, which, together with the effects of many other metabolic and neurohumoral factors, plays a pathogenetic role in the development of the enhanced excitability of the cardiac tissue (Flink et al., 1981; Kiss and Fazekas, 1983; Rasmussen et al., 1986; Keller and Aronson, 1990; Fazekas et al., 1992). The cause of the transient hypomagnesaemia observed in the early stage of MI is the enhancement of lipolysis, induced by the catecholamine excess, and the higher level of free fatty acids (FFAs) in the blood (Flink et al., 1981). The latter is accompanied by magnesium-FFA complex formation, which is followed by the sequestration of "magnesium soaps" in the fat cells. The levels of magnesium and FFA in the blood plasma in MI are therefore normalized later almost simultaneously (Flink et al., 1981).

Interest in the pathophysiology and clinical features of magnesium was increased considerably by epidemiological data indicating that the incidence of SCD and ischaemic heart disease is higher in those regions where the soil is poor in magnesium and the drinking-water is soft (Chipperfield and Chipperfield, 1973). Nevertheless, an account of the cardiovascular epidemiological data connected with a decreased magnesium intake is beyond the scope of the present section, which will not deal with the effect of magnesium on molecular pharmacology or with its biochemical functions in the cardiac metabolism. In this respect, reference may be made to a number of reviews (Garfinkel et al., 1986; Gums, 1987; Zwerling, 1987; Rude, 1989; Seelig, 1989; Surawicz, 1989; White and Hartzell, 1989; Iseri et al., 1992). The primary aim of the

present section is to provide an up-to-date survey of the electrophysiologic effects of magnesium, with particular regard to those clinical arrhythmias which have been found to be effectively treatable with magnesium administered intravenously.

Electrophysiology of magnesium

The cardiac electrophysiological role and characteristics of magnesium at a cellular level are less familiar than those of potassium, but it is known that the functions of the two cations are closely related (Rude, 1989; Iseri et al., 1992). A potassium loss by the myocardial cells is almost always accompanied by a magnesium depletion, and hypomagnesaemia is also present in 40% of the disease states involving hypopotaemia (Iseri et al., 1992). The latter can often be corrected by exogenous potassium only if magnesium is administered simultaneously ("refractory potassium repletion"; Rude, 1989; Seelig, 1989; Whang et al., 1992).

Most of the data connected with the electropharmacological actions of magnesium were obtained from investigations on isolated cardiac fibres and isolated cardiomyocytes by means of various *in vitro* methods, e.g. intracellular microelectrode, voltage clamp and patch clamp techniques (Shine, 1979; Sebeszta et al., 1981; Matsuda et al., 1987; Bailie et al., 1988; Kaseda et al., 1989). Magnesium acts on the Na^+ channels of the heart cells. As a consequence of the potassium loss and extracellular potassium concentration increase induced by myocardial ischaemia, the resting potential of the cells decreases, the normally very fast depolarization phase of the action potential (AP) slows down, and the AP becomes shorter. These electrophathological consequences of the excess of extracellular potassium can be counterbalanced by increase of the magnesium concentration of the perfusate, $[\text{Mg}^{2+}]_0$: the V_{max} kinetics is restored and the action potential duration (APD) is also normalized (Roden, 1989). Recent investigations suggest that the most important effects of magnesium are those exerted on the repolarizing K^+ currents and the K^+ conductance (Matsuda et al., 1987; Davidenko et al., 1989). Of the 8 repolarizing K^+ currents recognized to date, several are characterized by the property of inward rectification (I_{K1} , $I_{\text{K,ATP}}$ and $I_{\text{K,ACh}}$). Magnesium is a "blocker" of cardiac K^+ channels, since it is normally present inside cells and has been proposed to impart to K^+ channels the propensity of inward rectification, which is so important in maintenance of the cardiac AP plateau (White and Hartzell, 1989). In the absence of internal magnesium, the background current-voltage relationship of the cardiomyocytes becomes ohmic (Matsuda et al., 1987). Subsequent addition of physiological concentrations of magnesium to the internal side of the membrane reduces outward currents through the background K^+ channel without affecting inward currents, thereby restoring inward rectification. Internal magnesium has also been reported to decrease the maximum amplitude of the delayed rectifier current, and to block the ATP-regulated K^+ channel (White and Hartzell, 1989). The clear-cut voltage-dependent block of inward rectifying K^+ channels by internal magnesium could also underlie the membrane depolarization observed during acute ischaemia. Magnesium influences the slow transsarcolemmal Ca^{2+} inflow (I_{Ca}) proceeding via the Ca^{2+} channels of L-type and also seems to be a modulator of intracellular, sarcoplasmic reticular Ca^{2+} handling (Sebeszta et al., 1981; Davidenko, 1989; Krause and Rozanski,

1991; Iseri et al., 1992). An increase or a decrease in $[Mg^{2+}]_i$ inhibits or enhances I_{Ca} , which proves that intracellular magnesium plays an important role in the regulation of the transmembrane Ca inflow and Ca^{2+} channel function (White and Hartzell, 1989). The cardiac cells of the nodal regions (sinus and AV nodes) are primarily characterized by a calcium-dependent depolarization mechanism of "slow response" type, which is in concordance with those *in vitro* and *in vivo* observations demonstrating that the calcium-entry blocker magnesium exerts a marked electrophysiological effect particularly in these areas (Rogiers et al., 1989). The often-mentioned, apparently simplistic statement that magnesium is "nature's physiologic calcium blocker" is therefore essentially true (Iseri et al., 1992). It is also important that the sarcolemma is permeable to Mg^{2+} , but the mechanisms of entry via a supposed Mg^{2+} channel and removal from the cell via a Na^+-Mg^{2+} exchanger are not yet known (White and Hartzell, 1989).

On the above basis, it may be stated that the antitachyarrhythmic action of magnesium is complex: the conductances of Na^+ , K^+ and Ca^{2+} in the sarcolemma are all influenced by magnesium. From the inhibitory effect on the K^+ outflow, a lengthening of the APD would be expected, whereas its shortening would be expected from the calcium-antagonistic action (White and Hartzell, 1989). Further cellular electrophysiological and molecular pharmacological studies will lead to a more precise understanding of the mechanisms of the antiarrhythmic action of magnesium.

Arrhythmia mechanisms suppressible by magnesium

Only in the past decade has it become clear that, besides reentry and automaticity, a third arrhythmia mechanism can play a role in certain cardiac arrhythmias: afterdepolarizations leading to triggered activity (Brugada and Wellens, 1984). Afterdepolarizations may appear in the course of repolarization. These have been designated early afterdepolarizations (EADs) (January and Makielski, 1990). If afterdepolarizations occur after completion of the AP, during phase 4, they are designated delayed afterdepolarizations (DADs) (January and Makielski, 1990). Recent experiments have demonstrated that the EADs or DADs and the triggered rhythm induced by them are suppressible by magnesium, and the tachycardias ascribed to these phenomena can be eliminated by the addition of magnesium *in vitro* (Sebeszta et al., 1981; Davidenko et al., 1989; Kaseda et al., 1989) or by its injection *in vivo* (Székely and Wynne, 1951; Specter et al. 1975; Cohen and Kitzen, 1983; Bonatti et al., 1989; Tzivoni and Keren, 1990; Keren and Tzivoni, 1991). This is true despite the fact that the mechanisms of EAD and DAD partly differ (January and Fozzard, 1988; January and Makielski, 1990). The EAD can be attributed to the enhanced Ca^{2+} inflow proceeding via the L-type Ca^{2+} channels, but an important pathogenetic role is also played by the Na^+ flowing in via the non-inactivating Na^+ channels (January and Makielski, 1990; Zipes, 1991). The occurrence of the EADs is favoured by a long APD, and they therefore arise most frequently in the Purkinje cells of the mammalian heart, which possess the longest APD (January and Fozzard, 1988; Davidenko et al., 1989). Accordingly, the EAD is induced primarily by those substances/conditions which lengthen the APD: bradycardia or pauses in the heart rhythm, hypopotassaemia/hypomagnesaemia, the

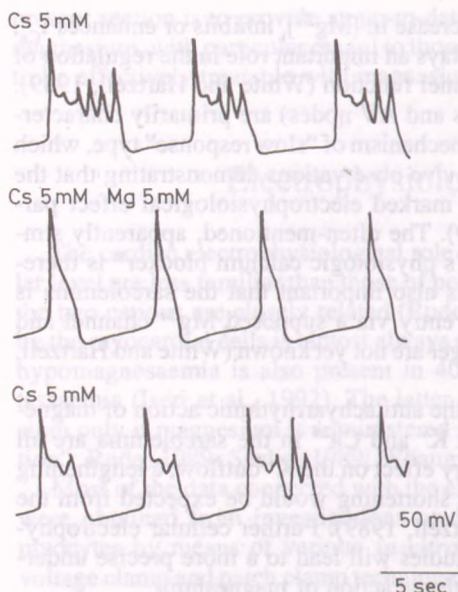


Fig. 7.1. The repetitive phase 2 early after depolarization (EAD) induced by caesium (Cs, 5 mmol/dm³) in the canine Purkinje cell can be extinguished with magnesium (Mg, 5 mmol/dm³) *in vitro*. After the wash-out of magnesium, EAD returns (reproduced with permission from Bailie et al., 1988)

calcium agonist Bay K 8644, quinidine, caesium (Fig. 7.1), barium, aconitine, veratrine or anthopleurin-A. Magnesium extinguishes the EAD that occurs during the plateau phase 2 of the AP, mainly by inhibiting Ca²⁺ inflow, but it also influences the EADs arising in phase 3, at membrane potentials more negative than -60 mV and mediated by Na⁺ currents (Bailie et al., 1988; Kaseda et al., 1989). The prototype of the clinical arrhythmias based on EADs is the pause-dependent "torsades de pointes" ventricular tachycardia (VT) associated with the drug-induced long QT/QTU syndrome.

The DAD can be ascribed to oscillation of the resting potential of calcium-overloaded heart cells associated with the decreased K⁺ conductivity, and activation of an inward non-selective transient inflow (I_{ti}) and of the Na⁺:Ca²⁺ exchanger (January and Fozzard, 1988). DAD can be induced in cardiac preparations by digitalis toxicity, catecholamines, lysophosphatidylcholine (LPC), caffeine and histamine (January and Fozzard, 1988; January and Makielski, 1990). The triggered activity based on DAD is responsible for the arrhythmias due to cardiac glycoside toxicity and is suppressible by magnesium. The multifarious cellular electrophysiologic actions of magnesium explains the ECG changes caused in humans by a magnesium deficiency or excess. The alterations are primarily expressed in the calcium-dependent nodal myocardial regions. Myocardial magnesium depletion enhances sinus automaticity, whereas magnesium supplementation has a negative chronotropic effect (Gums, 1987). The depressant effect exerted on the AV nodal conduction appears as a prolongation of the PQ/PR interval, and as a lengthening of the AH interval and AV nodal refractory period (Rogiers et al., 1989). Human electrophysiological studies show that magnesium has little influence on the electrical properties of the His-Purkinje system and the ventricular myocardium: the QRS, QT/QTc and HV durations are not prolonged,

and a recent preliminary report states that magnesium can also be given safely to bundle branch block patients (Gums, 1987; Perticone et al., 1990). It does not lengthen the ERP of the atrial and ventricular myocardium either (Rogiers et al., 1989). The ECG signs of hypomagnesaemia (serum Mg < 0.7 mmol/dm³) show the characteristics of a myocardial potassium deficiency (ST segment depression, flattening of the T wave and QT/QTU prolongation), but since the deficiencies of the two cations are very often associated, it is not known whether these changes are caused by the magnesium deficiency *per se* (Seelig, 1989; Iseri et al., 1992). It appears certain, however, that a magnesium deficiency enhances the excitability of the atrial and ventricular myocardium, whereas it is decreased by therapeutically administered magnesium (Ghani and Rabah, 1977; Kiss and Fazekas, 1982; Durlach and Durlach, 1987; Keren, 1990; Iseri et al., 1992). Hypermagnesaemia depresses the sinoatrial, AV nodal and intraventricular conduction alike: the PR interval is lengthened, the QRS complex is broadened, and the T waves are higher and sharper, as in hyperpotassaemia (Rasmussen et al., 1986; Gums, 1987). An excess of magnesium has a negative inotropic action too (Gums, 1987).

The undesirable cardiac effects of hypomagnesaemia can be counterbalanced by the acute i.v. administration of magnesium sulphate or magnesium chloride. In cases demanding chronic treatment, e.g. during long-term diuretic therapy, the result may be attained by oral magnesium supplementation or by the application of drugs sparing both potassium and magnesium, e.g. spironolactone, triamterene or amiloride (Sheehan, 1989; Iseri et al., 1992). In the event of hypermagnesaemia, 1–2 g calcium gluconate may be given i.v. In chronic hypermagnesaemia (e.g. renal insufficiency), magnesium can be removed from the blood by means of haemodialysis.

Treatment of clinical arrhythmias with magnesium

Many cardiac arrhythmias can be treated effectively with an appropriate i.v. dose of magnesium chloride or magnesium sulphate (Table 7.2). The antiarrhythmic effect of i.v. magnesium was first reported by Zwillinger in 1935: the sinus rhythm of 8 patients with atrial or ventricular tachyarrhythmia induced by digitalis toxicity was

Table 7.2. Arrhythmias suppressible by magnesium

1. "Torsades de pointes" VT
2. Cardiac glycoside toxicity-induced tachycardias
3. Ventricular extrasystoles/VT associated with MI
4. Reentrant supraventricular tachycardias
5. Multifocal atrial tachycardia
6. Magnesium deficiency-induced atrial fibrillation
7. Arrhythmias in mitral valve prolapse syndrome
8. Sustained monomorphic VT (?)
9. Postischaemic/reperfusion arrhythmias (?)

VT = ventricular tachycardia

MI = acute myocardial infarction

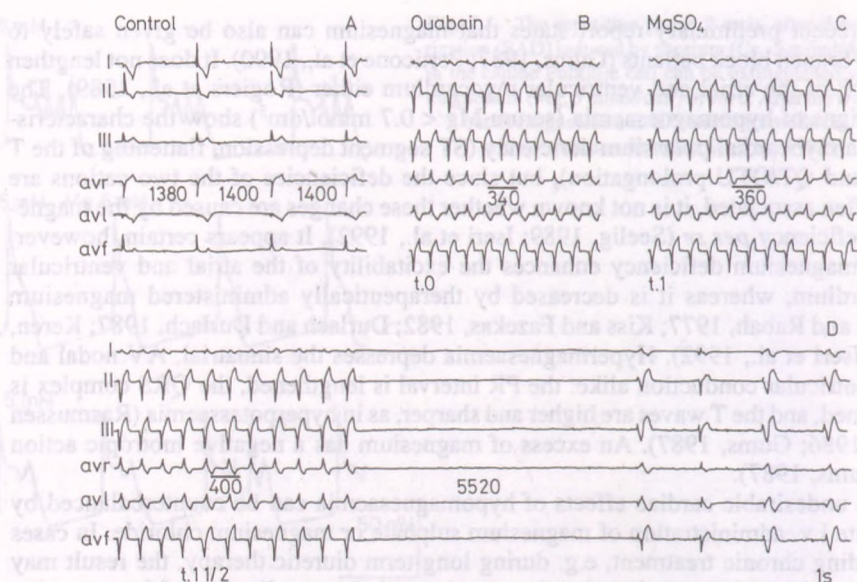


Fig. 7.2. Termination of ouabain-induced sustained monomorphic ventricular tachycardia (SMVT) with magnesium sulphate (100 mg/kg i.v.) in conscious dog. Panel A: idioventricular rhythm accompanying complete AV block, Panel B: ouabain-induced SMVT with mean cycle length (CL) of 340 ms, Panel C: the SMVT slows after the administration of magnesium sulphate (CL = 360 ms), Panel D: the SMVT stops 1.5 min after the injection following a further increase in RR interval (400 ms)

successfully restored by the i.v. injection of magnesium sulphate. It has subsequently been clearly demonstrated that the digitalis-induced tachycardias are sensitive and respond well to magnesium administration (Székely and Wynne, 1951; Specter et al., 1975; Cohen and Kitzes, 1983; Davidenko et al., 1989). Ouabain-induced sustained monomorphic VT is terminable by the "calcium overload inhibitor" flunarizine (Vos et al., 1991) and also by magnesium (Vos et al., 1994; Fig. 7.2). It has also become clear that the antiadrenergic activity of magnesium plays no role in the development of the antiarrhythmic action in this setting, for the cation also extinguishes digoxin-induced VT after β -receptor blockade (Specter et al., 1975). Hypomagnesaemia is known to be more frequent (19%) than hypopotassaemia (9%) among patients treated with digitalis preparations (Gums, 1987). Simultaneously, the sensitivity of the myocardium to cardiac glycosides is enhanced by hypomagnesaemia or myocardial magnesium depletion (Iseri et al., 1992). As concerns the mechanism of the antiarrhythmic effect of magnesium observed in digitalis-induced arrhythmias, it was long believed that the basis of the protective action of magnesium was the "reactivation" of the digitalis-blocked sarcolemmal ($\text{Na}^+\text{--K}^+$)–ATPase. Later studies disproved this view, and it emerged that magnesium does not increase the activity of this enzyme (Specter et al., 1975). It rather exerts a *direct* membrane effect and moderates the K^+ outflow and cellular K^+ loss via the K^+ channels in the presence of digitalis (Shine, 1979).

Another arrhythmia entity in whose treatment magnesium seems to be the most valuable drug is the often iatrogenic VT of "torsades de pointes" which accompanies the "acquired" long QT/QTU syndromes (Fazekas and Kiss, 1984; Ramee et al., 1985; Banai and Schuger, 1990; Keren and Tzivoni, 1990, 1991; Tzivoni and Keren, 1990). The origin of this bradycardia-dependent type of VT, which is frequently refractory to (or even induced by) antiarrhythmic therapy, is almost certainly EAD-based triggered activity (Bailie et al., 1988; January and Makielski, 1990; Zipes, 1991). "Torsades" is very often induced by Class Ia or Class III antiarrhythmic drugs during accompanying hypokalaemia and/or hypomagnesaemia. The first anecdotal reports on the successful magnesium therapy of "torsades de pointes" VT appeared in the late 1970s, when the mechanism of this arrhythmia was still unknown (Fig. 7.3) (Kiss and Fazekas, 1982, 1983; Fazekas and Kiss, 1984). "Torsades" can often be eliminated by i.v. magnesium when the QT interval has not yet been shortened, or to only a slight extent (Keren and Tzivoni, 1990). Intravenous magnesium was also found to be very effective in the treatment of barium- and organophosphate pesticide-induced clinical and experimental ventricular arrhythmias (Kiss and Fazekas, 1982; 1983). The initial dose of magnesium is 2–3 g in an i.v. bolus during 1–2 min, which can be repeated within 15 min, followed by a maintenance dose of 3–20 mg/min by infusion during 6–49 hours, because of the fast renal elimination (Banai and Schuger, 1990; Iseri et al., 1992).

In the early stage of MI, there is a transient hypomagnesaemia, lasting for up to about 48 hours (Flink et al., 1981). This can be ascribed not to a renal magnesium loss, but to the fat tissue sequestration of the magnesium soaps formed. Since magnesium has a fundamental role in preservation of the "electrical stability" of the myocardium, it may be assumed that the transient magnesium deficiency too contributes to the emergence of "subacute" postinfarction ventricular arrhythmias. Abraham et al. carried out a double-blind, placebo-controlled study on the continuously monitored ECG of MI patients, and found that the incidence of "complex" ventricular arrhythmias (R on T phenomenon, VT/VF) was lower in those treated with magnesium (i.v. on the first 3 days of MI) than in the placebo-treated group (Abraham et al., 1987). On the first 2 days of MI, Rasmussen et al. (1986) administered i.v. magnesium chloride in the form of a continuous infusion (50 mmol on day 1, and 12 mmol on day 2). The incidence of arrhythmias in the treated group was 21%, while in the placebo group it was 47%. Magnesium was observed to suppress supraventricular tachyarrhythmias, and the 4-week mortality was found to be lower in the treated group (7% vs. 19%). Teo et al. (1991) presented a meta-analysis of seven earlier double-blind clinical stud-

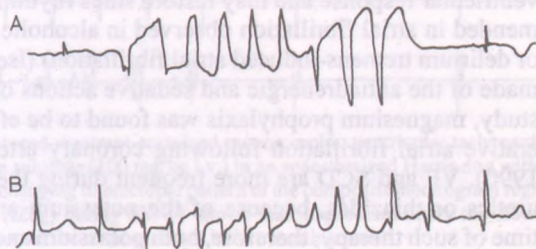


Fig. 7.3. Lidoflazine- (Panel A) and organophosphate pesticide-induced (Panel B) "torsades de pointes" ventricular tachycardia (VT) accompanying acquired long QT/QTU syndrome in two different patients. Despite the dissimilar etiology, these particular repetitive VTs were completely abolished by i.v. magnesium sulphate

ies, and concluded that i.v. magnesium decreased the short-term in-hospital death rate. This experience has led many authors to the view that it is of value to give i.v. magnesium routinely in the early stage of MI, if there are no contraindications (cardiogenic shock, a systolic blood pressure of 90 mmHg or less, or a 2nd or 3rd degree AV block). A recent paper, however, suggests that patients suffering from acute ischaemic heart syndromes do not benefit from i.v. magnesium supplementation: neither the in-hospital mortality nor the mortality after a follow-up period of 245 days was affected by magnesium administration (Feldstedt et al., 1991). The ongoing ISIS-4 trial also has an arm looking at the effects of i.v. magnesium.

The results of clinical and experimental studies indicate that magnesium diminishes postischaemic/reperfusion myocardial damage and prevents reperfusion-induced arrhythmias. The use of magnesium at the onset of reperfusion attenuates stunning and results in an enhanced recovery of the cardiac output in the isolated rat heart (du Toit and Opie, 1992). The widespread use of magnesium in cardiac surgery cardioplegic solutions can be ascribed to this 'cardioprotective' action.

Intravenous magnesium can be applied effectively in reentrant supraventricular tachycardias (SVT) using an AV-nodal circuit or an atrioventricular accessory pathway. Wesley et al. (1989) administered 2 g magnesium sulphate in a rapid i.v. bolus (5 s). In 7 of the 10 patients, the SVT were abolished after an anterograde block following AH interval prolongation, on average 31.4 ± 9.8 s after the injection. Despite the "aggressive" dosage, transient hypotension and marked sinus bradycardia with vomiting were observed in only one patient. The "verapamil-like" effect of i.v. magnesium on the AV node in SVT is in accordance with the calcium-antagonist activity of magnesium. Contributions are probably also made by the parasympathomimetic and antiadrenergic actions of magnesium (Wesley et al., 1989). Another group found that macro-reentrant SVT was eliminated in 3 of 5 AV-reciprocating SVT patients by magnesium treatment (2 g, i.v., in 15 s) via a retrograde block induced in the accessory pathway (Viskin et al., 1990). It appears that the fast injection (though this is not completely free of danger) plays an important role in the development of the therapeutic effect. Sager et al. administered 0.3 meq/kg of magnesium i.v. in 10 min, and observed that the reentrant SVT slowed, but did not stop, in response to magnesium, and that it could be reinduced by means of programmed electrical stimulation just as readily as without magnesium administration (Sager et al. 1990). In this area, therefore, further investigations are required and more experience must be obtained.

Iseri et al. reported that i.v. magnesium was very effective in multifocal atrial tachycardia presumably based on abnormal automaticity and associated with chronic lung disease: the sinus rhythm was restored in 7 of 8 patients (Iseri et al. 1992).

In atrial fibrillation associated with hypomagnesaemia, magnesium decreases the ventricular response and may restore sinus rhythm. Intravenous magnesium is recommended in atrial fibrillation observed in alcoholic disease forms (e.g. "holiday heart" or delirium tremens-induced atrial fibrillation) (Iseri et al., 1992). In such cases, use is made of the antiadrenergic and sedative actions of the drug. In a recent double-blind study, magnesium prophylaxis was found to be effective in the prevention of postoperative atrial fibrillation following coronary artery bypass grafting (Katholi et al., 1990). VF and SCD are more frequent during the chronic administration of loop diuretics or thiazides, because of the potassium and magnesium deficiencies. At the time of such therapy, therefore, both potassium and magnesium must be supplemented

(Gums, 1987; Iseri et al., 1992). In general, a potassium:magnesium ratio of 8:1 is accepted (Gums, 1987). Sustained-release magnesium chloride pills have recently come into favour because of the potassium, magnesium and chloride losses accompanying long-term saluretic treatment, and also because of the danger of hypochloraemic alkalosis (Seelig, 1989; Sheehan, 1989). Even a dose of 32 meq/day of such a preparation can be well tolerated.

A magnesium deficiency likewise plays a pathogenetic role in the development of the neuromuscular hyperexcitability frequently observed in the idiopathic mitral valve prolapse syndrome. Magnesium therefore has a place in the treatment or prevention of cardiac arrhythmias associated with mitral valve prolapse, in part because of its pharmacodynamic action, and in part for purposes of substitution, to eliminate latent tetany (Durlach and Durlach, 1987).

Magnesium can terminate post-MI sustained monomorphic VT (*Fig. 7.4*; Harris et al., 1953). Following a study on 11 patients, Allen et al. recently reported that i.v. magnesium sulphate eliminates the sustained monomorphic VT accompanying organic heart disease (coronary heart disease or congestive cardiomyopathy) (Allen et al., 1989). Naturally, magnesium can be injected exclusively in haemodynamically stable VT, and a postinjection deterioration must be reckoned with in every case. From investigations on a similar patient group, another group concluded that, if i.v. magnesium eliminates sustained monomorphic VT, it may be expected that prolonged oral calcium-antagonist treatment with verapamil or diltiazem will also be effective (Brooks et al., 1990).

To summarize our knowledge of the intravenous magnesium treatment of clinical arrhythmias, i.v. magnesium is the drug of choice in "torsades de pointes" VT accompanying drug-induced long QT syndrome. It is a complementary therapeutic agent in

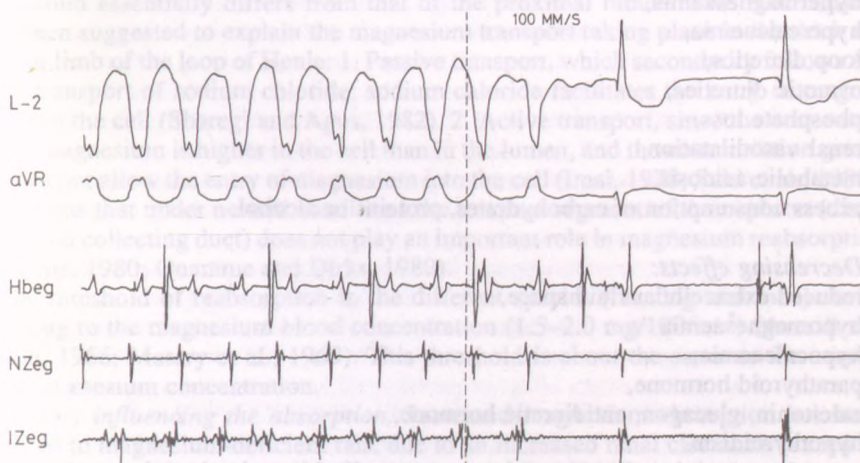


Fig. 7.4. Termination of a pacing-induced reentrant-sustained monomorphic ventricular tachycardia (SMVT) by a fast bolus of magnesium sulphate (100 mg/kg i.v.) in an anaesthetized Harris dog with a 4-day-old myocardial infarction. The changing interectopic pattern of the composite electrogram registered from the infarcted epicardium (IZeg) during SMVT shows that magnesium alters the slowly conducting portion of the reentry circuit before termination

digitalis-induced tachycardias. Magnesium is particularly effective in those cases in which the putative arrhythmia mechanism involves EADs or DADs and triggered activity. As concerns the treatment of SVTs and sustained monomorphic VTs, further studies must be performed on a larger groups of patients.

7.3. The relation of the magnesium metabolism with the renal functions and blood pressure regulation

The role of the kidney in the magnesium metabolism

The magnesium metabolism does not have an independent homeostatic regulation. The most important regulator of the constancy of the normal level of magnesium in the blood is the excretion of magnesium (Aikawa, 1980; Wacker, 1980), but the gastrointestinal tract and bone also take part in the regulation. For humans on an unrestricted diet, the daily magnesium excretion is about 100–150 mg, which is roughly 5% of the filtered amount (Sutton and Watson, 1969). In the event of an increased magnesium intake, the excretion may rise up to 500–600 mg/day (Alfrey et al., 1970); if the intake is reduced, the excretion may be as low as 10–12 mg (0.5 mmol).

The excretion of magnesium is influenced by the following factors:

Increasing effects:

increased extracellular fluid space (Conn syndrome),
hypermagnesaemia,
hypercalcaemia,
loop diuretics,
osmotic diuretics,
phosphate loss,
renal vasodilatation,
metabolic acidosis,
excess consumption of carbohydrates, proteins or alcohol.

Decreasing effects:

reduced extracellular fluid space,
hypomagnesaemia
hypocalcaemia,
parathyroid hormone,
calcitonin, glucagon, antidiuretic hormone,
hypothyroidism,
potassium-retaining diuretics (triamterene, amiloride and spironolactone).

These factors usually, but not always, shift the blood magnesium level in the same direction. The extent of magnesium excretion is determined by its filtration, reabsorption and secretion.

Renal magnesium filtration

Under normal conditions, the kidney filters about 2.4 g (100 mmol) magnesium daily, 95% of which is reabsorbed, i.e. about 100 mg is excreted. The amount of filtered magnesium is not influenced (or only slightly) by the magnesium-deficient or magnesium-supersaturated condition of the organism or by elevated plasma calcium concentrations (Carney et al., 1980). It is affected rather by such factors as acidosis, alkalosis, or changes in the plasma renin and protein concentrations.

Renal magnesium reabsorption

Magnesium reabsorption has a limit (threshold) beyond which there is no further reabsorption. This means that every hypermagnesaemia is followed by a compensatory hypermagnesuria (Mordes and Wacker, 1977; Quamme et al., 1980). Magnesium is reabsorbed at two sites of the nephron. About 25% is reabsorbed passively in the proximal tubule (Wong et al., 1983), depending on the sodium and fluid transport. Most of the magnesium reabsorption (about 60%) takes place in the thick ascending limb of the loop of Henle; this may be observed, for example, in connection with furosemide treatment (Rude, 1989).

Quamme and Dirks (1980) investigated the mechanism of the reabsorption of the loop of Henle, and demonstrated that at the normal blood magnesium levels the reabsorption of the magnesium is taking place in the ratio of the intraluminal concentration of the magnesium.

An increase in the magnesium concentration of the blood may reduce the absorption of magnesium considerably. The permeability of the thick ascending limb for magnesium essentially differs from that of the proximal tubule. Two mechanisms have been suggested to explain the magnesium transport taking place in the thick ascending limb of the loop of Henle: 1. Passive transport, which secondarily follows the active transport of sodium chloride; sodium chloride facilitates the entry of magnesium into the cell (Sharegi and Agus, 1982). 2. Active transport, since the concentration of magnesium is higher in the cell than in the lumen, and the concentration gradient does not allow the entry of magnesium into the cell (Imai, 1978; Suki et al., 1980).

It seems that under normal conditions the terminal segment of the nephron (distal tubule and collecting duct) does not play an important role in magnesium reabsorption (Quamme, 1980; Quamme and Dirks, 1980).

The threshold of reabsorption in the different species (rat, dog and man) varies according to the magnesium blood concentration ($1.5\text{--}2.0\text{ mg}/100\text{ cm}^3$) (Averill and Heaton, 1966; Massry et al., 1969). This threshold is about the same as the normal blood magnesium concentration.

Factors influencing the absorption. Increased magnesium absorption has been observed in magnesium-deficient rats, due to an increased renal clearance caused by loop diuretics or triiodothyronine (Peerenboom et al., 1980).

The passive magnesium reabsorption in the proximal tubule (Wong et al., 1983) differs from the absorption of sodium and calcium, since about 60% of the latter is reabsorbed in this segment. The magnesium content of the tubular fluid is 1.5 times as high as that of the blood.

Renal magnesium secretion

The renal excretion of magnesium is therefore determined primarily by the combination of glomerular filtration and tubular reabsorption, although tubular magnesium secretion could also be provoked by magnesium loading (Averill and Heaton, 1966; Wen et al., 1971). Magnesium is secreted from the vasa recta or the interstitium in the juxtamedullary nephrons, in the descending limb of the loop of Henle.

The relationship of renal magnesium transport with other cations

The urinary excretion of magnesium is connected with several cations. For example, sodium loading increases the excretion of both sodium and magnesium (Brunette et al., 1969). Calcium loading increased the excretion of both calcium and magnesium (Wesson, 1962). On the other hand, under certain conditions the excretion of calcium and magnesium may be dissociated. For example, following thiazide administration the urinary excretion of calcium decreases considerably, while that of magnesium increases slightly (Brickman et al., 1972).

The interaction of the calcium and magnesium metabolisms has not yet been completely clarified. In rats, a reduction of the magnesium intake results in a negative potassium equilibrium and a decreased muscular potassium concentration (Whang and Welt, 1963). In humans with a magnesium depletion, reduced potassium levels were found in the muscles and the serum (Shils, 1964); nevertheless, the finding could not be corroborated by other authors (Dunn and Walser, 1966). Martindale and Heaton (1964) revealed the magnesium loss of the myocardial and renal parenchymal cells in magnesium-deficient rats. In man, the changes in blood magnesium level are usually connected with those in potassium (Whang et al., 1978).

Hormonal regulation of the renal magnesium transport

None of the hormones play a main regulatory role in the homeostasis of magnesium. Nevertheless, there are some hormones which influence the magnesium metabolism.

Parathyroid hormone administered in a bolus decreases the urinary excretion of magnesium and calcium (MacIntyre et al., 1963), although T_m is the same for either an excess or a deficiency of this hormone, which means that it cannot be an important regulator of the magnesium metabolism (Rude et al., 1980). It has not been clarified either whether this is a direct effect of parathyroid hormone on magnesium, or a secondary consequence of the increased calcium absorption.

Although aldosterone, calcitonin, ADH and insulin may influence the renal transport of magnesium, their physiological roles are unclarified. Aldosterone increases the urinary excretion of magnesium (Horton and Biglieri, 1962). A reduction in the blood magnesium level was observed following adrenaline administration, which may explain the fact that the serum magnesium level is usually decreased in stress (Abraham et al., 1980).

Aldosterone, growth hormone, thyroxine and calcitonin decrease the magnesium level of the blood (Gums, 1987). Calcitonin increased the absorption of magnesium in the loop of Henle only in hypocalcaemia (Poujbol et al., 1980). It has recently been shown that both ADH (de Rouffignac et al., 1983) and glucagon (Bailly et al., 1984) reduced the excretion of magnesium by increasing its reabsorption in the loop of Henle.

Magnesium metabolism and blood pressure regulation

The role of magnesium in blood pressure regulation

It must first be emphasized that the plasma magnesium concentration does not reflect either the condition of the organism as a whole or the intracellular state. A magnesium deficiency may be present in spite of normal or elevated plasma levels. A magnesium-deficient state may be a result of a reduced intake, including alcoholism, starvation and anorexia, or of a great magnesium loss via the gastrointestinal tract (diarrhoea, malabsorption, etc.) or via the kidney (following the administration of diuretics or gentamycin, etc.). The magnesium intake is reduced in regions where the water is soft and has a low magnesium content (Flink, 1980).

In vitro experiments have proved that in magnesium-deficient states the vascular tone and reactivity to vasopressor agents are increased (Peterson et al., 1977; Altura and Altura, 1978). A clinical study revealed an inverse relation between the serum magnesium concentration and the blood pressure. An increased magnesium intake was accompanied by a proportionally less frequent occurrence of essential hypertension (McCarron, 1983). Some authors report lower blood pressures following the administration of magnesium salts. The hypotensive effect of magnesium has also been demonstrated in animal experiments (Friedman et al., 1987). Since this relationship may be influenced by innumerable factors, it is not surprising that it has not been corroborated by all authors.

It was long ago observed (Hazard and Wurmser, 1932) that an acute increase in serum magnesium level is accompanied by a decrease in blood pressure. Recent *in vitro* studies have revealed that hypermagnesaemia results in vasodilatation and a decreased reactivity to pressor agents (Altura and Altura, 1981). The sensitivity to pressor agents increases together with the decrease in magnesium level. The same study also demonstrated that magnesium has a direct influence on the intake, content and distribution of calcium in the vascular smooth muscle cells.

Magnesium metabolism and the renin-angiotensin system (RAS)

To date, relatively few publications are available with respect to the connection between magnesium and the RAS.

Dechaux et al. (1988) reported on the increase in plasma renin level following infusion of a magnesium salt. This finding is in accordance with the earlier observa-

tion that magnesium perfused in the isolated kidney of dogs increased the release of renin (Wilcox, 1978).

Fuentes and Goldkrand (1987) found elevated levels of the angiotensin-converting enzyme in pregnancy hypertension. They also observed that the administration of magnesium sulphate decreased not only the blood pressure, but the blood level of this enzyme, too.

In patients with essential hypertension, 4-week oral magnesium treatment led to a decrease in blood pressure, while the plasma renin activity and aldosterone concentration did not change substantially (Motoyama et al., 1986).

Resnick et al. (1983) found the serum magnesium levels to be elevated in hypertension with low renin activity, and decreased in that with high renin activity. Without the classification relating to the renin activity, no connections could be revealed. This finding is not yet clarified. In heart failure, the activity of the RAS may be increased, but during diuretic treatment the renal loss of magnesium is increased in part by the diuretics, and in part by the RAS they activate (Dargie, 1990). This reduces the chances of compensating the circulatory failure and facilitates the development of arrhythmias.

The connection of magnesium and hypertension

Capuccio et al. (1985) administered magnesium aspartate to patients with mild or moderate essential hypertension. Despite the significant increases in blood magnesium level and in urinary magnesium excretion, the blood pressure was not substantially lower than in the controls.

Excess alcohol consumption is a frequent cause of hypomagnesaemia and hypertension (Adeniyi, 1980). This is explained by the change in the sodium homeostasis, which is a consequence of the magnesium deficiency and at the same time the cause of hypertension.

If spontaneously hypertensive animals were kept on a diet with high magnesium content, their hypertension developed more slowly, while diets with low magnesium contents aggravated the hypertension (Berthelot and Esposito, 1983).

In both animals and man, acute hypomagnesaemia is frequently accompanied by an elevated blood pressure and an increased peripheral resistance at various points of the vascular system (Dagirmanjian and Goldman, 1970; Page and Polimeni, 1972; Altura and Altura, 1978). There are numerous pathophysiological conditions and diseases which are accompanied by hypertension and hypomagnesaemia (e.g. diabetes mellitus, alcoholism or essential hypertension). In diabetes mellitus, hypomagnesaemia and hypertension are often encountered. *In vitro* experiments revealed that the changes in the magnesium and calcium exchange of the vascular smooth muscle cell membrane may be held responsible for the change in the vascular tone of alloxan-diabetic rats (McNair et al., 1978; Flink et al., 1979; Turlapaty et al., 1980). On the other hand, hypermagnesaemia, which frequently occurs in renal vascular diseases and circulatory shock, is often accompanied by hypotensive episodes (Beecher et al., 1947; Mordes and Wacker, 1977).

Fujita et al. (1990) observed that magnesium sulphate infused in the circulation of patients with borderline hypertension decreased the vascular resistance to a smaller

extent, i.e. it had a smaller vasodilating effect, than in the age- and sex-matched normotensive controls.

Intravenously administered magnesium has a very favourable effect in eliminating the eclamptic convulsions in eclamptic hypertension (Pritchard and Pritchard, 1975). It is not yet known whether this hypotensive effect is brought about by vasodilatation or by the reduction or discontinuation of the eclamptic convulsions. Some authors, for example Hurley (1981), assume causality in the above phenomenon.

In pre-eclamptic pregnant women, the blood magnesium level was found to be lower than in the controls (Koberlin and Mischell, 1958). It has been reported that the magnesium loss caused by the diuretic treatment of hypertension is inversely correlated with the responsiveness of the blood pressure. A recent study revealed that magnesium replacement resulted in a clinically effective reduction in blood pressure in patients receiving long-term diuretic treatment (Dyckner and Wester, 1987). Nevertheless, this could not be corroborated by other authors (Henderson et al., 1986).

Furthermore, it has been observed that diuretic treatment does not decrease mortality; in fact, it increases the proportion of cardiac events. It may be assumed that the adverse effects of magnesium loss caused by diuretics are responsible for this. Such adverse effects include arrhythmias, coronary spasm, an increased susceptibility to vasopressor agents, an elevated blood pressure and an increased platelet aggregation.

Several authors have confirmed that an acute increase in blood magnesium level results in a rapid vasodilatation and hypotension (Mordes and Wacker, 1977).

Resnick et al. (1983) examined the connection between the blood magnesium level and hypertension in man. As mentioned in the previous section, a strong inverse correlation was found between the magnitude of the blood pressure and the reduction in blood magnesium level. Other studies revealed that the urinary excretion of magnesium is lower in patients with essential hypertension than in normotensive individuals (Tillman and Semple, 1988), and that there is an inverse relation between blood pressure and urinary magnesium secretion.

It was demonstrated in animal experiments that permanent magnesium-deficient states may result in hypertension (Altura et al., 1984).

Whelton and Klag (1989) reviewed publications relating to oral magnesium treatment. Some studies did not detect a substantial blood pressure reduction following magnesium treatment, whereas such a reduction was reported by others. With respect to the methodology, the latter finding seems more convincing. In one such study, it was observed that long-lasting oral magnesium treatment was followed not only by a considerable reduction in blood pressure, but also by activation of the $(\text{Na}^+, \text{K}^+)\text{-ATPase}$ in the cell membrane.

The magnesium content of the erythrocytes of untreated 50-year-old hypertensive patients was found to be higher than that of normotensive controls matched with respect to age, sex, height, weight and smoking habits (Kjeldsen et al., 1990).

Magnesium metabolism in renal diseases; clinical aspects

This section summarizes those conditions and diseases which influence the magnesium metabolism directly or indirectly via the kidney.

Hypermagnesaemia

In hypermagnesaemia, the blood magnesium level is higher than normal ($2.3 \text{ mg}/100 \text{ cm}^3$ or 0.95 mmol/dm^3). Its causes may be acute or chronic renal insufficiency or drugs: magnesium sulphate (during pregnancy), or magnesium-containing antacids.

Hypermagnesaemia occurs only rarely if the renal functions are normal.

In acute renal insufficiency (in the oligo-anuric phase), the blood magnesium level is usually considerably elevated, but returns to normal when the renal insufficiency is resolved (diuretic phase).

Therapy. All effects of hypermagnesaemia may be antagonized by the intravenous administration of calcium. This treatment should be applied only temporarily, until the excess magnesium can be removed by dialysis.

Hypomagnesaemia

In hypomagnesaemia, the blood magnesium concentration is less than $1.8 \text{ mg}/100 \text{ cm}^3$ or 0.75 mmol/dm^3 . Its causes may include an increased renal magnesium loss due to chronic alcoholism, diabetic ketoacidosis, hypercalcaemia, primary hyperaldosteronism, Bartter's syndrome, the polyuric phase of acute renal insufficiency, renal tubular acidosis, hypercalciuria, the condition of salt loss, and drugs (diuretics, and mainly the loop diuretics; aminoglycosides such as tobramycin and gentamycin; cisplatin; calcitonin, carbenicillin, digoxin, thyroxine, growth hormone and cyclosporine).

Hypomagnesaemia is most frequently caused by chronic alcoholism (Heaton et al., 1962). Acute alcohol consumption increases the urinary excretion of magnesium and, if this is not followed by an adequate magnesium intake, hypomagnesaemia develops.

Magnesium loss also leads to a considerable potassium loss, which can be corrected only by magnesium replacement. In explicit hypomagnesaemia, twitches may appear, accompanied by positive Chvostek and Trousseau signs. The ECG characteristics may resemble those in hypokalaemia (prolonged QT, flat T waves with U wave).

For the above reasons, in hypomagnesaemia the blood levels of potassium and calcium should also be determined.

Ryan et al. (1984) proved that in patients with cardiac insufficiency and hyperaldosteronism the magnesium and potassium contents of the blood and of the leukocytes were permanently decreased, in all probability because of the above-mentioned promotion of magnesium and potassium excretion by aldosterone. This condition did not respond satisfactorily to potassium replacement, but parenteral magnesium administration led to substantial increases in the magnesium and potassium contents of the blood and leukocytes.

Therapy. In hypomagnesaemia: intravenous magnesium sulphate. 1 g magnesium sulphate contains 98 mg or 8.2 mmol magnesium. In the event of a normal renal function, 6 g (24 mmol) magnesium sulphate may be infused in 1000 ml fluid during 6 hours.

For permanent supplementation, 1 g magnesium daily is required ($4 \times 250 \text{ mg}$).

The effect of diuretics on the renal magnesium transport

Loop diuretics increase the excretion of magnesium to a greater extent than that of calcium or sodium (Quamme, 1978).

Furosemide has already been mentioned to inhibit the reabsorption of magnesium and sodium chloride in the loop of Henle. Ethacrinic acid and the mercury-containing diuretics have a similar effect. The thiazides cause mild magnesuria. The potassium-retaining triamterene and amiloride diuretics also cause magnesium retention by decreasing its excretion (Ryan et al., 1984). Such an effect was likewise observed with spironolactone (Horton and Biglieri, 1962).

The osmotic diuretics, i.e. mannitol and urea, may increase the excretion of magnesium by as much as 30-40% by increasing the filtration (Wong et al., 1979). Acetazolamide, a carboanhydrase inhibitor, slightly increased magnesium excretion by affecting the proximal tubule (Barker et al., 1959).

The effect of antihypertensive treatment on the magnesium metabolism

It is already beyond any doubt that hypertension is a risk factor, and its treatment is therefore important and necessary. Nevertheless, it is indispensable to know whether the drug selected for the treatment has side-effects which directly or indirectly impair the benefits of decreasing the blood pressure. Such a side-effect could be the imbalance of an electrolyte e.g. magnesium, in the organism. In a magnesium deficiency, not only magnesium, but also potassium leaves the cells, and the hypomagnesaemia has the result that potassium hardly enters the cells, or even not at all, despite its replacement. In such cases, therefore, magnesium should be supplemented in addition to potassium.

As already mentioned, a magnesium deficiency results not only in a potassium loss, but also in an increased contractility of the vascular smooth muscles, an increased vascular reactivity to pressor agents, and, because of the disturbance of the cellular membrane potential, an increased tendency to arrhythmias.

The effects of hypotensive agents on the magnesium metabolism should next be dealt with. This aspect of the diuretic agents has already been discussed in the previous section.

Only relatively few data are available concerning the influence of hypotensive agents on the magnesium metabolism. It has been shown that the beta-blocker propranolol and atenolol increase the magnesium contents of the heart and skeletal muscles, but they do not change the plasma magnesium level appreciably (Dyckner and Wester, 1987).

Among the inhibitors of the angiotensin-converting enzyme, captopril increases the loss of magnesium, while enalapril does not affect it (Leary et al., 1985). Reserpine considerably decreases the magnesium concentration in the arterial tissues and in the plasma.

Finally, two aspects should be pointed out:

1. in the course of hypotensive treatment, the blood magnesium level should be routinely controlled;
2. magnesium-deficient states may be accompanied by normal, and even by elevated blood magnesium levels.

Magnesium in the organism of dialysed patients with renal diseases

The serum magnesium level of a patient who is regularly dialysed because of renal disease depends on several factors, including the magnesium intake with the food and during dialysis, and the magnesium concentration of the dialysate. Urinary magnesium excretion does not usually come into consideration, for in this phase the patient no longer produces urine.

In patients undergoing dialysis regularly, the magnesium contents of the muscles and leukocytes are normal, while that of the erythrocytes is increased. The magnesium status of dialysed patients should be controlled, with regard to the clinical experience that hypermagnesaemia may aggravate the uraemic osteodystrophy (Gonella and Calabrese, 1989).

As a rule, a magnesium concentration of $0.25\text{--}35\text{ mmol/dm}^3$ in the dialysate keeps the serum magnesium content at a normal level. Since magnesium is retained in uraemia, a proportion of it should be removed by the dialysis. For adequate maintenance of the magnesium metabolism, dialysis with calcium carbonate is more advantageous than that with aluminium hydroxide (Statopolsky et al., 1986).

7.4. Significance of magnesium in functioning of the nervous system

Nearly one hundred year have passed since the observation that magnesium sulphate induces anaesthesia and relaxation in experimental animals, indicating that the targets of its effects on the nervous system are both central and peripheral (Meltzer and Auer, 1905). Although magnesium itself cannot actually be used for anaesthesia, these features of its action reflect a basically depressant character on various neural functions. Magnesium takes part in a number of energetic and metabolic processes in the human organism; it is a cofactor of more than 300 enzymes, including $(\text{Na}^+, \text{K}^+)\text{-ATPase}$, which maintains the resting cell membrane potential. All these cellular processes occur in the nervous system and, considering the electric phenomena based on ion movements in neurones, seem to be of particular importance.

Magnesium homeostasis in the nervous system

About 1% of the magnesium content of the human body is extracellular, and 64–75% of the serum magnesium is diffusible, ca. four-fifths of this being the free ion (Mg^{2+}). The magnesium concentration of the cerebrospinal fluid (CSF) is higher (1.03--

1.24 mmol/dm³) than that of the serum, but simple ultrafiltration cannot explain this difference. The most acceptable explanation is that the epithelial cells of the choroid plexus presumably actively transport magnesium into the CSF against an electrochemical gradient and the maintenance of a higher magnesium level is dependent on the intactness of the blood-brain barrier (Aikawa, 1981). About 55% of magnesium in the CSF is in the free ionic form (Mg^{2+}) and the remaining 45% is in bound (complex) forms. The magnesium concentration of the CSF is fairly constant, and is practically not influenced by either experimental magnesium loading or depletion; fluctuations in the plasma magnesium concentration are not discernibly reflected in the CSF magnesium level (Chutkow, 1978). However, meningeal inflammation may decrease the CSF magnesium concentration (Aikawa, 1981). Regulation of the magnesium homeostasis in the central nervous system is dependent on the functions of the blood-CSF barrier and the blood-brain barrier, the former participating in an active way, though data are also available on the active transport function of the latter (Bito, 1969),

Cellular magnesium levels and membrane transport of magnesium

Several methodological difficulties arise in accurate determinations of intracellular free Mg^{2+} concentrations. The microinjection of dyes, the application of Mg^{2+} -sensitive microelectrodes and nuclear magnetic resonance (NMR) spectroscopy are among the most up-to-date methods. However, the intracellular Mg^{2+} is compartmentalized and no reliable data are available on its distribution in the various compartments. The mitochondria (one of these compartments) of several cells (cardiac muscle, smooth muscles, liver and brain) can take up and accumulate the Mg^{2+} ion through energy-dependent transport (Rugolo and Zoccarato, 1984), but the cellular homeostasis of magnesium is not known. The free Mg^{2+} level of the cytosol is fairly steady and any change in total magnesium content occurs at the expense of bound magnesium. Measurements have shown intracellular Mg^{2+} concentrations of less than 1 mmol/dm³ (except for the cardiac and skeletal muscles), which suggests that Mg^{2+} is not distributed passively on the two sides of the cell membrane: there must be an efflux mechanism. At electrochemical equilibrium, the ratio of intra/extracellular Mg^{2+} , e. g. in the ganglion cells of *Helix aspersa*, should by calculation be 55, but experimentally it is not the case (Alvarez-Leefmans et al., 1984).

Nevertheless, a Na^{+} -dependent Mg^{2+} efflux transport has been characterized in human red blood cells (Ludi and Schatzmann, 1989). The transport is only outward-directed, with separate binding sites for Na^{+} and Mg^{2+} ions. It requires metabolic energy (ATP hydrolysis) and is not maintained by the inward-directed Na^{+} electrochemical gradient. Its stoichiometry is presumably 1 (2?) Na^{+} :1 Mg^{2+} , and compensating the passive Mg^{2+} uptake by the cell too, it adjusts the intracellular Mg^{2+} concentration at about half of the equilibrium value. Experiments with skeletal (Blatter, 1990) and cardiac muscles (Rotevatn et al., 1989) and with nerve cells (Somogyi, 1987) indicated a Na^{+}/Mg^{2+} exchange transport mechanism similar to the cell membrane Na^{+}/Ca^{2+} exchange.

Magnesium interactions in cell functions

Magnesium acts as an enzyme substrate for kinases, ATPases, GTPases and cyclases, and also activates numerous enzymes (e. g. adenylate cyclase and $(\text{Na}^+, \text{K}^+)\text{-ATPase}$) directly. It can regulate cellular iontransport processes, like the $\text{Na}^+\text{-K}^+\text{-2Cl}^-$ cotransport system, which presumably plays a role in the pathogenesis of hypertension (Ellory et al., 1983; Flatman, 1988), and also the $\text{Na}^+/\text{Ca}^{2+}$ exchange, pH-dependent Cl^- fluxes (in competition with the H^+ ion), which can be inhibited with disulphonic acid stilbene compounds (SITS or DIDS) and also the voltage-dependent Na^+ and Ca^{2+} channels (Hartzell and White, 1989). It can alter the affinity of nerve cell receptors, such as D_2 dopamine receptors (Watanabe et al., 1985), opioid receptors (Demoliou-Mason and Barnard, 1986; Rodriguez et al., 1992), A_1 adenosine receptors (Parkinson and Fredholm, 1992), and the muscarinic cholinergic receptors of the heart (Sulakhe et al., 1990). The free Mg^{2+} ion modulates the activation of the hormone-sensitive adenylate cyclase, but it has also been found that there is a relatively small subcytoplasmic magnesium pool (some 2% of the total cellular magnesium) which is linked to the hormone-sensitive magnesium transport (influx) and regulates the hormone response of the cell (Maguire, 1984).

Synaptic effect of magnesium

It has long been observed that magnesium blocks neuromuscular transmission by inhibiting acetylcholine release; in this respect its effect is opposite to that of calcium (Del Castillo and Engbaek, 1954). Magnesium exerts a similar inhibitory effect in sympathetic ganglions (Hutter and Kostial, 1954), and in synapses of the central nervous system (Katz and Miledi, 1968). Since these early electrophysiological observations, magnesium at high concentration has been routinely applied to arrest synaptic transmission (Czeh and Somjen, 1989), especially in light of the "calcium hypothesis" of neurotransmitter release (Katz, 1971).

Apart from electrophysiological studies, ultrastructural findings indicate that a higher magnesium concentration results in a significant increase in the number of synaptic vesicles in the presynaptic terminals. This has been shown with electron microscopic fixatives containing elevated magnesium level (Birks, 1974; McKinlay and Usherwood, 1978) and also by long- and short-term magnesium exposure in tissue cultures (Bird, 1980; Janka and Jones, 1982a, 1984). Figure 7.5 demonstrates the effects of exposure to various cations on synaptic profiles in cerebral cortex tissue cultures; the schematic drawing is based upon quantitative morphological data. The application of even 11 mmol/dm^3 magnesium in the culture medium *in vitro* for 3 weeks did not significantly influence the numbers of developing synapses and glia gap junctions in brain tissue (Janka and Jones, 1982b). Data are also available that the metabolic communication of gap junction-type cell connections (if these are already developed) is not affected by magnesium withdrawal, while presence of the Mg^{2+} ion is necessary for the metabolic communication of those newly developed, similarly to neurite formation induced by nerve growth factor *in vitro* (Koike, 1983).

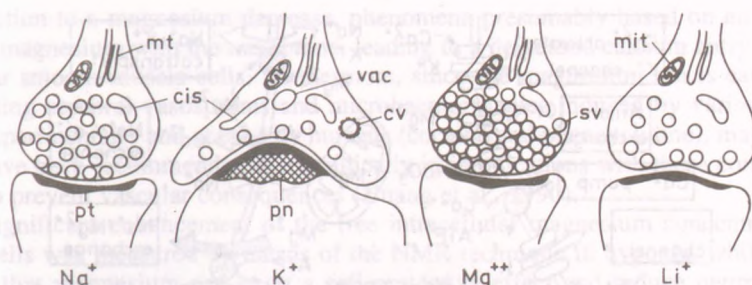


Fig. 7.5. Schematic drawing, based on morphometric parameters, of cerebral cortical synapses in culture after incubation in different ionic media

In contrast with the depolarizing and neurotransmitter-releasing effects of the K^+ ion, in synapses exposed to a Mg^{2+} medium a significantly increased number of synaptic vesicles can be observed in the presynaptic terminal, and the curvature of the active zone does not change as compared with the control (Na^+ medium) synapses. This effect can be explained by the inhibitory action of the Mg^{2+} ion on neurotransmitter release. Abbreviations: cis – cistern; cv – coated vesicle; mit – mitochondrion; mt – microtubule; pn – postsynaptic network; pt – postsynaptic membrane thickening; sv – synaptic vesicle; vac – vacuole (Janka and Jones 1982a)

Magnesium and *in vitro* seizure models

While an enhanced magnesium concentration in *in vitro* systems leads to the inhibition of neurotransmitter release and synaptic transmission, resulting in silenced synapses, a decrease of the magnesium level in the bathing medium induces an increase in electric activity in certain brain regions and in the excitability of the neurones. Spontaneous seizure-like activities can be detected in slices of rat hippocampus and entorhinal cortex in magnesium-free medium, with ictal and interictal periods, which can be alleviated with various anticonvulsive substances (Mody et al., 1987; Ashton et al., 1988; Jones, 1989). This system can therefore be regarded as an “*in vitro* epilepsy model”.

It has also been shown that extracellular Mg^{2+} ion plays a role in the blockade of cation channels associated with the N-methyl-D-aspartate (NMDA) receptor subtype of the glutamate receptor (widespread in the central nervous system; physiologically activated by the endogenous excitatory neurotransmitters glutamate and aspartate). Consequently, elimination of the blockade, i. e. reduction or depletion of the extracellular magnesium level, results in the activation of NMDA receptor-linked channels, presumably leading to “epileptic” electric phenomena (Brorson, 1991). Recent studies demonstrate that a decrease of the magnesium level in the bathing medium leads to the appearance of spontaneous epileptiform discharges in slices of human epileptogenic neocortex maintained *in vitro*, a phenomenon explained by removal of the voltage-dependent gating effect of extracellular magnesium on the NMDA ionophore (Avoli et al., 1991). Besides electrophysiological data, biochemical findings indicate that the Mg^{2+} ion in physiological concentration can inhibit endogenous amino acid neurotransmitter-stimulated membrane inositol phospholipid hydrolysis as a signal transduction mechanism (Nicoletti et al., 1987). Figure 7.6 illustrates the membrane transport processes, neurotransmitter release and receptor-mediated signal transduction mechanisms of a nerve cell (synapse as a model) and also some proved or putative effects exerted on these functions by magnesium.

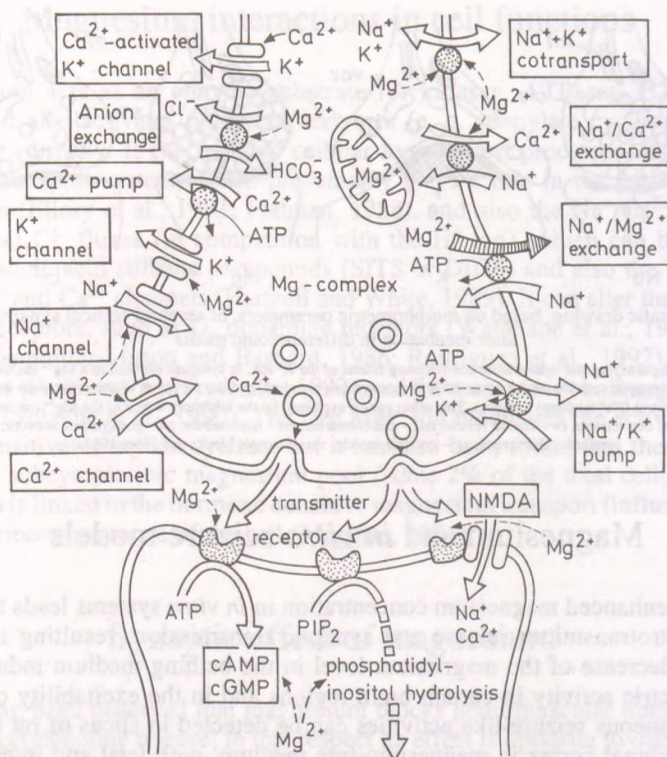


Fig. 7.6. Some assumed interactions of the Mg^{2+} ion with neural cell membrane functions

In the maintenance of the uneven intra/extracellular distribution of Mg^{2+} , a Na^+/Mg^{2+} exchange mechanism, similarly to the Na^+/Ca^{2+} exchange, may play a role. This transport is energy-dependent (ATP hydrolysis). The Mg^{2+} ion exerts an inhibitory effect on the voltage-dependent Ca^{2+} channel, thereby decreasing influx of the Ca^{2+} ion and consequently neurotransmitter liberation. Magnesium also influences the functioning of the voltage-dependent Na^+ and K^+ channels, and inhibits the bumetamide-sensitive $Na^+ + K^+$ cotransport and the pH-dependent Cl^- efflux. The intracellular Mg^{2+} ion activates the membrane (Na^+ , K^+)-ATPase-dependent K^+ uptake, and a magnesium deficiency leads to a K^+ loss and a resting membrane potential decrease of the cell, which in turn makes the cell more excitable. The mitochondria accumulate Mg^{2+} through energy-consuming transport. The Mg^{2+} ion blocks the function of the NMDA receptor-linked cation channel and modifies the binding characteristics of other neurotransmitter or modulator receptors and signal transduction (phosphoinositide hydrolysis, cyclic nucleotide systems (*cAMP* and *cGMP*)) mechanisms. Abbreviations: PIP_2 , phosphatidylinositol 4,5-bisphosphate; ATP, adenosine triphosphate; NMDA, N-methyl-D-aspartate

Cerebral blood vessels and magnesium

The relationship of hypertension and magnesium is the topic of another section in this book. A magnesium-free diet has led to a decrease in the lumen size of the microvessels and to hypertension under experimental conditions (Altura et al., 1984). Nevertheless, some recent data suggest that, contrary to previous findings, the magnesium content of the red blood cells in essential hypertension is not reduced, but elevated (Kjeldsen et al., 1990). Arterioles of the pia mater respond with vasodilation to an increase of the extracellular magnesium concentration and respond with vaso-

constriction to a magnesium decrease, phenomena presumably based on an interaction of magnesium with the membrane, leading to a decreased calcium entry into the vascular smooth muscle cells. Furthermore, since the magnesium ion is capable of preventing cerebral vasospasms and microhaemorrhages induced by various drugs used experimentally and abused by humans (cocaine and phencyclidine), magnesium salts have been recommended therapeutically in intoxications with these compounds so as to prevent vascular consequences (Huang et al., 1990).

A significant enhancement of the free intracellular magnesium concentration in brain cells was measured by means of the NMR technique in hypoxia, while it was shown that magnesium can exert a cell-protective effect and reduce neurotoxicity through inhibition of the calcium influx in anoxic (*in vitro*) and ischaemic (*in vivo*) models. By virtue of these actions and the NMDA receptor-blocking effect, therefore magnesium sulphate has been suggested for the safe and potentially efficient therapy of certain cases of cerebral ischaemia, particularly if it is accompanied by convulsions (Goldman and Finkbeiner, 1988). In experiments on rats with cerebral ischaemia produced by ligation of the middle cerebral artery, magnesium sulphate infusion significantly increased blood flow in the ischaemic brain regions. However, the calcium channel antagonist nifedipine lacked this effect (Chi et al., 1990).

Neural symptoms of magnesium deficiency

The first experiments involving studies on animals fed a magnesium-deficient diet for several weeks date from early 1930s (Kruse et al., 1932). The animals became excitable and irritable, and exhibited tremor, muscle spasms, increased reactivity and tonic-clonic fits, leading eventually to death. Increased excitability in magnesium deficiency can be observed at the cellular level too; inadequate activation of the membrane (Na^+ , K^+)-ATPase results in a loss of potassium from the cell, which decreases the resting membrane potential, leading to an enhanced excitability of the cell (Aikawa, 1981). The human magnesium-deficiency state may be characterized by various neurologic and psychiatric symptoms, such as the Trousseau and Chvostek signs, tremor, fasciculation, muscle weakness, convulsions, hyperreflexia, personality change, and occasionally coma (Reinhart, 1988). The increased neural excitability observed in magnesium deficiency is correlated with the synaptic and cell membrane effects of magnesium and can be regarded as latent tetania or spasmophilia (Durlach, 1988).

Data recorded in the USA indicate that a proportion of the population suffer from hypomagnesaemia due to a deficient magnesium intake with the food (Reinhart, 1988). Neurotic symptoms may be induced by latent tetania, and symptoms such as anxiety, pharyngeal paresthesia, dyspnoea, chest discomfort, tremor, morning asthenia, headache, neck pain, giddiness, fainting and sleeping disturbance may develop, but muscle spasms, numbness in the extremities, radical pains, myoclonus and vegetative signs (palpitation, sweating, etc.) may also occur. Formulation of a proper diagnosis is helped by positive Trousseau and Chvostek signs, the hyperventilation test, the presence of mitral prolapse, diminished magnesium contents in the plasma and red blood cells with normal calcium levels, and EMG, EEG and ECG measurements (Durlach, 1988). Among the psychological tests, the subscales (hysteria, depression,

hypochondria, neurasthenia, psychasthenia and schizophrenia) of the Minnesota Multiphasic Personality Inventory (MMPI) displayed an inverse correlation with the plasma magnesium concentration (Durlach, 1988). As concerns these findings, the relationship of the "neurotic triad" is to be stressed, as is the fact that no correlation could be observed with the magnesium content of the red blood cells. Development of vertical nystagmus was also described in severe magnesium depletion.

Magnesium status in neurologic disorders

In control and patient populations, the magnesium concentrations of the CSF were found to be higher than those of the serum. In control subjects ($n = 112$), the average CSF/serum magnesium ratio was $1.37 (\pm 0.14, \text{SD})$, while the changes in the different patient groups did not reach the level of significance (Heipertz et al., 1979). The patient group with intracerebral haemorrhage was an exception in this respect; an elevated magnesium level was detected in the CSF, which was presumably associated with the cell necrosis. The average magnesium concentration in the CSF of patients with multiple sclerosis did not differ from the control; recent data obtained from autopsies of this disease, however, demonstrated significant decreases in the magnesium contents of the brain and spinal cord, and particularly in the white matter containing demyelinated plaques (Yasui et al., 1990).

In patients with Duchenne muscular dystrophy, the magnesium content of the muscle was decreased to about half, while the calcium level was increased, which might suggest a possible pathogenetic significance of magnesium, besides calcium in this disease (Bertorini et al., 1982). Further, a case of progressive cardioskeletal mitochondrial myopathy associated with a chronic magnesium deficiency was reported recently (Riggs et al., 1992). The role of environmental factors was postulated in the pathogenesis of amyotrophic lateral sclerosis (ALS, motoneurone disease) and Parkinsonism-dementia complex, which occur with enhanced frequency in the Chamorro population living on Guam Island in the Western Pacific Ocean; this was explained in terms of the lower magnesium and calcium contents and higher aluminium contents of the soil and drinking water, and the consequent neurotoxicity. Experimental quantitative morphological data indicate that degenerative processes of the motoneurons in the primate spinal cord are amplified by chronic deficient magnesium and calcium intakes and an increased aluminium intake (Yoshida et al., 1990). However, recent studies reveal that, in the southern part of the Kii peninsula in Japan, where the incidence of ALS is also high and some features of the soil and drinking water are similar to those on Guam (i.e. unusually low magnesium and calcium and high aluminium levels), postmortem analysis demonstrated significant decreases in magnesium and increases in calcium concentrations in various brain areas of ALS cases, as compared with the controls (Yasui et al., 1992).

Results obtained from animal experiments might be of potential clinical significance; these reveal that the intracellular free Mg^{2+} ion concentration in the brain decreases following head trauma, while the sodium and tissue water contents do not. The reduction in brain tissue magnesium content ensues immediately after the trauma; its extent is dependent on the severity of the trauma and might be a critical factor in

the formation of irreversible tissue damage. It was also suggested that the administration of magnesium chloride after head trauma can prevent the neurological sequelae of brain injury (McIntosh et al., 1989).

Magnesium and convulsion

It might follow from Section "Magnesium and *in vitro* seizure models" that the clinical therapeutic efficacy of magnesium in controlling the seizure activity of the brain is unambiguous. Nevertheless, with regard to the debate in the literature on eclampsia and pre-eclampsia in this respect, this is clearly not true. Clinicians overseas, and particularly gynaecologists, regard the parenteral administration of magnesium sulphate as ideal anticonvulsive treatment (Dinsdale, 1988; Sibai, 1990). However, there are opponents too (Kaplan et al., 1988), who prefer the application of traditional anticonvulsants of documented value (e.g. phenytoin). The controversy is continuing, though up-to-date reliable data are relatively scarce (Sibai, 1990; Brorson, 1991).

Magnesium decreases the activity of the epileptic focus induced experimentally with penicillin and is also an efficacious depressant *in vitro*. However, magnesium sulphate is not often applied in human epileptic seizures or status epilepticus (Kaplan et al., 1988). The blood-brain barrier is fairly resistant to changes in magnesium concentration, and thus the cerebral and CSF magnesium levels hardly vary. Both decreased and increased CSF magnesium contents have been described in epileptic patients; though the data are not conclusive, a tendency to an increase seems more characteristic. A decreased magnesium level may be a result of the administration of anticonvulsants. The protective effect of magnesium sulphate against epileptic seizures has been reported in large populations treated in alcohol detoxication centres (Daus et al., 1985).

Magnesium and chronic alcoholism

Chronic alcoholism can be regarded as one of the most important causes of a secondary magnesium deficiency. Factors related to an insufficient food intake or absorption, and excessive loss via the kidney or some other route, might play a role in the development of a magnesium deficiency. The stress factor cannot be neglected either, since the released catecholamines facilitate the formation of magnesium chelates by the stimulation of lipolysis, resulting in the formation of free fatty acids, and enhance the elimination through the kidney (Durlach, 1988). Magnesium depletion leads to hyperexcitability of the central nervous and neuromuscular systems, manifested in symptoms such as tremor, myoclonus, agitation, anxiety, and depressive and aggressive behavioural signs. In a more severe form, withdrawal syndrome, alcoholic seizure, delirium tremens, alcoholic encephalopathy, alcoholic polyneuritis and myopathy, and psychotic episodes may occur. Magnesium is frequently applied in clinical practice to control alcoholic withdrawal syndrome and pre-delirium tremens, while

some centres report favourable results on magnesium treatment of alcoholic convulsions (Daus et al., 1985). It should be noted that vitamin B₁ is involved in synergism with magnesium, and their combined administration is therefore justified in the treatment of neural symptoms of alcoholism (e.g. Wernicke's encephalopathy). The synergism of magnesium can be observed with other vitamin Bs. A magnesium deficiency may play a role in the pathogenesis of withdrawal states with other (e.g. barbiturate) origins (Aikawa, 1981).

Magnesium and affective-emotional disorders

Stress stimulates magnesium voidance through the increase of catecholamine secretion. In addition, as regards magnesium homeostasis, it has an unfavourable effect on the metabolism of two magnesium-retaining factors: insulin and taurine (Durlach, 1988). A correlation has been found between the extent of stress and the magnesium content of the urine (Classen, 1981) but not with the magnesium parameters of the blood. It should be noted that the connection between the magnesium status and stress is mutual: stress can induce a magnesium deficiency, and a magnesium deficiency developing for other reasons can increase the sensitivity of the organism to stress. These combined effects may impair the functioning of the immune system too, thereby decreasing the resistance to infections.

Lowered magnesium levels have been observed in affective disorders, particularly before treatment. The alteration was more pronounced in females than in males, more in unipolar than in bipolar affective illness, and rather in depression than in mania (Durlach, 1988). It is also known that the plasma magnesium concentration increases upon prophylactic maintenance therapy of mood disorders with lithium (Herzberg and Herzberg, 1977; Lipcsey et al., 1986) which has been suggested as a predictive parameter for the potential efficacy of lithium treatment (Carman et al., 1974). The interrelationship of magnesium and lithium is not really understood, but they presumably interact in numerous membrane and metabolic processes, since their similarity in ionic radius is striking (Lipcsey et al., 1986). However, recent studies reported significant positive correlations between the severity of depression measured by clinical scales and the serum magnesium concentration (Linder et al., 1989; Hasey et al., 1993). In addition, the serum magnesium content showed a negative correlation with the serum thyrotropin level in depressed subjects, and a tendency to, but non-significant association with T4 (Hasey et al., 1993).

It is rather difficult to form a clear view regarding anxiety symptoms since the syndrome of magnesium deficiency and the symptoms of neurosis (anxiety) exhibit a series of similarities. Further, they intermingle and the real cause is difficult to explore. The combined administration of anxiolytics and magnesium can therefore be recommended. The inverse relationship of the "neurotic triad" of the MMPI test and the plasma magnesium level has already been mentioned. An intriguing observation was the lower magnesium content in CSF of subjects who attempted suicide. Recent data corroborate the significant decrease in magnesium content of the red blood cells in pre-menstrual syndrome, which underlines the significance of combined magnesium (and vitamin B₆) therapy in this state (Sherwood et al., 1986).

Magnesium and other psychiatric disorders

Heterogeneous data are available on the magnesium status in schizophrenia, which might well be due to methodological reasons, as the research parameters differ widely. Nevertheless, a magnesium excess is more acceptable, as is the observation that neuroleptics (phenothiazines and butyrophenones alike) deplete magnesium, and this correlates with the development of extrapyramidal symptoms. Hypomagnesaemia found in patients with chronic schizophrenia is most probably a consequence of neuroleptic treatment (Durlach, 1988).

A relative magnesium deficiency with a high aluminium uptake by the cerebral cells and a deleterious magnesium-aluminium interrelationship have been postulated in the pathogenesis of Alzheimer's disease too (Glick, 1990), while lowered magnesium contents of the red blood cells and platelets have been observed in Down syndrome.

Several studies on treatment of autism in childhood have confirmed that the combined administration of magnesium and a high dose of vitamin B₆ has a beneficial effect on the behavioural symptoms. Further, it favourably affects the electrophysiological (evoked potential) and biochemical parameters (urinary homovanillic acid excretion). None of these changes was observed if either magnesium or vitamin B₆ was administered alone (Martineau et al., 1985). A survey of 4,000 questionnaires reflecting the opinions of the parents also suggested a favourable effect of combined treatment with magnesium and vitamin B₆.

Neural symptoms of hypermagnesaemia in clinical practice

The incidence of hypermagnesaemia is lower than that of a magnesium deficiency. Its most frequent cause is kidney failure, particularly if there is an enhanced magnesium intake (e.g. therapy). From the effects of magnesium on synapses and cellular membrane functions (cf. corresponding Sections), it has been concluded that the clinical neural symptoms originate from the blockade of neuromuscular transmission and neurotransmitter release. A decreased muscle tone, ECG changes, hyporeflexia, areflexia (tendon reflexes), and muscular and respiratory paralysis accompany the increase in serum magnesium level (from 1.5 mmol/dm³ upward). It is particularly important to test the state of the tendon reflexes: on the appearance of areflexia, measures should be taken to be ready for artificial respiration. Treatment of hypermagnesaemia includes the cessation of magnesium intake, intravenous administration of calcium (as antagonist), or peritoneal or haemodialysis if necessary (Reinhart, 1988).

Magnesium administration can provoke myasthenia gravis (Bashuk and Krendel, 1990); it follows from the physiological effects of the magnesium ion that its therapeutic application for other purposes is contraindicated in this disease, where the neuromuscular transmission is otherwise impaired. Periodic paralysis with hypermagnesaemia may be the only disease in which the elevated serum magnesium concentration is not of iatrogenic origin. It resembles familial hypokalaemic periodic paralysis.

Similarly to the hypokalaemic type, the inheritance is recessive, but the plasma potassium level is normal. However, the plasma magnesium concentration is about 2.5 times the normal value. Administration of potassium or insulin does not help; instead, digitalis and lithium may be used therapeutically (Emser, 1982).

7.5. The role of magnesium metabolism in physiologic and pathologic pregnancy

Magnesium metabolism in pregnancy

The first data referring to the role of magnesium in human pregnancy originate from Michel (1899), who found that the magnesium content of the human foetus increased from 0.069 g to 0.812 g between the fourth month of pregnancy and term.

The magnesium concentration of the blood in healthy adults is usually about 0.9 mmol/dm³ (Seelig and Berger, 1974). Since most of the magnesium is located intracellularly, its concentration in the tissues is higher, e.g. in the myometrium it is 16.6±2.5 mmol/kg on a dry mass basis. A survey of the literature by Seelig (1981a, b) indicated that Krebs and Briggs (1923) and Bogart and Plass (1923) were the first to report a decreased serum magnesium level in pregnancy. In 75% of the publications reviewed, the serum magnesium concentration was found to be 20% lower in pregnant than in non-pregnant women. Spätling et al. (1989) reported 0.83±0.05 mmol/dm³ in non-pregnant women and 0.71±0.07 mmol/dm³ in the 40th week of pregnancy. The results of the study by Baltzer and Daume (1976) are presented in Fig. 7.7. A number of investigators observed a similarly decreasing serum magnesium concentration during pregnancy (Mahran and Hanna, 1968; Rosner and Garfien, 1968; Stefanini et al., 1968; Lim et al., 1969). The almost consonant data in the literature appear to justify the conclusion of Aikawa (1981): "There may exist a subclinical deficiency of Mg even in normal pregnancy." This seems to be acceptable, even if the dilution

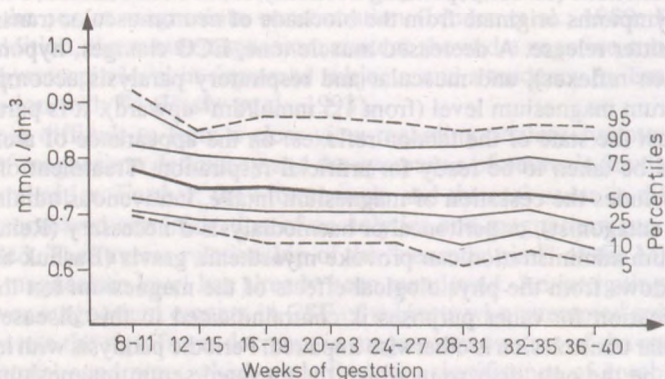


Fig. 7.7. Magnesium serum levels in pregnancy (Baltzer and Daume, 1976)

effect caused by the plasma volume expansion in normal pregnancy is considered, together with the fact that the serum magnesium concentration alone is of limited value in the determination of a magnesium deficiency.

The literature data indicate that during pregnancy the normal serum magnesium concentration is between 0.7 and 1.05 mmol/dm³. Although an increased urinary magnesium excretion has been demonstrated in pregnancy (Spätling et al., 1983), most authors agree that a magnesium deficiency in pregnancy is caused by an insufficient alimentary intake of magnesium. Broad limits of 400–700 mg have been postulated by the different authors for the daily magnesium need (Holtmeier, 1968; Fischer and Fischer, 1981; Kovács, 1989), but it is generally agreed that the demand is greater during pregnancy and lactation than in a non-pregnant state (Kuti et al., 1982; Rigó et al., 1987; Kovács, 1989). The daily magnesium requirement in pregnancy is generally regarded as 10–15 mg magnesium per kg body mass, which in most cases is insufficiently covered by the present alimentary habits.

The usual daily dietary intake of magnesium is estimated as between 230 mg (Holtmeier, 1968) and 350 mg (Ising et al., 1981), or 5 mg/kg body mass (Rigó et al., 1987). These results support the significance of regular magnesium supplementation in the course of antenatal care.

Magnesium supplementation during pregnancy

Various observations have indicated that magnesium treatment for different reasons during pregnancy has an advantageous influence on the outcome of the pregnancy. In a study in Germany in the late 1960s, the outcome of nearly 8000 pregnancies was analysed, in the course of which it was observed that among pregnant women who regularly used magnesium-containing antacid drugs for gastrointestinal complaints the proportions of spontaneous abortion and premature labour were lower than usual (Koller, 1983). Retrospective analysis of the results in a group of pregnant women treated for threatening miscarriage or premature labour with beta-mimetic drugs supplemented with magnesium to prevent cardiac side-effects indicated that the significant reductions in incidence of pre-eclamptic toxæmia and intrauterine growth-retarded fetuses were most probably attributable to the magnesium therapy (Conradt et al., 1984). In the study by Kuti et al. (1982), the incidence of spontaneous abortion was lower, the duration of pregnancy was longer and the average birthweight was higher in the group of pregnant women treated with magnesium citrate as compared with the non-treated control group.

The results of three prospective double blind comparative clinical trials were reported recently (Kovács et al., 1988a, b; Spätling and Spätling, 1988; Sibai et al., 1989).

In the randomized study by Kovács et al. (1988a, b), the patients were given either Magnesium-5-Longoral or placebo, which was identical in appearance to the magnesium pills. Patients received 3 pills daily (5 mmol magnesium-aspartate) from the first day they attended the antenatal clinic. They were provided with a month's supply, and the same quantity at each 4-weekly visit. 997 patients were recruited; 12 excluded for various reasons (*Table 7.3*).

Table 7.3. Composition of study groups (Kovács et al., 1988b)

Number of admitted patients		Total 997	Magnesium treatment 490	Placebo treatment 507
Excluded				
not pregnant	4			
twins	7	12	5	7
anencephalus	1			
Evaluated cases		985	485	500

Of the remaining 985 subjects, 485 were given magnesium and 500 placebo. In the majority of cases, the treatment was started before the 9th week of pregnancy, and in almost all of them before the end of the first trimester. For different reasons, 129 pregnant dropped out of the study. Thus, the outcome of pregnancy was known in 856 cases. 60 pregnancies ended in miscarriage (7.1%) and 796 in delivery (92.9%). The proportion of miscarriages was slightly lower in the magnesium group than in the placebo group, but the difference was negligible (Table 7.4). The majority of the miscarriages, 41 cases, took place while the first supply of medication was being taken, i.e. during less than 4 weeks' treatment. Effective results cannot be expected to manifest themselves after such a short period of medication.

The evaluation of the effect of magnesium treatment on birthweight showed that only approximately one-third of the low-birthweight (less than 2500 g) infants (36.8%) were in the magnesium group, with about two-thirds (63.2%) in the placebo group. A statistical analysis (chi-square test) of the data revealed a significant advantage of magnesium treatment ($p < 0.05$). Analysis of the onset of labour relative to gestational age proved that the ratio of births before the 259th day of pregnancy was much higher in the placebo group (62.3%). Statistical evaluation demonstrated a significant difference ($p < 0.05$) between the results of the magnesium and placebo group. The ratio of small for gestational age newborns (birthweight below the 10th percentile) was significantly lower in the magnesium group ($p < 0.001$) (Table 7.5). It was found that the proportion of magnesium-treated cases progressively increased in the higher percentile categories. This seems to prove the effect of magnesium substitution on foetal growth. The study population was analysed as regards EPH gestosis (pre-eclampsia). During checks at the antenatal visits, a gestosis index greater than 0 occurred almost twice as frequently in the placebo group as in the magnesium group. The difference was statistically significant.

The study of magnesium substitution stemmed from the hypothesis that a certain number of pregnant in the population suffered from a magnesium deficiency, and

Table 7.4. Outcome of pregnancy (Kovács et al., 1988b)

	Miscarriage	Birth	Total
Magnesium-treated	28 (6.4%)	400 (93.6%)	428
Placebo-treated	32 (7.5%)	396 (92.5%)	428
Total	60 (7.1%)	796 (92.9%)	856 (100%)

Table 7.5. Comparison of certain gestational age, birthweight and weight percentile data in the magnesium and placebo-treated groups (Kovács et al., 1988b)

	<i>n</i>	Gestational age < 259 days	Birthweight < 2500 g	Birthweight percentile < 10th
Magnesium-treated	400	33 (8.3%)	18 (4.5%)	33 (8.3%)
Placebo-treated	396	54 (13.6%)	31 (7.8%)	59 (14.9%)
Total	796	87 (10.9%)	49 (6.2%)	92 (11.5%)
Significance		$p < 0.05$	$p < 0.05$	$p < 0.001$

that if this could be corrected by an increased magnesium intake during pregnancy, the obstetric results would improve. There were no data on the actual magnesium supply of the patients, but the difference in obstetric results between the patients given magnesium or placebo indicate that at least a proportion of the patients most probably had a magnesium deficiency. The results disclosed a convincing difference between the magnesium and placebo-treated groups. The statistical analysis showed that a statistical significance level of $p < 0.05$ was reached in the majority of comparisons. Greater differences cannot be expected, since it may be supposed that in each group only a certain number of patients displayed a degree of magnesium deficiency sufficient for the effect of supplementation to be noticeable. For the remaining patients, the outcome of the pregnancy would probably have been the same without the treatment.

To summarize the results of the study by Kovács et al. (1988a, b), it can be concluded that magnesium supplementation in a dose of 15 mmol/day during pregnancy considerably improved the outcome of the pregnancy as compared with the outcome in the group given placebo. In the magnesium-treated group, there were fewer premature births, and the number of low-birthweight newborns and the proportion of intra-uterine growth-retarded fetuses were lower. These results permit the conclusion that magnesium supplementation during pregnancy has a beneficial effect on the obstetric results. It is therefore advisable to provide magnesium treatment in the course of antenatal care from as early a stage of pregnancy as possible.

In the study by Spätling and Spätling (1988) at the Department of Obstetrics of the University of Zürich, 568 pregnant women were treated daily either with 15 mmol magnesium aspartate or with a placebo containing aspartic acid; the daily dose was taken in six tablets at uniform intervals. The method of allocation was the even or odd birth date of the patient. 278 patients were admitted to the magnesium group and 290 received placebo. Normal and high-risk patients were included in the study, all of them before the 16th week of their pregnancy. Notably fewer women needed hospitalization in the magnesium group (44) than in the placebo group (65). Among the indications for admission to hospital, haemorrhage, incompetent cervix and preterm labour were significantly more frequent in the placebo group. For the women treated with magnesium, the gestational age at birth of the newborns was significantly higher, their average birthweight was higher, and the proportion of growth-retarded fetuses (below the 10th percentile) was lower. The better condition of the newborns in the magnesium-treated group was expressed in the lower frequency of referral to the neonatal intensive care unit: only 20, compared with 36 in the placebo-treated group.

It was concluded that magnesium supplementation was associated with significant reductions in maternal and foetal morbidity both before and after delivery. The results of the study suggested that magnesium supplementation during pregnancy may have important benefits.

The studies by Kovács et al. and Spätling et al. led to the same conclusions, but a similar clinical trial by Sibai et al. (1989) indicated quite different results. In this latter trial, 185 primigravid women from between 13 and 24 weeks of pregnancy received oral magnesium supplementation with 15 mmol magnesium aspartate daily, and were compared with 189 placebo-treated patients with regard to the outcome of pregnancy and the development of pre-eclamptic toxæmia. The design of this study was essentially different from the two previously reported ones because both the magnesium and placebo groups were treated with an additional 100 mg magnesium dose daily. Thus, low-dosage and higher-dosage magnesium supplementation were compared. The study groups were restricted to primigravidae, and the magnesium supplementation was started at a later stage of pregnancy: an average of 17.8 weeks versus less than 16 weeks (in the majority of cases less than 12 weeks) in the two other studies.

The mean diastolic blood pressure did not exceed 77 mm Hg in any group, and thus a blood pressure-reducing effect of magnesium was not observed.

No difference could be demonstrated in any data relating to the outcome of pregnancy, e.g. the incidence of premature birth, the mean birthweight, or the mean gestational age at delivery.

The serum magnesium levels differed significantly at the end of the study (0.64 mmol/dm³ in the placebo, and 0.69 mmol/dm³ in the magnesium group). The level in the magnesium group, however, was still very low. 90% of the population in the study consisted of indigent, mostly black volunteers, whose basal daily dietary magnesium intake was estimated to amount to 260 mg, which is very low. It appears most probable, therefore, that the existing hypomagnesaemia could not be corrected in most patients, even in the magnesium group. This may be one explanation of the difference between the findings in this study and the two European ones, besides the above-mentioned differences in the study design.

The relatively small numbers of subjects in the study groups might also play a role in the fact that this latter study failed to support the usefulness of magnesium supplementation during pregnancy.

In the study by Skajaa et al. (1991), the magnesium intake was assessed in a Danish population of pregnant women characterized by a generally good socio-economic status. In the population under investigation, the mean magnesium intake, which included intake through food, water and other nutritional supplements, was as high as 445 mg per day. This intake level was high in comparison with estimates in previous surveys based on dietary records. Doyle et al. (1989) and Black et al. (1986) reported an intake of magnesium by pregnant women of about 250 mg and 300 mg/day, respectively.

In the population studied by Skajaa et al. (1991), there was no association between pre-eclampsia, small for gestational age infants or preterm labour and a low intake of magnesium when compared with the intake in normal pregnant women. They concluded, therefore, that routine magnesium supplementation during pregnancy is not recommended for populations of relatively good socio-economic status.

The value of magnesium supplementation in pregnancy was convincingly proved by the clinical data and by the advantageous changes in the outcome of pregnancy. The effect of the supplementation on the serum magnesium level is less unequivocal. In the study by Jaspers et al. (1981), the serum magnesium concentration was followed in 437 pregnant women treated daily with either 15 mmol magnesium aspartate or placebo from before the 16th week of pregnancy. No difference was found between the two groups: the serum magnesium level decreased up to the 20th week of gestation and then remained at that low level until term (Fig. 7.8). The clinical results were

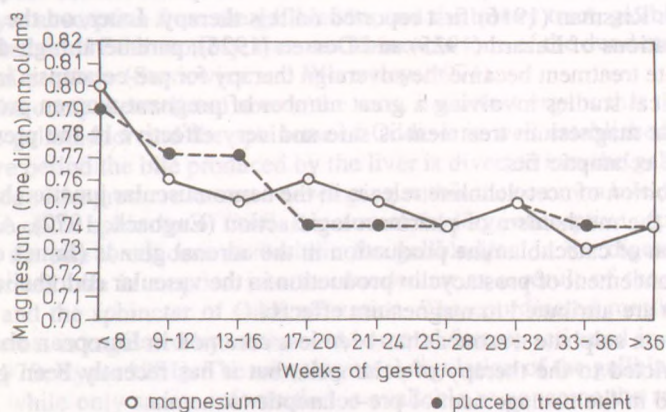


Fig. 7.8. Changes in magnesium serum levels in pregnancy during magnesium or placebo treatment (Jaspers et al., 1981)

much better in the magnesium group, however. The authors supposed that the magnesium treatment was effective in eliminating the latent magnesium deficit, in increasing the intracellular magnesium content and in completing the magnesium stores, and its action is not reflected in the serum magnesium level. This hypothesis was supported by the data of Dyckner et al. (1988). In their investigations, the intracellular magnesium concentration in the striated musculature was significantly increased following magnesium aspartate treatment, but the serum magnesium concentration remained unchanged. In contrast, Bartl and Riss (1984) found a notable increase in serum magnesium level in pregnant women as soon as 2 weeks following the start of treatment with magnesium aspartate for cramps in the leg.

In the course of treatment with magnesium in pregnancy, the selection of the preparation and the problem of dosage should be considered. On oral administration, attention should be paid to the degree of absorption and the laxative effect of magnesium. Several investigations have proved that magnesium aspartate is superior to other magnesium salts. Aspartic acid has an extraordinary affinity for the intracellular space, where it can reach a concentration 200 times higher than that in the serum (Wischnik and Weidinger, 1985). There is experimental evidence that cations bound to aspartic acid can pass the cell membranes more quickly than in other bindings (Staib and

Kretzschmar, 1968; Ring et al., 1975). The laxative effect of magnesium aspartate is significantly lower than that of magnesium sulphate. The daily intake of 15–20 mmol magnesium aspartate is therefore well tolerated in a long-term treatment lasting for weeks or throughout pregnancy.

Magnesium treatment of pre-eclampsia

Magnesium has been used in the treatment of eclampsia since the early decades of this century. Rissman (1916) first reported on this therapy. Later, on the basis of the recommendations of Lazard (1925) and Dorsett (1926), parenteral high-dose magnesium sulphate treatment became the sovereign therapy for pre-eclampsia in the United States. Clinical studies involving a great number of pregnant women provided clear evidence that magnesium treatment is safe and very effective in the prevention and treatment of eclamptic fits.

The inhibition of acetylcholine release in the neuromuscular junction has a significant role in the mechanism of pharmacologic action (Engback, 1972). Additionally, the inhibition of catecholamine production in the adrenal glands (James et al., 1988) and the enhancement of prostacyclin production in the vascular endothelium (Watson et al., 1986) are attributed to magnesium effects.

Magnesium sulphate treatment has been less common in European obstetrics, and mainly restricted to the therapy of eclampsia, but it has recently been gaining ever more ground in the management of pre-eclamptic toxæmia.

The usual mode of treatment in cases of eclamptic convulsions or in imminent eclampsia is the slow intravenous administration of 4 g magnesium sulphate, followed by a maintenance dose of 1 g/hour magnesium sulphate in an intravenous infusion. Sibai (1990) recommended 6 g as a loading dose and 2 g/hour as a maintenance dose.

Magnesium in the treatment of preterm labour

Intravenous administration of magnesium sulphate is an effective tocolytic treatment mode to inhibit preterm uterine activity (Kiss and Szőke, 1975; Elliot, 1983; Wilkins et al., 1986). This is the method of choice when there are contraindications to beta-mimetic treatment, or it is an alternative method to attempt in cases of unsuccessful beta-mimetic therapy. The usual mode of treatment is an intravenous 2–4 g magnesium sulphate bolus as a loading dose, followed by 1–2 g/hour intravenous maintenance treatment for 24–48 hours. If the symptoms disappear, the maintenance therapy can be continued with the oral administration of 20–30 mmol daily.

Magnesium is useful as a complementary drug in the treatment of premature labour, in addition to the beta-mimetic therapy. The main value of the combined treatment is the possibility for reduction of the effective dose of beta-mimetics (Spätling, 1981), with an accompanying lower risk of cardiac side-effects of the beta-mimetic therapy (Wischnik et al., 1982).

7.6. Magnesium and biliary tract motility

The biliary tract plays an essential role in the discharge of bile into the duodenum. For centuries the tract was considered to be a simple set of tubes with a terminal bulb through which bile would pass passively in response to the pressure gradient between the intrahepatic bile ducts and the duodenal lumen. It is now understood that the bile flow is regulated by means of a complicated neurohumoral mechanism which affects mainly the motility of the biliary tract. The major components of those factors which participate in the control of bile flow are as follows: bile produced by the liver, water and electrolyte absorption from the gallbladder and the biliary tract, gallbladder contraction, sphincter of Oddi motility, the smooth muscle tone of the duodenum, and the intraduodenal pressure (Stasiewicz and Wormsley, 1974).

Among the components listed above, the most important organs that regulate bile flow are the gallbladder and the sphincter of Oddi. It is well established that in the interdigestive period the bile produced by the liver is diverted into the gallbladder, as a consequence of the pressure increase developing within the common bile duct through the resistance of the sphincter of Oddi. Because of the large absorptive capacity of the gallbladder, the bile is concentrated within the gallbladder. In the digestive period, this concentrated bile is emptied into the duodenum as a result of the gallbladder contraction and the sphincter of Oddi relaxation. The coordinated motility of these two components is regulated by neural and humoral factors activated in response to food (Lin, 1975; Ryan, 1981). The neurohumoral regulation of the gallbladder is well established, while only scarce information is available as concerns the regulation of the sphincter of Oddi. The reason for this is the peculiar anatomic location of the sphincter of Oddi, which lies between the duodenal muscle layers in most species, this hampering study of its function independently from the duodenum.

Since cholecystokinin (CCK) plays a central role in the regulation of biliary tract motility, this review will summarize present knowledge on the effects of the magnesium ion (Mg^{2+}) on CCK release, and on the regulation of the gallbladder and sphincter of Oddi motility. The role of magnesium in the catabolism of CCK will also be discussed.

The role of magnesium in CCK release

It has been known since the early years of this century that gallbladder emptying is promoted by the presence of food in the small intestine or intraduodenal hydrochloric acid instillation. Ivy and Oldberg (1928) and Ivy (1934) extracted from the upper small intestinal mucosa of the pig a substance which, when injected intravenously into the dog, caused contraction and evacuation of the gallbladder. They named the substance cholecystokinin. The hormonal nature of the meal-induced stimulus was confirmed by bioassay and radioimmunoassay measurement of CCK (Meyer, 1975; Wiener et al., 1981; Lilja et al., 1982). Studies aimed at exploration of the mechanism of CCK release have demonstrated that, among the nutrients, amino acids (tryptophan and phenylalanine) and fatty acids are the strongest stimulants of CCK release. Divalent cations, such as Mg^{2+} , Zn^{2+} and Ca^{2+} (Fried et al., 1981; Inoue et al., 1981), have

also been shown to be strong stimulants of CCK release, while hydrochloric acid proved to be a rather weak CCK stimulant (Chen et al., 1985). Magnesium sulphate applied intraduodenally has long been used to evoke gallbladder contraction in humans. The Mg^{2+} ion is capable of releasing CCK in both humans and experimental animals (Fried et al., 1981; Inoue et al., 1981), which favours the possibility that magnesium sulphate exerts its gallbladder contracting effect through CCK release (Marx et al., 1987). By means of a rat pancreatic acini bioassay method it was recently shown that in humans intraduodenal magnesium sulphate caused significant elevations in plasma CCK levels. When these levels were compared with the gallbladder contractions, a strong correlation was established (Lonovics, unpublished results). Further evidence of the indirect action of magnesium sulphate was provided by in vitro studies which showed that this salt itself was unable to cause gallbladder contractions (Lonovics et al., 1991c).

The role of magnesium in the mechanism of CCK-stimulated gallbladder contraction and in the regulation of the sphincter of Oddi motility

CCK plays a central role in the humoral regulation of the gallbladder and the sphincter of Oddi. While the gallbladder responds with contraction to CCK stimulation in every species, striking species differences exist as concerns the responses of the sphincter of Oddi. In humans, dogs and cats, CCK causes sphincter of Oddi relaxation, which is accompanied by the absence of phasic contraction. In these species, the sphincter plays a passive role in the bile delivery, directed into the duodenum. In

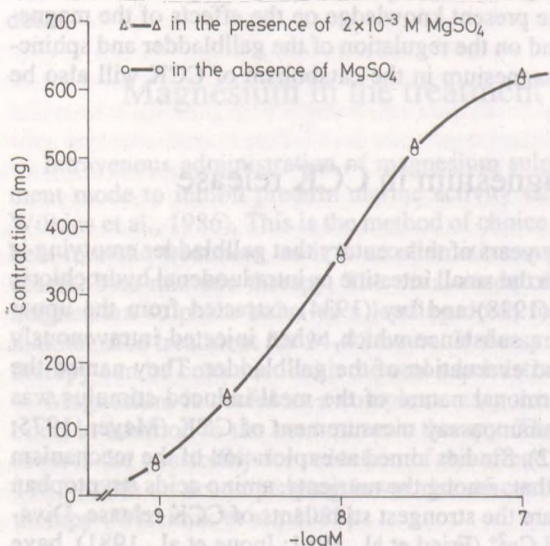
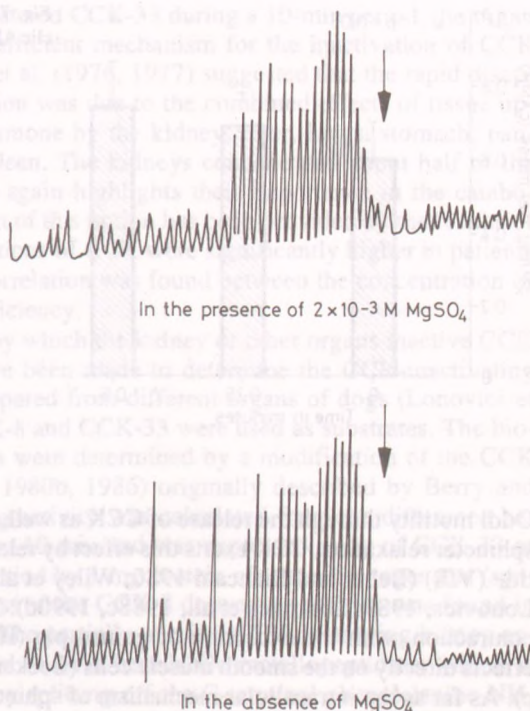


Fig. 7.9. Effect of Mg^{2+} removal on CCK-8-stimulated rabbit gallbladder strip contraction

Fig. 7.10. Effect of Mg^{2+} removal on CCK-8-stimulated isolated rabbit sphincter of Oddi contraction



rabbits, opossums and guinea pigs, CCK enhances the amplitude and frequency of the phasic contractions (in a pharmacologic dose, it causes contraction as well); thus, by stimulating the ejection-like pump mechanism in the sphincter, the sphincter of Oddi actively participates in the bile delivery, as described above (Becker et al., 1982; Harada et al., 1986; Lonovics et al., 1990b, c, d).

Magnesium sulphate is known to stimulate gallbladder contraction indirectly by releasing CCK from the I cells of the small intestine. It is also well established that the Ca^{2+} ion plays a crucial role in the development of gallbladder contraction (Chen and Peikin, 1982; Brotschi et al., 1984; Crochelt et al., 1984; Ryan, 1985; Marx et al., 1987; Lonovics, 1989; Lonovics et al., 1985a, b, c, 1988a, b, 1990a, c). It is not known yet whether magnesium plays any role in the development of CCK-induced gallbladder contraction, e.g. in the stimulation-contraction coupling process. It has recently been shown that, by activating calmodulin and protein kinase C in the gallbladder smooth muscle cells, the Ca^{2+} ion leads to the interaction of contractile proteins and thus results in contraction (Marx et al., 1987; Lonovics et al., 1988a, b, 1990a, c, 1991b; Lonovics and Gomez, 1991a). Since removal of magnesium from the Krebs solution did not influence CCK-induced gallbladder contractions (Fig. 7.9), it is believed that magnesium does not play any role in the stimulation-contraction coupling process of gallbladder smooth muscle cells (Lonovics et al., 1991c).

The role of magnesium in the regulation of sphincter of Oddi motility has not yet been investigated. It may only be speculated that magnesium influences sphincter of

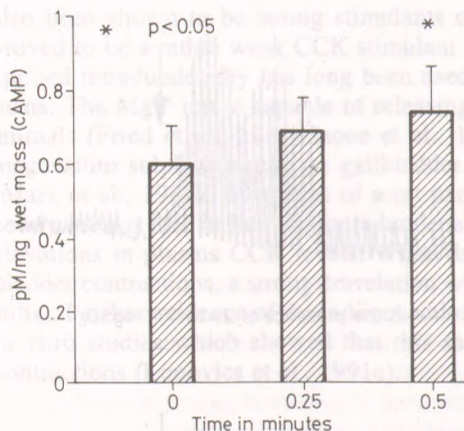


Fig. 7.11. Effect of MgSO_4 (2.5×10^{-2} M) on cyclic AMP levels of isolated rabbit sphincter of Oddi

Oddi motility through the release of CCK as well. In those species where CCK causes sphincter relaxation, CCK exerts this effect by releasing vasoactive intestinal polypeptide (VIP) (Behar and Biancani 1980; Wiley et al., 1988; Varró and Lonovics, 1988; Lonovics, 1989; Lonovics et al., 1988c, 1990d). In those species where CCK causes contraction, with the exception of guinea pig (Harada et al., 1986), CCK exerts its effects directly on the smooth muscle cells (Becker et al., 1982; Lonovics et al., 1990b, c). As far as the intracellular mechanism of sphincter relaxation is concerned, *in vitro* studies indicate that VIP causes relaxation by increasing cyclic AMP levels (Wiley et al., 1988; Lonovics et al., 1991b), while phasic contractions are mediated by calcium (Lonovics et al., 1990b, c, d). *In vitro* results demonstrate that calcium causes contraction by activating calmodulin and protein kinase C, at least in the rabbit sphincter of Oddi (Lonovics et al., 1990c, 1991b). Removal of magnesium did not influence either phasic wave or CCK-8-induced contractions of isolated rabbit sphincters (Fig. 7.10), providing evidence that the magnesium ion does not play any role in the development of myogenic or CCK-8-stimulated contractions of the sphincter of Oddi. On the other hand, magnesium sulphate applied *in vitro*, similarly to nifedipin, relaxed the rabbit sphincter of Oddi and inhibited CCK-8-induced sphincter contractions. The direct inhibitory effect of magnesium sulphate may be explained by a complex mechanism, which includes adenylate cyclase activation (Fig. 7.11) and a Ca^{2+} -antagonistic effect of the Mg^{2+} ion (Lonovics et al., 1991c).

The role of magnesium in the catabolism of CCK

The metabolism of CCK has been studied by means of sensitive and specific radioimmunoassay in humans and dogs. The disappearance half-life of endogenous CCK in humans has been found to be 5–7 min (Harvey et al., 1973), and that of exogenous CCK in both humans and dogs to be 2–3 min (Reeder et al., 1974; Rayford et al., 1975; Harvey et al., 1978; Lilja et al., 1981). Since the kidney has been shown to

extract 56% of exogenously administered CCK-33 during a 10-min period, the organ is thought to provide a rapid and efficient mechanism for the inactivation of CCK (Thompson et al., 1975). Owyang et al. (1976, 1977) suggested that the rapid disappearance of CCK from the circulation was due to the combined effects of tissue uptake and the degradation of the hormone by the kidney, liver, lungs, stomach, pancreas, intestine, gallbladder and spleen. The kidneys concentrated about half of the labelled CCK administered, which again highlights their importance in the catabolism of the hormone. Further support of this notion has been provided by the results of clinical studies: the basal concentrations of CCK were significantly higher in patients with renal failure; and a positive correlation was found between the concentration of CCK and the degree of renal insufficiency.

Since the mechanism of action by which the kidney or other organs inactivate CCK was unknown, *in vitro* studies have been made to determine the CCK-inactivating capacity of tissue homogenates prepared from different organs of dogs (Lonovics et al., 1979, 1980a, 1981, 1986). CCK-8 and CCK-33 were used as substrates. The biologic activities of these CCK forms were determined by a modification of the CCK bioassay method (Lonovics et al., 1980b, 1986) originally described by Berry and Flower (1971); the CCK-destroying activity was calculated from the difference between the CCK potencies at 0 and at 10 min and was expressed as ng of CCK-33 or CCK-8 destroyed during a 1-min period by 1 mg protein of tissue homogenates (specific activity = $\text{ng mg}^{-1} \text{min}^{-1}$). Most of the CCK-8 destroying activity was found in the kidney (Lonovics et al., 1986). The partially purified CCK-destroying kidney enzyme was characterized and proved to be a heat-labile metallopeptidase, which is thought to inactivate the hormone by splitting off the C-terminal phenylalanine- NH_2 of CCK (Lonovics et al., 1986). An attempt was made to reactivate the EDTA-inactivated CCK-destroying enzyme following removal of the EDTA-cation complex by dialysis. The enzyme activity was restored by Mn^{2+} , Ca^{2+} and Mg^{2+} ions, the effectivity decreasing in this sequence (Fig. 7.12). The Mn^{2+} -supplemented enzyme activity was completely restored through the additional application of Ca^{2+} and Mg^{2+} , indicating that these ions may at least partially substitute each other (Fig. 7.13). The CCK-destroying enzyme is therefore considered to be a metallopeptidase, the activity of which depends upon the presence of a cation complex, which includes Mg^{2+} .

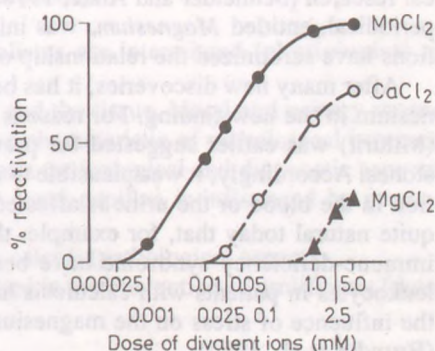


Fig. 7.12. Reconstitution of EDTA-inhibited CCK-destroying enzyme by divalent cations (Lonovics et al., 1986)

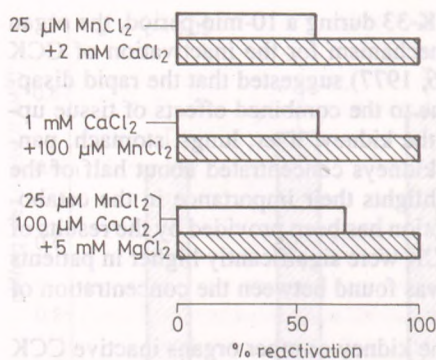


Fig. 7.13. Effects of Ca^{2+} and Mg^{2+} on EDTA-inhibited CCK-destroying activity in the presence of Mn^{2+} (Lonovics et al., 1986)

Summary

On entering the duodenum, magnesium causes gallbladder contractions and species-specific sphincter of Oddi responses by releasing CCK from the I cells of the intestinal mucosa. Magnesium itself does not play any role in the stimulation-contraction coupling process responsible for the CCK-induced gallbladder and sphincter of Oddi responses. In the CCK-induced sphincter of Oddi relaxation, VIP mediation is possible. VIP causes relaxation by increasing cyclic AMP levels, probably by stimulating magnesium-dependent adenylate cyclase or by inhibiting cyclic AMP phosphodiesterase. In the catabolism of CCK, a metallopeptidase-type enzyme plays a central role. The CCK-destroying enzyme originates from the renal cortex and requires a Mn^{2+} , Ca^{2+} and Mg^{2+} complex for its biologic activity.

7.7. The role of magnesium in urolithiasis

Magnesium, as the free ion or in compounds, provides an abundant field for medical research (Schneider and Anke, 1976; The Magnesium Ion, 1982). In 1982, a new periodical, entitled *Magnesium*, was initiated in Basel, in which numerous publications have scrutinized the relationship of magnesium and lithiasis.

After many new discoveries, it has become almost a rule to study the role of magnesium in the new finding. For reasons which cannot be gone into here, allopurinol (Milurit) was earlier suggested for prevention of the formation of calcium oxalate stones. Accordingly, it was plausible to determine whether the magnesium concentration in the blood or the urine is affected by allopurinol (it is not). Furthermore, it is quite natural today that, for example, the changes in blood magnesium level in the immune-deficiency syndrome have been followed, the magnesium content of the leukocytes in patients with calculosis has been studied (Revúsová et al., 1989), and the influence of stress on the magnesium content of the urine has been investigated (Brundig et al., 1985).

It is generally accepted by urolithologists that the formation of calcium oxalate and calcium phosphate stones is a multifactorial process which may be divided into the following phases:

- supersaturation of the urine,
- heterogeneous or homogeneous nucleation,
- growth of the foci of crystallization,
- agglomeration of the crystals and their fixation in the urinary tract,
- growth to stone.

The formation and growth of crystals may be influenced by natural or synthetic inhibitors, e.g. via the formation of complexes, or the blocking of certain points of the lattice, or through the zeta potential. Magnesium ion is a natural inhibitor of calcium oxalate and calcium phosphate crystallization, and is reported to affect all five phases of stone formation. This complex effect has been the subject of a great number of experimental and clinical studies (Elliot and Ribeiro, 1973; Resnick et al., 1982; Gershoff, 1985).

The role of magnesium in the aetiology of urolithiasis was first examined at the beginning of the century by Klemperer and Trischler (1902), and then by Hammarsten (1929). The experiments of the latter author formed the basis of magnesium therapy against the formation of the most frequently occurring stone, calcium oxalate. Since that time, the aspects of the effects of magnesium have always been involved in the research programmes, e.g. in the modelling of stone-formation or in pharmacological trials. Although thousands of publications have dealt with the results, knowledge on the characteristics of magnesium in this respect is far from complete. The same holds true for the effects of magnesium as for the inhibitors of crystallization in general: the effects have been observed or measured by means of innumerable methods, but the results are often contradictory.

Magnesium deficiency and lithogenesis

The relationship of magnesium and urolithiasis is characterized by diversity. The following aspects are illustrative of this complexity:

- the magnesium and calcium metabolisms are interrelated (physiological aspect),
- the degree of magnesium absorption and the tissue, blood and urinary magnesium levels may be the consequences of and characteristic of pathological processes which serve the background of the urolithiasis (pathological and diagnostic aspects),
- the magnesium concentration of the renal papillae is influenced by prerenal factors (pathological aspect),
- there are also magnesium-containing calculi (pathological aspect),
- magnesium-containing drugs are applied in the prevention of urolithiasis (therapeutic aspect),

— there are interactions between magnesium and some drugs, which may impair both the absorption of magnesium and the effects of the drugs (pharmacological aspect).

In this section a very schematically survey will be presented of those features of magnesium which are connected with the formation and therapy of calcium- and magnesium-containing calculi.

The significance of a magnesium deficiency may be inferred from precipitation tests with simple aqueous solutions and more complex, urine-resembling solutions, and also from animal experiments.

Aqueous solutions

Magnesium forms readily soluble, stable anionic or cationic complexes, $[\text{Mg}_n(\text{C}_2\text{O}_4)_{n+1}]^{2-}$ or $(\text{Mg}_2\text{C}_2\text{O}_4)^{2+}$, with the oxalate ion, decreasing thereby the amount of free oxalate ion available for the precipitation of calcium oxalate. Magnesium chloride increases the solubility of calcium oxalate monohydrate (whewellite), which is likewise explained by complex formation (Fig. 7.14). The increase in solubility of calcium oxalate is proportional to the square root of the magnesium concentration (Hammarsten, 1929; Schneider and Anke, 1976; Knappwost, 1977). For example, 10 mmol/dm³ magnesium chloride increases the solubility of calcium oxalate from 8 mg/

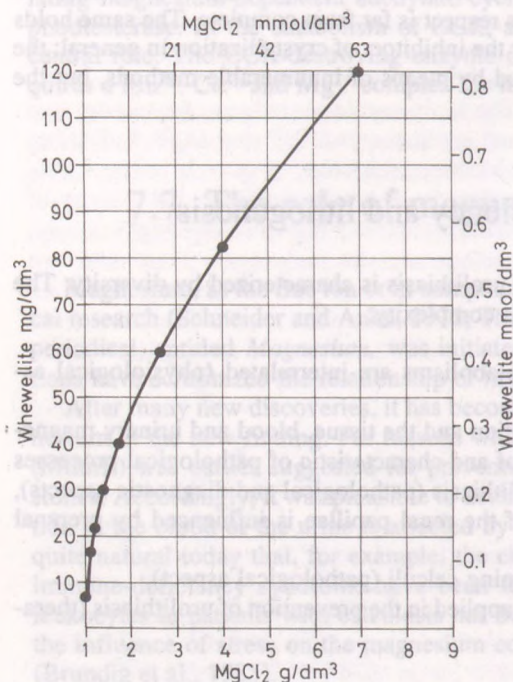


Fig. 7.14. The solubility of calcium oxalate monohydrate (whewellite) in distilled water at 37 °C, in the presence of magnesium chloride

dm^3 to 46 mg/dm^3 , i.e. almost 6-fold. Nevertheless, such a high Mg/Ca ratio (10:0.314, or 31.8:1) cannot be established in the urine. It should be pointed out that this considerable increase in solubility may be ascribed to the magnesium ion alone only if the pH and ionic strength of the solution do not change in the meantime, magnesium chloride undergoes acid hydrolysis. In the range of the physiologic Mg/Ca ratio (about 1.0 mmol/dm^3) the increased solubility or inhibitory effect attributable to magnesium cannot always be observed (Berg et al., 1976).

The urine cannot be regarded as a simple aqueous solution; it is much more complex than a two-component solution in distilled water. As an example, the situation may be examined when not only calcium oxalate and magnesium chloride, but also sodium citrate is present in the solution, as a third component. The citrate ion is itself an inhibitor of crystallization, while it binds both the calcium ion and the magnesium ion: thus, the two inhibitor ions may neutralize each other (Knappwost and Matouschek, 1975). In this solution the solubility of calcium oxalate may vary considerably, depending on the quantitative proportions of the components and on the pH. In the presence of the citrate ion, magnesium may be expected to increase the solubility only if it is in excess. Some investigators have found the solubility-increasing effects of the magnesium and citrate ions to be additive, while others consider magnesium citrate to be ineffective (Tischmann et al., 1988; Grases et al., 1989) or then again effective (Vermeulen et al., 1958).

The existence of the inhibitory effect of magnesium was supported by studies with the gel-diffusion technique (aqueous agar-agar or silica gel, calcium chloride, ammonium oxalate and magnesium chloride) (Schneider et al., 1983).

The results obtained with artificial urine come closer to the real conditions. By means of solutions resembling urine it has been proved that the Mg^{2+} ion unambiguously increases oxalate tolerance, i.e. if the magnesium concentration is higher, more oxalate ion is necessary to initiate the crystallization of calcium oxalate (Briellmann et al., 1988). In the range $0.5\text{--}15 \text{ mmol/dm}^3$, magnesium sulphate decreased the rate of nucleation of calcium oxalate and the growth rate of already existing crystals (Li et al., 1985).

In the experiments of Berg et al. (1976), magnesium did not reveal a significant solubility-increasing or inhibitory effect. Nevertheless, it was observed that an increasing Mg/Ca ratio is favourable for the precipitation of thermodynamically unstable calcium oxalate dihydrate (weddelite), which is thermally more stable than precipitates induced otherwise: it undergoes dehydration to the monohydrate with more difficulty. This phenomenon may be interpreted in various ways:

- the precipitation of the thermodynamically unstable dihydrate begins at a much higher supersaturation in the urine, i.e. magnesium inhibits formation of the crystals,
- magnesium in great amounts causes precipitation of the clinically more malignant dihydrate, which grows more rapidly and leaves the urinary tract more reluctantly (Kohri et al., 1988).

In a simple, but still urine-resembling solution, magnesium citrate increased the solubility of calcium phosphate; moreover, it was even able to delay the precipitation (Vermeulen et al., 1958). In a similar solution, magnesium sulphate decreased the rates of nucleation and growth of calcium oxalate, but if the oxalate concentration of

the solution was higher than 2.0 mmol/dm^3 , magnesium became a promoter of crystallization (Kohri et al., 1988).

Results obtained with EQUIL, a computer programme designed specially for the study of lithogenesis, e.g. for computation of the supersaturation caused by calcium oxalate, revealed that citrate is directly followed by magnesium in the sequence of ions decreasing the supersaturation of calcium oxalate (Kavanagh and Rao, 1990).

The use of diluted (1–5%) urine presents even more “real-life” conditions for the examination of crystallization inhibitors than does artificial urine. It was surprising that in diluted urine the magnesium ion in very low concentrations ($0.1\text{--}0.01 \text{ mmol/dm}^3$) proved to promote stone growth, whereas in higher concentrations ($1\text{--}10 \text{ mmol/dm}^3$) it inhibited not only the growth, but also the agglomeration of the crystals (Rosemary et al., 1981; Li et al., 1985).

Urine itself may be studied, too. Magnesium chloride was found to be unambiguously effective in inhibiting crystallization in human urine (Hallson et al., 1982). In the urine of stone-forming patients, nephelometry revealed that magnesium nitrate also exerted an inhibitory effect on the precipitation of calcium oxalate (Grases et al., 1989). At present, the majority of authors consider the inhibitory effect of magnesium to be proved.

The influence of magnesium on nucleation in the course of cholelithogenesis has also been investigated (Neithercut, 1989).

The significance of a magnesium deficiency

Recognition of the solubility-increasing effect of the magnesium ion in aqueous solution naturally led to the assumption that a magnesium deficiency may be one of the causes of stone-formation in calcium oxalate lithiasis. About half of the authors consider that hypomagnesiuria (in a mild, absolute or relative form) is in fact present in some patients. Others are of the opinion that there is practically no difference in this respect between patients with calculi and healthy individuals, or that even hypermagnesiuria is a regular finding in lithiatic patients (Martinez et al., 1985). Additionally, there are reports that lithiatic patients are characterized not only by hypomagnesiuria, but also by a relationship between the frequency of stone-formation and the degree of hypomagnesiuria (Leskovar et al., 1988). A number of studies have revealed that the frequency or rarity of calcium oxalate stones may be correlated to the high or low magnesium content of the soil (and consequently that of the food) in a given region (Kohri et al., 1989).

The urinary magnesium concentration and the daily magnesium excretion of patients with calcium oxalate stones and of healthy controls on a standard diet differed only slightly (Bach, 1984). The influence of various foods and standard diets on the magnesium content of the urine has been studied extensively (Hesse, 1984).

A possible reason for the contradictory results is the heterogeneity of the patient groups. In fact, patient groups may be set up in which the patients are characterized by a magnesium deficiency on the basis of their hypomagnesiuria, but then again, hypermagnesiuria may be revealed in some other groups (Salinas et al., 1985). All in all, it is not very likely that a magnesium deficiency is the only or the main cause of multifactorial stone-formation.

The organism of adult humans contains 19–27 g (an average of 1 mol) of magnesium, mainly in the bones, the teeth included (Brautbar and Gruber, 1986). The absorption and excretion of magnesium are influenced by various conditions. The transport processes of magnesium have not been sufficiently well elucidated to allow a clear-cut opinion concerning the existence, causes and importance of a magnesium deficiency with respect to lithiasis. In order to characterize the complexity of the relationships, the connection of gastric resection and of the magnesium concentration of renal papillae with stone formation should serve as an example.

It has been observed that the low gastrin level in the fasting blood of stone formers is associated with supersaturation of urine with hydroxyapatite (Schwille et al., 1987). Due to hypogastrinaemia induced by gastric resection in rats, there was a decrease in the magnesium concentration of renal papillae with an increase in the phosphate concentration. Compared to the cortex and the medulla, however, the otherwise also high calcium concentration did not change. Based on the direction and extent of changes, the danger of calcium phosphate precipitation within the papillae also increased. Now it can only be assumed that these changes affect in some way the stone-forming ability of urine in the collecting tubules partly as a result of magnesium deficiency (Fries et al., 1990).

Magnesium is associated with calculus formation indirectly or also in a wider sense. Without giving the specific reasons, here we refer to diseases which arise also due to magnesium deficiency, and the disease itself (hypertension, atherosclerosis, diabetes, osteomalacia, etc.) can be assumed to be related with urinary stone formation (Rayssiguier, 1984; Meema et al., 1987; Neumann and Jensen, 1989; Salvarani et al., 1989; Ponder et al., 1990).

Evidence against a presumed magnesium deficiency is that in healthy individuals and lithiatic patients the serum magnesium levels, the magnesium retention after intravenous magnesium loading and the gastrointestinal magnesium absorption are identical (Johansson et al., 1981b). There is a significant difference between the proportions of urinary magnesium and calcium in the two groups (1.0 ± 0.5 mmol/day in healthy individuals, and 0.7 ± 0.3 mmol/day in stone-formers), but only because of the hypercalciuria of the lithiatic patients.

A severe magnesium deficiency induced in animal experiments results in stone-formation: in the kidneys of rats kept on a magnesium-deficient diet, calcareous deposits appear. Magnesium is not the only such substance: for example, a choline-free diet causes similar calcifications. If ethylene glycol is administered to animals, the tubular deposition of calcium oxalate is facilitated by a magnesium deficiency, but is not inhibited by excess amounts of magnesium (Ebisuno et al., 1987).

The stone-forming effect of magnesium deficiency is supported by recalcification experiments on the cartilage of rachitic rats involving the development of hydroxylapatite (Mukai and Howard, 1963). During incubation in the urine of healthy humans, this cartilage is not mineralized (or only slowly) but if the magnesium has previously been removed from the urine, the calcification is accelerated. In the urine of lithiatic patients, recalcification of the cartilage is faster. It is presumed that the Mg/Ca ratio, and the competition between the two cations, is in part responsible for this phenomenon. It should be mentioned here that in chondrocalcinosis hypomagnesaemia possibly plays a role in the precipitation of calcium pyrophosphate dihydrate (Salvarani et al., 1989).

Magnesium-containing calculi

Since magnesium is a component of the most malignant stones and of some other, rare calculi, its high concentration in the urine is not always desirable, in contrast with all the above.

Magnesium may be found as a trace element in practically all uroliths. Because of the published contradictions, its significance is not yet clarified. For example, some authors were not able to detect magnesium in weddellite, while others found the magnesium content of weddellite to be higher than that of whewellite, or observed changes in the texture of oxalate stones formed during treatment with magnesium.

As main component, magnesium is the characteristic cation of phosphate calculi. In the lattice of whitlockite (tricalcium phosphate), naturally occurring as urolith, dental calculus or mineral, the calcium ion may be substituted non-stoichiometrically by the magnesium ion, up to a maximum of 9.5% (Jensen and Rowles, 1957; Brautbar and Gruber, 1986). Magnesium may also be incorporated into the lattice of apatites. In such cases, the characteristic diffraction lines of the powder diagram are shifted in proportion to the magnesium content. The incorporation of magnesium is expressed by different formulae, e.g. $(\text{Ca}, \text{Mg}) (\text{OH}) \text{PO}_4 \cdot 2\text{H}_2\text{O}$ or $\text{Ca}_9\text{Mg}(\text{HPO}_4) (\text{PO}_4)_6$.

Struvite ($\text{MgNH}_4\text{PO}_4 \cdot 6\text{H}_2\text{O}$)

This is found in 5–15% of uroliths, rarely in the developed countries, but more frequently in the underdeveloped countries. Struvite has even been demonstrated in Egyptian mummies. It is a frequent component of calculi in animals (dogs, cats, cows, etc.). Struvite may be dissolved from the stones of corpses buried in acidic soil or may be transformed into other compounds by metasomatism.

Struvite is a component which precipitates from the most alkaline ($\text{pH} = 6.9\text{--}8.5$) human urine. The basicity of the urine is caused by bacteria capable of urease synthesis (*Proteus*, *Reitterella*, *Ureaplasma*, etc.). Urease decomposes the urea of the urine into NH_4^+ , HCO_3^- and HO^- ions. Supersaturation with respect to struvite is brought about by ammonia formation and alkalization; magnesium does not usually play an important role (Tarttelin, 1987; McLean et al., 1990). Of all stone-forming components, the solubility of struvite is increased most by reduction of the urinary pH. The local dissolution of calculi (a method developed for the removal of uroliths without surgical intervention, in which an acidic solvent is forwarded to the stone via a catheter or nephrostomic drain) proved most successful for stones with a high struvite content (Mulvaney, 1959).

As a rule, struvite forms calculi together with carbonate apatite; in man, these stones are the softest, grow the most rapidly and reach the largest size. They may be readily crushed by shock wave lithotripsy and other methods. Struvite is found in its purest form in the stones of animals and in the calyceal processes of human staghorn calculi. At these sites, due to the high pH and high concentration of ammonia, magnesium has the advantage in the competition between the magnesium and calcium ions for phosphate. Crystals containing only struvite may be excreted as characteristic coffin-lid crystals during crystalluria.

Rare stones

On long storage, struvite may be decomposed into products which are not genuine stone components. Through the loss of five molecules of water of crystallization, dittmarite ($\text{MgNH}_4\text{PO}_4 \cdot \text{H}_2\text{O}$) is produced; if the decomposition also involves the loss of ammonia, the product is newberyite ($\text{MgHPO}_4 \cdot 3\text{H}_2\text{O}$), which is almost always to be found on the surface of the calculi (Sutor, 1968). Very rarely, bobierite [$\text{Mg}_3(\text{PO}_4)_2 \cdot 8\text{H}_2\text{O}$] too can be detected by means of X-ray diffraction, but it is a well-founded assumption that other hydrates of trimagnesium phosphate may likewise be present in human uroliths (del Moral et al., 1989). Another curiosity is hannayite [$\text{Mg}_3(\text{NH}_4)_2\text{H}_4(\text{PO}_4)_2 \cdot 8\text{H}_2\text{O}$] (Cifuentes Delatte et al., 1977; Carmona et al., 1980).

As a consequence of inaccurate analyses, the components of calculi of the urinary tract have also been found (obviously erroneously) to include compounds e.g. magnesium oxalate or even magnesium hydroxide administered to counteract lithogenesis (Andersen, 1962).

Brief mention should also be made here of those calculi which do not contain magnesium, but which are products of magnesium-containing compounds. Quartz-containing calculi are extremely rare. Their development has been connected with the regular consumption of magnesium trisilicate antacids (Jacobs et al., 1990). Nevertheless, it should be pointed out that the uncrushably hard "calculi" consisting of silica are usually ordinary pebbles qualified as being urinary only by mistake or fraud; in such cases, it is needless to switch to another antacid. It is noteworthy that the magnesium-containing antacids may cause a phosphorus deficiency and osteomalacia (Neumann and Jensen, 1989).

The diagnostic importance of magnesium determination

As concerns the diagnostics of urolithiasis, only determination of the magnesium concentrations in the serum and urine comes into consideration. For this purpose, atomic absorption spectrophotometry is the suggested method (Willis et al., 1961; Durak et al., 1988).

The serum magnesium level

The normal concentration is $0.83 \pm 0.06 \text{ mmol/dm}^3$, which is relatively constant. It is increased in renal insufficiency. Since there is no difference in serum magnesium level between healthy and urolithiatic individuals, this parameter does not play an important part in the diagnostics of urolithiasis. Its changes are studied mostly in experiments or in pharmacological trials.

The urinary magnesium level

The normal magnesium excretion is 4.3 ± 1.3 mmol/day, while the urinary magnesium concentration is 3.0 ± 1.3 mmol/dm³. Its concentration as related to creatinine, i.e. the magnesium/creatinine ratio is 0.35 ± 0.13 mmol/mmol. Determination of these parameters may be omitted in the course of a simple informative examination, but for a detailed check-up it is indispensable. The urine should be slightly acidic so that the results is not distorted by the precipitation of crystals from neutral or slightly alkaline urine.

The amount of magnesium excreted in the urine varies with the age, the sex, and also the time of day. It may also be decreased in hepatic cirrhosis or during lactation, for example (Brautbar and Gruber, 1986). For study of the possible hypomagnesiuria of urolithiatic patients, the above points should be taken into consideration in the selection of the controls (Johansson et al., 1981b).

Some authors consider that hypomagnesiuria is present in at most 30% of patients with oxalate calculi (Terhorst and Lübke, 1971); for example, the amount of magnesium excreted daily in the stone-forming group was 3.2 mmol. Others — at other part of the Earth — did not observe such a reduction (Takasaki, 1972). The decrease of 1 mmol/day may be explained by the fact that the stone-formers were 10 years older than the controls. The complexity of the problem is reflected by the situation that the excretion of magnesium is also increased in renal hypercalciuria (Salinas et al., 1985). There is no difference in magnesium excretion between patients with uric acid stones and healthy controls. A number of reports suggest that magnesium is excreted in different amounts in the urine of white and black individuals on the same diet (Thomas, 1976). Magnesiuria may also be influenced by diuretics; for example, it is increased by aldosterone and hydrochlorothiazide (Hypothiazide), and decreased by the infusion of acetazolamide. Magnesiuria may likewise be reduced as a side-effect of drugs, e.g. orthophosphate therapy. In animal experiments, the urinary magnesium concentration was increased by stress.

The ratio of magnesium and calcium in the urine

Its normal value is 1.0 ± 0.5 mmol/mmol. There is a moderate positive correlation between magnesiuria and calciuria. A calcium load (cheese + salt) slightly increased the amount of magnesium excreted daily, but reduced the Mg/Ca ratio (Hesse, 1984). The low Mg/Ca ratio in hyperparathyroidism has been emphasized by several authors (King and Stanbury, 1970; Rude et al., 1978). The reduction may be caused by a decreased magnesium excretion and or by an increased calcium excretion. Both possibilities are considered to be lithogenic (Kohri et al., 1989). Following the removal of parathyroid adenomas, the Mg/Ca ratio increases, in spite of the postoperative hypomagnesiuria (Oreopoulos et al., 1968).

Immobilization is a well-known lithogenic condition. The Mg/Ca ratio in the urine gradually decreases, not only because of the decreasing magnesium excretion, but also because of increasing calcium excretion (Respondek et al., 1988). The same is true for oxalate stones: the Mg/Ca ratio is more often reduced than the excretion of

magnesium, mainly because of the hypercalciuria (Takasaki and Shimano, 1967; Takasaki, 1972).

With regard to the facts that calcium infusion is followed by an increased magnesium excretion and that an excess magnesium intake may result in hypercalciuria, many authors consider the Mg/Ca ratio in the urine to be more informative than the numerator or denominator themselves. Hypothiazide is widely used in the prevention of oxalate calculi. Following its administration, the Mg/Ca ratio increases, the excretion of calcium decreases, but opinions are divided as concerns the increase of magnesiumuria.

Other expressions too are applied as measures of the stone-forming nature of the urine the concentration of magnesium featuring in the denominator of these, e.g. $[\text{Ca}]/[\text{oxalate}]/[\text{citrate}]/[\text{Mg}]$.

Therapeutic significance of magnesium

Attempts to utilize magnesium therapeutically are essentially based on the conditions depicted in *Fig. 7.14*. Such attempts were initiated in the hope that the increased solubility of stones observed in the presence of magnesium in water also holds for urine. In the course of the examination of urolithiatic patients, a magnesium deficiency was searched for, as a basis of the promising magnesium replacement. Magnesium therapy aimed at the prevention of urolithiasis is also founded on animal experiments. The amount of calcium oxalate precipitated from the urine upon the addition of oxalic acid decreases if magnesium chloride has previously been added to the urine.

Some authors explain the necessity of magnesium therapy by the fact that magnesium is indispensable for the activation of several enzymes, including those which participate in endogenous oxalate synthesis or in production of the pyrophosphate ion, which is considered to have an inhibitory effect on crystallization (Unger, 1976). In rats, urolithiasis induced by a vitamin B₆ deficiency or by the administration of ethylene glycol may be almost completely prevented with magnesium oxide. In cats, the formation of weddellite-containing bladder stones is blocked by magnesium; instead of weddellite, newberyite is crystallized. In rats, a magnesium deficiency causes calcifications in the cells and lumen of the proximal tubuli. It is obvious that these unequivocal precedents had to be followed by attempts to apply magnesium therapeutically.

The value of a preventive drug may be judged after either short-term or long-term administration. In acute experiments, primarily the changes in the composition of the urine are examined on the basis of theoretical considerations, whereas in the chronic experiments lasting several years, the frequency of occurrence of stones is compared with that in the pretherapeutic period.

It is considered favourable if at the beginning of the therapy the urinary Mg/Ca ratio and the concentrations of the magnesium and citrate ions increase, while the concentrations of the stone-forming ions (calcium, oxalate and phosphate) decrease. Even so, it may not be concluded that the prevalence of stone formation will in fact decrease, because there are many other factors which influence lithogenesis (variations in the pH, the daily amount of urine, the diet and the living conditions). For

evaluation of the effects of chronic therapy, a matching control group must be selected, the only difference between the two groups being that in one of them 3×100 mg magnesium oxide is, for example, administered daily.

The magnesium requirements of humans are covered by plant foods, seeds and drinking water. Magnesium absorption takes place mainly in the small intestine, under the influence of vitamin D and parathyroid hormone, among others. Only about 10–30% of the magnesium content of the food is absorbed (Schamschula et al., 1988). Diseases of the small intestine may affect absorption; nevertheless, there are not sufficient data with respect to the changes in the absorption of calcium and oxalate, or urolithogenesis in these conditions.

Various magnesium compounds (oxide, hydroxide, chloride, citrate, nicotinate, glutamate, aspartate, etc.) have been tested, partly with contradictory results, but the preventive effect of magnesium has generally been approved (Ettinger and Citron, 1988; Hallson and Rose, 1988; Respondek et al., 1988; Tischmann et al., 1988). It is also accepted overall that the absorption of magnesium salts is influenced to a great extent by the anions. The ions which mutually form precipitates or complexes (e.g. calcium, magnesium, oxalate, citrate, phosphate, phytate and stearate) affect the various adsorptions of each other in a very complicated way. For example, stearate produced during the digestion of fat decreases the absorption of calcium, which in turn increases the amount of absorbable oxalate. Large amounts of alimentary magnesium bind the phosphate ion, and therefore the amount of absorbable calcium increases (Ulmann et al., 1985). Magnesium absorption is also affected by drugs. In enteral hyperoxaluria, magnesium administration is recommended for the reduction of oxalate absorption.

The usual therapeutic dose of magnesium oxide is 200–500 mg daily. This compound is readily available, it has the highest magnesium content, and it is therefore administered most frequently (Ettinger and Citron, 1988). It acts not only as a source of magnesium, but also as a base; in rabbits, it may even induce lethal metabolic alkalosis (Ogilviet et al., 1983). On the other hand, it is well known that alkalosis reduces the excretion of calcium and increases that of citrate (Hallson and Rose, 1988). Magnesium chloride in large amounts comprises an acid load; if administered in infusion, it increases the excretion of magnesium considerably, and to some extent that of calcium as well.

Mineral waters and even sea-water are used in drinking cures with the aim of increasing the excretion of magnesium (Schneider and Horn, 1976). During magnesium therapy the expected increase in magnesium discharge does not always occur immediately but weeks later (Melnick et al., 1971). The magnesium-rich, bicarbonate-containing mineral waters are advantageous: they cause the relative supersaturation of the urine with respect to calcium oxalate to decrease, while the Mg/Ca ratio and the citrate excretion are increased (Strohmaier et al., 1988).

One of the most widely used and successful forms of magnesium therapy is the combination of a magnesium compound and vitamin B₆ (Prien and Gershoff, 1974), which was developed on the basis of animal experiments (Lyon et al., 1966). In rats and cats a vitamin B₆ deficiency results in formation of calcium oxalate calculi, which is suppressed by magnesium salts added to the feed. In man, mild hyperoxaluria sometimes disappears for ever, or are normalized during the administration of large doses of vitamin B₆. Magnesium and vitamin B₆ participate in the membrane transport of

the aminoacids (Unger, 1976), while some of the aminoacids (glycine, serine and threonine) play a role in oxalate synthesis. In spite of these experimental results, it must be admitted that this form of magnesium therapy was accepted in practice without reliable answers to the existing questions. (Is there a magnesium deficiency? Does oxalate excretion decrease upon magnesium administration? Is there a synergism between the two substances? And so on.) Clinical practice indicates excellent results for the combination: the administration of 3×100 mg magnesium oxide and 3×100 mg vitamin B₆ daily decreased the incidence from 1.3 to even 0.1 calculi/patient/year during 4–6 years of treatment (Prién and Gershoff, 1974).

Similarly good results were obtained with magnesium hydroxide in amounts corresponding to 2×250 mg magnesium daily: the incidence of stones decreased from 0.8 to 0.05 stones/patient/year during 3 years (Johansson et al., 1981a). It is noteworthy that a considerable reduction (from 0.5 to 0.14) was found in the control group, too. During treatment, the magnesium concentrations of the serum and the muscles and also the calcium excretion remained constant, while the magnesium excretion increased by 1.5–2 mmol/day, and the urinary Mg/Ca ratio increased from 0.7 ± 0.2 to 1.1 ± 0.5 , i.e. it normalized. The citrate excretion also changed very favourably (from 2.6 ± 1.4 to 3.0 ± 1.3 mmol/day. 20.6 mmol magnesium hydroxide corresponds to 500 mg magnesium daily; by comparison, 20.6 mmol potassium carbonate amounts to 2.85 g.

The regular supplementation of magnesium is desirable if the excretion of magnesium is decreased as a side-effect of various drugs. For example, for the moderation of hypercalciuria, macromolecules (cation-exchange resins and sodium cellulose phosphate) are widely used. When mixed with the food, these bind not only calcium, but also some of the magnesium. Magnesium gluconate too may be administered as a replacement, obviously in such a way that it does not meet the macromolecule. In such cases, it is difficult to reveal the extent to which magnesium contributes to the success of therapy; nevertheless, clinical experience suggests that the combination has a more favourable effect (Hallson et al., 1982; Rayssiguier, 1984). The combination of sodium cellulose phosphate and Hypothiazide is also considered advantageous, since it increases the excretion of magnesium in some cases.

Magnesium administration is contraindicated in the following cases:

- there are urease-containing bacteria in the urine, and the risk of struvite precipitation is increased;
- some drugs (tetracyclines, Doxycycline, Naprosyn, Vibramycin, etc.) form complexes or precipitates with magnesium and therefore their absorption is reduced;
- there is an impaired renal function, myasthenia gravis, an atrioventricular block, etc.

References to Chapter 7

7.1. The cardiovasoprotective effect of magnesium supplementation

- Aikawa, J. K. (1960): Effect of pyridoxine and desoxypyridoxine on magnesium metabolism in the rabbit. *Proc. Soc. Exp. Biol. Med.* (N. Y.) **104**, 461.
- Albert, D. G., Morita, Y., Iseri, L. T. (1958): Serum magnesium and plasma sodium levels in essential vascular hypertension. *Circulation* **17**, 761.
- Alcock, N., McIntyre (1962): Interrelation of calcium and magnesium absorption. *Clin. Sci.* **22**, 185.
- Anstall, H. B., Hunstmann, R. G., Lehmann, H., Hayward, G., Wetzmann, D. (1959): The effect of magnesium on blood coagulation. *Lancet* **1**, 814.
- Bajusz, E., Selye, J. (1960): Anion-cation interaction in the chemical prevention of cardiac infarction. *Kísérl. Orvostud.* **12**, 283. (In Hung.)
- Bersohn, I., Oelofse, P. J. (1957): Correlation of serum magnesium and serum cholesterol levels in South Africa Bantu and European subjects. *Lancet* **1**, 1020.
- Bíró, Gy. (1990): Nutrition and cardiovascular risk in the Hungarian experience. *Acta Cardiologica* **45**, 3.
- Bunce, G. E., Jenkins, K. J., Phillips, P. H. (1962): The mineral requirements of the dog. II. *J. Nutr.* **76**, 17.
- Colby, R. W., Frye, C. M. (1951): Effect of feeding high levels of protein and calcium in rat ratios on magnesium deficiency syndrome. *Am. J. Physiol.* **166**, 408.
- Dennis, J., Moore, R. M. (1938): Potassium changes in the functioning heart under conditions of ischaemia and of congestions. *Am. J. Physiol.* **128**, 443.
- Durlach, J. (1989a): *Le Magnésium en Pratique Clinique*. Ed.: Baillière, J. B. E. M. I., Paris, 162.
- Durlach, J. (1989b): Recommended dietary amounts of magnesium: RDA. *Magnesium Research* **2**, 195.
- Durlach, J., Bara, M., Guet-Bara, A. (1989): Magnesium level in drinking water: its importance in cardiovascular risk. In: Itokawa, Durlach, J. (eds): *Magnesium in Health and Disease*. John Libbey and Co. Ltd., London, 173.
- Fazekas, T., Karcsú, S., Karácsony, G., Némecz, Gy., Tószaki, Á., Szekeres, L. (1985): The effect of a soy-diet on the severity of infarctoid cardiomyopathy provoked by isoproterenol. *Cardiol. Hung.* **14**, 253. (In Hung.)
- Fischer, B., Fischer, U. (1981): Magnesium in der inneren Medizin, Pathophysiologie und Klinik. *Magnesium-Bull.* **1a**, 249.
- Fischer, P. W., Giroux, A. (1987): Effect of dietary magnesium on sodium-potassium pump action in the hearts of rats. *J. Nutr.* **117**, 2091.
- Gáti, T., Rigó, J., Gyenge, K., Sós, J. (1964): Wirkung der kardiovasopathogenen Diät, von Ca und Mg auf die Größe des Coldpressor-Reflexes bei Ratten. *Zeitschrift für Kreislaufforschung* **53**, 518.
- Hackethal, K. H. (1949): Vorläufige Mitteilung über den Einfluß des Magnesiums auf die Fibrino- bzw. Thrombolyse. *Klin. Wschr.* **27**, 315.
- Hara, A., Matsumara, H., Abiko, T. (1990): Beneficial effect of magnesium on the isolated perfused rat heart during reperfusion after ischaemia: Comparison between pre-ischaemic and post-ischaemic administration of magnesium. *Naunyn-Schmiedeberg's Arch. Pharmacol.* **342**, 100.

- Haury, V. G., Cantarov, A. (1942): Variations in serum magnesium in 52 normal and 440 pathologic patients. *J. Lab. Clin. Med.* **27**, 616.
- Hess, R., McIntyre, I., Alcock, N., Pearse, A. G. E. (1959): Histochemical changes in rat kidney in magnesium deprivation. *Brit. J. Exper. Path.* **40**, 80.
- Hänze, S. (1960): Untersuchungen zur Wirkung verschiedener Diuretika auf die renale Magnesium- und Calcium-Ausscheidung. *Klin. Wschr.* **38**, 1168.
- International Life Sciences Institute. European Branch: Recommended Dietary Amounts of Minerals (1989). Limelette Castle, May 5-6.
- Ising, H. (1981): Interaction of noise-induced stress and Mg decrease. *Artery* **9**, 205.
- Janke, I., Fleckenstein, A., Hein, B., Leder, O., Sigel, H. (1975): Prevention of myocardial Ca overload and necrotization by Mg and K salts or acidosis. In: Fleckenstein, A., Rona, G. (eds): *Recent Advances in Studies on Cardiac Structure and Metabolism*. A. Urban and Schwarzenberg, München - Berlin - Wien, 33.
- Kaltenbach, J. (1961): Metabolism of ischaemic cardiac muscle. *Circ. Res.* **8**, 207.
- Kubena, K. S., Durlach, J. (1990): Historical review of the effects of marginal intake of magnesium in chronic experimental magnesium deficiency. *Magnesium Research* **3**, 219.
- Lehr, D. (1981): Magnesium and cardiac necrosis. *Magnesium-Bull.* **1a**, 178.
- Levence, C. I., Poole, J. C. F. (1962): The collagen content of the normal and atherosclerotic human aortic intima. *Brit. J. Exper. Path.* **43**, 469.
- Marier, J. R. (1981): Nutritional and myocardial aspects of magnesium in drinking-water. *Magnesium-Bull.* **1a**, 48.
- McIntyre, I., Davidson, D. (1958): The production of secondary potassium depletion, sodium retention nephrocalcinosis and hypercalcaemia by magnesium deficiency. *Biochem. J.* **70**, 456.
- Mills, L. (1959): Stress as an etiologic factor in essential hypertension. *Amer. J. Cardiol.* **11**, 1705.
- Mori, K. J., Duruisseau, P. (1960): Water and electrolyte changes in aging process with special reference to calcium and magnesium in cardiac muscle. *Canad. J. Biochem.* **38**, 919.
- Morton, B. C., Smith, F. M., Kibbon, T. J., Nair, R. C., Poznanski, W. J. (1981): Magnesium therapy in acute myocardial infarction. *Magnesium-Bull.* **1a**, 192.
- Nickerson, M., Karr, G. W., Dresel, P. E. (1961): Pathogenesis of electrolyte-steroid-cardiopathy. *Circ. Res.* **9**, 209.
- Osten, W. (1955): Soll eine Vitamin-E-Behandlung mit Kalzium oder Magnesium kombiniert werden? *Internat. Ztschr. Vitaminforsch.* **26**, 19.
- Porta, S., Emsenhuber, W., Helbig, J., Classen, H. G. (1989): High doses of magnesium prevent stress induced catecholamine secretion: mode of action. 11. Hohenheimer Magnesium Symposium, *Magnesium Research* **2**, 293.
- Reinhart, R. A. (1988): Magnesium metabolism. *Arch. Intern. Med.* **148**, 2415.
- Rigó, J. (1965): Veränderungen des Kollagens der Aorta beim Altern und Calciferol- und Magnesiumbehandlung. *Gerontologia* **11**, 25.
- Rigó, J. (1971): The relationship between magnesium and the vascular system. In: Durlach, J. (ed.): *1st International Symposium on Magnesium deficit in Human Pathology*. Vittel, 213.
- Rigó, J., Budavári, I., Sós, J. (1961): Potassium sodium magnesium and calcium levels in rats during alimentary provocation of infarctoid cardiac lesions. *Acta Med. Sci. Hung.* **17**, 85.
- Rigó, J., Gáti, T., Pósch, E., Szelényi, I. (1966): Die infolge eines Astes der A. coronaria zustandekommenden Elektrolytveränderungen im Myokard. *Vitalstoffe-Zivilisationskrankheiten* **5**, 181.
- Rigó, J., Horváth, L., Szelényi, I. (1971): Die Wirkung der hohen magnesiumhaltigen Diät auf die kapillare Resistenzänderung bei älteren Atherosklerosekranken. In: Durlach, J. (ed.): *Symp. Int. I. Le Déficit Magnésique en Pathologie Humain*. Vol. II. Vittel, 385.

- Rigó, J., Simon, Gy., Hegyvári, CS., Sós, J. (1963): Effect of magnesium on dietary infarctoid changes in the heart. *Acta Med. Sci. Hung.* **19**, 231.
- Rigó, J., Sós, J. (1963): The effect of magnesium on the renal injury provoked by cardiovascular pathogenic diet. *Kísérlet. Orvostud.* **15**, 42. (In Hung.)
- Rigó, J., Szelényi, I. (1963): Die Wirkung von Magnesium auf die neurogene und alimentäre Hypertonie bei Ratten. *Acta Physiol. Acad. Sci. Hung.* **24**, 353.
- Rigó, J., Szelényi, I. (1964): The effect of magnesium on experimental hypertension of rats. *Kísérlet. Orvostud.* **16**, 24. (In Hung.)
- Rigó, J., Szelényi, I. (1967): The effect of magnesium upon the increased coagulability provoked by acute fat-loading. *Kísérlet. Orvostud.* **19**, 17. (In Hung.)
- Rigó, J., Szelényi, I., Sós, J. (1966): The effect of magnesium upon blood-coagulation of rats kept on a high-fat (butter) diet. *Kísérlet. Orvostud.* **18**, 645. (In Hung.)
- Rigó, J., Tölgyesi, Gy., Gerencsér, Gy. (1986): Magnesium and environmental damages. In: *Man and Environment, Health and High Technology*. XII. SIRMCE Congr. Yokohama. SIRMCE, Bruxelles, 72.
- Rigó, J. Jr., Hídvégi, J., Csömör, S., Györe, I., Tölgyesi, Gy., Rigó, J. (1987): Examination of the relationship between serum magnesium and some lipid parameters in pregnant women. *Magyar Nőorv. L.* **50**, 150. (In Hung.)
- Russel, R. A., Crafood, J., Harris, A. S. (1961): Changes in myocardial composition after coronary artery ligation. *Am. J. Physiol.* **200**, 995.
- Seelig, M. (1989): Cardiovascular consequences of magnesium deficiency and loss: pathogenesis, prevalence, and manifestation — magnesium and chloride loss in refractory potassium repletion. *Am. J. Cardiol.* **63**, 4G.
- Selye, H. (1958): Prevention by $MgCl_2$ and KCl of the myocardial necrosis normally produced by papain. *Cardiologia* (Basel) **33**, 3015.
- Simon, G., Harmos, G., Rigó, J., Gáti, T., Kemény, T., Sós, J. (1963): The effects of vitamin E in rats kept on cardiopathogenic diet. *Acta Med. Sci. Hung.* **19**, 357.
- Schnitzler, B. (1957): Thromboseprophylaxe mit Magnesium. *Münch. med. Wschr.* **99**, 81.
- Skou, J. S. (1988): Further investigations on a $Mg^{++} + Na^{+}$ -activated adenosinetriphosphatase possibly related to the active, linked transport of Na^{+} and K^{+} across the nerve membrane. *Biochim. Biophys. Acta* **42**, 6.
- Sós, J., Rigó, J., Gáti, T. (1964): Die Wirkung von Asparaginat-Salzen auf die experimentelle Hypertonie, die myokardiale Veränderungen und den Serumelektrolyt-Gehalt von Ratten. *Arzneim. Forsch.* **14**, 1134.
- Sós, J., Gáti, F., Kemény, T., Rigó, J. (1964a): Infarctoid cardiac lesions induced by dietetic factors in the dog. *Acta Med. Sci. Hung.* **20**, 1.
- Sós, J., Rigó, J., Kemény, T., Gáti, T. (1964b): Infarctoid cardiac lesions induced by dietetic factors in the cock. *Acta Med. Sci. Hung.* **20**, 9.
- Szelényi, I., Li Bok Nam, Rigó, J., Simon, Gy., Nemesánszky, E., Pósch, E. (1957): Alteration of magnesium metabolism in hypothyroid rats. *Kísérlet. Orvostud.* **19**, 616. (In Hung.)
- Szelényi, I., Rigó, J., Ahmed, B. O., Sós, J. (1967): The role of magnesium in blood coagulation. *Thrombos. Diathes. Haemorrh.* (Stuttg.) **18**, 626.
- Szelényi, I., Rigó, J., Nemesánszky, E., Sós, J. (1969): The in vivo effect of magnesium salts on cardiac function. *Kísérlet. Orvostud.* **21**, 622. (In Hung.)
- Szelényi, I., Rigó, J., Sós, J. (1969): Correlation between vitamin B_6 supply and magnesium metabolism. *Kísérlet. Orvostud.* **21**, 519. (In Hung.)
- Szelényi, I., Sós, J., Rigó, J. (1970): Wirkung des Magnesium-Orotats und der Orotsäure auf die tierexperimentell ausgelösten Blutdruckerhöhung und kardiopathogene Veränderungen in Herzmuskel. *Deutsche Med. J.* **21**, 1406.
- Székács, B., Szathmári, I., Tóth, T., Szelényi, I., Rigó, J. (1969): The effect of magnesium on the renin sensitivity of rats. *Kísérlet. Orvostud.* **21**, 225. (In Hung.)

- Verzár, F. (1963): Differenzierung verschiedener Vernetzungen (Crosslinks) des Kollagens durch Spannungsmessungen. *Hoppe-Selyers z. für Physiol. Chem.* **335**, 38.
- Vitale, J. J., Nakamura, M., Hegsted, D. M. (1957a): The effect of magnesium deficiency on oxidative phosphorylation. *J. Biol. Chem.* **228**, 573.
- Vitale, J. J., Hellerstein, E. E., Nakamura, M., Lown, B. (1957b): Effects of magnesium deficient diet upon puppies. *Circ. Res.* **9**, 387.
- Vitale, J. J., White, P. L., Nakamura, M., Hegsted, D. M., Zamchek, N., Hellerstein, E. E. (1957c): Interrelationships between experimental hypercholesterinaemia, magnesium requirement and experimental atherosclerosis. *J. Exp. Med.* **106**, 757.
- Walker, B. S., Walker, E. W. (1936): Normal magnesium metabolism and its significant disturbances. *J. Lab. Clin. Med.* **21**, 713.

7.2. Cardiac electrophysiology and clinical use of magnesium

- Abraham, A. S., Rosenmann, D., Kramer, M., Balkin, J., Zion, M. M., Farbstein, H., Eylath, U. (1987): Magnesium in the prevention of lethal arrhythmias in acute myocardial infarction. *Arch. Intern. Med.* **147**, 753.
- Allen, B. J., Brodsky, M. A., Capparelli, E. V., Luckett, C. R., Iseri, L. T. (1989): Magnesium sulfate therapy for sustained monomorphic ventricular tachycardia. *Am. J. Cardiol.* **64**, 1202.
- Bailie, D. S., Inoue, H., Kaseda, S., Ben-David, J., Zipes, D. P. (1988): Magnesium suppression of early afterdepolarizations and ventricular tachyarrhythmias induced by cesium in dogs. *Circulation* **77**, 1395.
- Banai, S., Schuger, C. (1990): Magnesium sulfate is the treatment for "torsades de pointes" if the right dose is given. *Am. J. Cardiol.* **65**, 266.
- Brooks, R., McGovern, B. A., Chernow, B., Garan, H., Ruskin, J. N. (1990): Suppression of monomorphic ventricular tachycardia by intravenous magnesium chloride predicts the effectiveness of oral calcium blocker therapy. *Circulation* **82**, Suppl. III, 82.
- Brugada, P., Wellens, H. J. J. (1984): The role of triggered activity in clinical ventricular arrhythmias. *PACE* **7**, 260.
- Chipperfield, B., Chipperfield, J. R. (1973): Relation of myocardial metal concentration to water hardness and death rate from ischaemic heart disease. *Lancet* **2**, 709.
- Cohen, L., Kitzes, R. (1983): Magnesium sulfate and digitalis-toxic arrhythmias. *JAMA* **249**, 2808.
- Davidenko, J. M., Cohen, L., Goodrow, R., Antzelevitch, Ch. (1989): Quinidine-induced action potential prolongation, early afterdepolarizations, and triggered activity in canine Purkinje fibers. Effects of stimulation rate, potassium, and magnesium. *Circulation* **79**, 674.
- DeCarli, Ch., Sprouse, G., LaRosa, J. C. (1986): Serum magnesium levels in symptomatic atrial fibrillation and their relation to rhythm control by intravenous digoxin. *Am. J. Cardiol.* **57**, 956.
- Dubey, A., Solomon, R. (1989): Magnesium, myocardial ischaemia and arrhythmias. The role of magnesium in myocardial infarction. *Drugs* **37**, 1.
- Durlach, J., Durlach, V. (1987): Idiopathic mitral valve prolapse and magnesium. State of the art. In: Lasserre, B. (ed.): *Magnesium. Physiologische Aspekte für die Praxis*. Panscientia Verlag, Hedingen - Zürich, 46.

- Fazekas, T. (1989a): Antiarrhythmic treatment with Ca^{2+} -antagonists. *Orvosi Hetilap* **130**, 1195. (In Hung.)
- Fazekas, T. (1989b): Quinidine syncope with "torsade de pointes" ventricular tachycardia. In: Varró, V., Fazekas, T. (eds): *Clinical Case Presentations*. Selected chapters of the internal medicine. Medicina Könyvkiadó, Budapest, 7. (In Hung.)
- Fazekas, T. (1990): The proarrhythmic effect of antiarrhythmic drugs. *Magy. Belorv. Arch.* **43**, 251. (In Hung.)
- Fazekas, T., Kiss, Z. (1979): Ventricular tachycardia with "torsades de pointes". *Magy. Belorv. Arch.* **32**, 199. (In Hung.)
- Fazekas, T., Kiss, Z. (1984): "Torsade de pointes" ventricular tachycardia associated with lidoflazine therapy. *Eur. Heart J.* **5**, 343.
- Fazekas, T., Papp, Gy. (1989): The pharmacological basis of the clinical application of calcium antagonists. In: *Az orvostud. aktuális problémái* **63**, 5. (In Hung.)
- Fazekas, T., Szerdahelyi, P. (1989): Loss of magnesium from the ischaemic myocardium. *Magnesium Research* **2**, 228.
- Ferrara, N., Longobardi, G., Abete, P. (1988): Electrical and mechanical actions of magnesium sulfate during ischaemia and reperfusion on isolated perfused rat heart. *Arch. Int. Pharmacodyn.* **293**, 84.
- Flink, E. B., Brick, J. E., Shane, S. R. (1981): Alteration of long-chain free fatty acid and magnesium concentration in acute myocardial infarction. *Arch. Intern. Med.* **141**, 441.
- Garfinkel, L., Altschuld, R. A., Garfinkel, D. (1986): Magnesium in cardiac energy metabolism. Review article. **18**, 1003.
- Gorgels, A. P. M., Vos, M. A., Smeets, J. L. R. M., Kriek, E., Brugada, P., Wellens, H. J. J. (1990): Delayed afterdepolarizations and atrial and ventricular arrhythmias. In: Rosen, M. R., Janse, M. J., Wit, A. L. (eds): *Cardiac Electrophysiology: A Textbook*. Futura Publishing Co., Inc., Mount Kisco, 341.
- Gums, J. G. (1987): Clinical significance of magnesium: a review. *Drug. Intell. Clin. Pharm.* **21**, 240.
- Iseri, L. T. (1990): Role of magnesium in cardiac tachyarrhythmias. *Am. J. Cardiol.* **65**, 47K.
- January, C. T., Fozzard, H. A. (1988): Delayed afterdepolarizations in heart muscle: mechanisms and relevance. *Pharmacol. Reviews* **40**, 219.
- January, C. T., Makielski, J. C. (1990): Triggered arrhythmias: new insights into basic mechanisms. *Curr. Opinion Cardiol.* **5**, 65.
- January, C. T., Riddle, J. M., Salata, J. J. (1988): A model for early afterdepolarizations: induction with the Ca^{2+} channel agonist Bay K 8644. *Circ. Res.* **62**, 563.
- Katholi, R. E., Taylor, G. J., Woods, W. T., Jr., Womack, K. A., Mikell, F. L., Moses, H. W., Dove, I. T., Woodruff, R. C., Miller, B. D., Song, A., Wellons, H. A., Hamm, D. P., Schneider, I. A. (1990): MgCl_2 replacement after bypass surgery to prevent atrial fibrillation: a double randomized trial. *Circulation* **82**, Suppl. III, 58.
- Keller, P. K., Aronson, R. S. (1990): The role of magnesium in cardiac arrhythmias. *Prog. Cardiovasc. Dis.* **32**, 433.
- Keren, A., Tzivoni, D. (1990): Magnesium therapy in ventricular arrhythmias. *PACE* **13**, 937.
- Kiss, Z., Fazekas, T. (1979): Arrhythmias in barium intoxication. *Magy. Belorv. Arch.* **32**, 297. (In Hung.)
- Kiss, Z., Fazekas, T. (1982): Toxic ECG-signs in organophosphate and barium poisonings. In: Antalóczy, Z., Préda, I. (eds): *Electrocardiology '81*. Akadémiai Kiadó, Budapest, 441.
- Kiss, Z., Fazekas, T. (1983): Organophosphates and "torsade de pointes" ventricular tachycardia. *J. Royal Soc. Med.* **76**, 984.
- Matsuda, H. (1988): Open-state substructure of inwardly rectifying potassium channels revealed by magnesium block in guinea-pig heart cells. *J. Physiol. (London)* **397**, 237.

- Mugelli, A., Amerini, S., Piazzesi, G., Giotti, A. (1983): Barium-induced spontaneous activity in sheep cardiac Purkinje fibers. *J. Mol. Cell. Cardiol.* **15**, 697.
- Perticone, F., Ceravolo, R., Borelli, D., Mistico, A., Mattioli, P. L. (1990): Electrophysiological effects of magnesium sulfate on intraventricular conduction delay. *Eur. Heart J.* **11**, 240, 1199.
- Ramee, S. R., White, C. J., Svinarich, J. T. (1985): "Torsade de pointes" and magnesium deficiency. *Am. Heart J.* **109**, 164.
- Rasmussen, H. S. (1989): Clinical intervention studies on magnesium in myocardial infarction. *Magnesium* **8**, 316.
- Rasmussen, H. S., Aurup, P., Hojberg, S., Jensen, E. K., McNair, P. (1986a): Magnesium and acute myocardial infarction. Transient hypomagnesemia not induced by renal magnesium loss in patients with acute myocardial infarction. *Arch. Intern. Med.* **146**, 872.
- Rasmussen, H. S., McNair, P., Norregard, P., Backer, V., Lindeneg, O., Balslev, S. (1986b): Intravenous magnesium in acute myocardial infarction. *Lancet* **1**, 234.
- Roden, D. M. (1989): Magnesium treatment of ventricular arrhythmias. *Am. J. Cardiol.* **63**, 43G.
- Rogiers, Ph., Vermeier, W., Kesteloot, H., Stroobandt, R. (1989): Effect of infusion of magnesium sulfate during atrial pacing on ECG intervals, serum electrolytes, and blood pressure. *Am. Heart J.* **117**, 1278.
- Rudas, L., Szabados, S., Szegedsi, I. (1985): Magnesium therapy for "torsade de pointes" ventricular tachycardia. *Orvosi Hetilap* **126**, 1167. (In Hung.)
- Rude, R. K. (1989): Physiology of magnesium metabolism and the important role of magnesium in potassium deficiency. *Am. J. Cardiol.* **63**, 31G.
- Sager, Ph. T., Widerhorn, J., Petersen, R., Leon, C., Ryzen, E., Rude, R., Rahimtoola, S. H., Bhandari, A. K. (1990): Prospective evaluation of parenteral magnesium sulfate in the treatment of patients with reentrant AV supraventricular tachycardia. *Am. Heart J.* **119**, 308.
- Sebeszta, M., Coraboeuf, E., Deroubaix, E., Le Floch, M. (1981): Effect of tetraethylammonium, 4-aminopyridine, cesium and magnesium on slow responses in the guinea pig papillary muscle. *Cardiovasc. Res.* **15**, 468.
- Seelig, M. (1989): Cardiovascular consequences of magnesium deficiency and loss: pathogenesis, prevalence and manifestations – magnesium and chloride loss in refractory potassium repletion. *Am. J. Cardiol.* **63**, 4G.
- Sheehan, J. (1989): Importance of magnesium chloride repletion after myocardial infarction. *Am. J. Cardiol.* **63**, 35G.
- Shine, K. I. (1979): Myocardial effects of magnesium. *Am. J. Physiol.* **237**, H413.
- Sjöberg, A., Edvinsson, L., Fallgren, B. (1989): Magnesium deficiency in coronary artery disease and cardiac arrhythmias. Review article. *J. Intern. Med.* **226**, 213.
- Specter, M. J., Schweizer, E., Goldman, R. H. (1975): Studies on magnesium's mechanism of action in digitalis-induced arrhythmias. *Circulation* **52**, 1001.
- Teo, A., Held, P., Collins, R., Yusuf, S. (1990): Effect of intravenous magnesium on mortality in myocardial infarction. *Circulation* **82**, Suppl. III-393.
- Tzivoni, D., Keren, A. (1990): Suppression of ventricular arrhythmias by magnesium. Editorial. *Am. J. Cardiol.* **65**, 1397.
- Tzivoni, D., Keren, A., Cohen, A. M., Loebel, H., Zavahi, I., Chenzbraun, A., Stern, S. (1984): Magnesium therapy for "torsades de pointes". *Am. J. Cardiol.* **53**, 528.
- Viskin, S., Belhassen, B., Laniado, S. (1990): Termination of paroxysmal reentrant junctional tachycardia by magnesium sulfate. Comparison with adenosine triphosphate. *Circulation* **82**, Suppl. III-435.
- Vos, A. M., Fazekas, T., Gorgels, A. P. M., Leunissen, J. D. M., Wellens, H. J. J. (1994): Action of $MgSO_4$ differs from moricizine and verapamil on ouabain-induced ventricular tachycardia in normomagnesemic conscious dogs. *J. Cardiovasc. Pharmacol.* **23**, 252.

- Wesley, R. C., Haines, D. E., Lerman, B. B., DiMarco, I. P., Crampton, R. S. (1989): Effect of intravenous magnesium sulfate on supraventricular tachycardia. *Am. J. Cardiol.* **63**, 1129.
- White, R. E., Hartzell, H. C. (1989): Magnesium ions in cardiac function. Regulator of ion channels and second messengers. *Biochem. Pharmacol.* **38**, 859.
- Zwerlich, H. K. (1987): Does exogenous magnesium suppress myocardial irritability and tachyarrhythmias in the nondigitalized patient? *Am. Heart J.* **113**, 1046.
- Zwillinger, L. (1935): Über die Magnesiumwirkung auf das Herz. *Klin. Wschr.* **14**, 1429.

7.3. The relation of the magnesium metabolism with the renal functions and blood pressure regulation

- Abraham, A. S., Shuaoul, R., Shimonovitz, S., Eylath, U., Weinstein, M. (1980): Serum Mg in acute medical and surgical conditions. *Biochem. Med.* **24**, 21.
- Adeniyi, T. A. A. (1980): Interactive roles of monovalent and divalent cations in pathogenesis of hypertension caused by alcohol. *J. Clin. Path.* **39**, 1264.
- Aikawa, J. K. (1980): *Mg: Its Biologic Significance*. CRC Press, Boca Raton, 129.
- Alfrey, A. C., Terman, D. S., Bretteschneider, L., Simpson, K. M., Ogden, D. A. (1970): Hypermagnesemia after renal homotransplantation. *Ann. Intern. Med.* **73**, 367.
- Altura, B. M., Altura, B. T. (1978): Magnesium and vascular tone and reactivity. *Blood Vessels* **15**, 5.
- Altura, B. M., Altura, B. T. (1981): Magnesium ion and contraction of vascular smooth muscles: Relationship to some vascular diseases. *Fred. Proc.* **40**, 2672.
- Altura, B. M., Altura, B. T., Gebrewold, A., Ising, H., Gunther, T. (1984): Magnesium deficiency and hypertension. Correlation between magnesium-deficient diets and micro-circulatory changes in situ. *Science* **223**, 1315.
- Averill, C. M., Heaton, F. W. (1966): The renal handling of magnesium. *Clin. Sci.* **31**, 353.
- Bailly, C., Roinel, N., Amiel, C. (1984): PTH-like glucagon stimulation of Ca and Mg reabsorption in Henle's loop of the rat. *Am. J. Physiol.* **246**, F205.
- Barker, E. S., Elkinton, J. R., Clark, J. K. (1959): Studies on the renal excretion of magnesium in man. *J. Clin. Invest.* **38**, 1733.
- Beecher, H. K., Simeone, F. A., Burnett, C. H., Shapiro, S. L., Sullivan, E. R. (1947): Internal state of several wounded men on entry to most forward hospital. *Surgery* **22**, 672.
- Berthelot, A., Esposito, J. (1983): Effects of dietary Mg on the development of hypertension in the spontaneously hypertensive rat. *J. Am. Coll. Nutr.* **4**, 343.
- Brickman, A. S., Massry, S. G., Coburn, J. W. (1972): Changes in serum and urinary calcium during treatment with hydrochlorothiazide: Studies on mechanisms. *J. Clin. Invest.* **51**, 945.
- Brunette, M., Wen, S. F., Evanston, R. L. (1969): Micropuncture study of magnesium reabsorption in the proximal tubule of the dog. *Am. J. Physiol.* **216**, 1510.
- Capuccio, F. P., Markandu, N. D., Beynon, G. W., Shore, A. C., Sampson, B., McGregor, G. A. (1985): Lack of effect of oral magnesium on high blood pressure: a double blind study. *Br. Med. J.* **291**, 235.
- Carney, S. L., Wong, N. L. M., Quamme, G. A., Dirks, J. H. (1980): Effect of Mg deficiency on renal magnesium and calcium transport in the rat. *J. Clin. Invest.* **65**, 180.
- Dagirmanjian, R., Goldman, H. (1970): Magnesium deficiency and distribution of blood in the rat. *Am. J. Physiol.* **218**, 1464.
- Dargie, H. J. (1990): Interrelation of electrolytes and renin-angiotensin system in congestive heart failure. *Am. J. Cardiol.* **65**, 28E.

- De Rouffignac, C., Corman, B., Roinel, N. (1983): Stimulation by antidiuretic hormone of electrolyte tubular reabsorption in rat kidney. *Am. J. Physiol.* **244**, F156.
- Dechaux, M., Kindermans, C., Lambordi, K., Blazy, I., Sachs, C. (1988): Magnesium and plasma renin concentration. *Kidney International* **34** (Suppl. 25), S 12.
- Dunn, M. J., Walser, M. (1966): Magnesium depletion in normal man. *Metabolism* **15**, 884.
- Dyckner, T., Wester, P. O. (1983): Effect of magnesium on blood pressure. *Br. Med. J.* **286**, 1847.
- Dyckner, T., Wester, P. O. (1987): Antihypertensive therapy — effects on magnesium metabolism. *Danish Med. Bull.* **34**, 14.
- Flink, E. B. (1980): Nutritional aspects of magnesium metabolism. *West. J. Med.* **133**, 304.
- Flink, E. B., Shane, S. R., Scobbo, R. R., Graham-Blenschmidt, N., McDowell, P. (1979): Relationship of free fatty acids and magnesium in ethanol withdrawal in dogs. *Metabolism* **28**, 858.
- Friedman, H. S., Nguyen, T. N., Mokraoui, A. M., Barbour, R. L., Murakawa, T., Altura, B. M. (1987): Effect of magnesium chloride on cardiovascular hemodynamics in the neurally intact dog. *J. Pharmacol. Exp. Ther.* **243**, 126.
- Fuentes, A., Goldkrand, J. W. (1987): Angiotensin converting enzyme activity in hypertensive subjects after magnesium sulfate therapy. *Am. J. Obstet. Gynecol.* **156**, 1375.
- Fujita, T., Ito, Y., Ando, K., Noda, H., Ogata, E. (1990): Attenuated vasodilator responses to Mg^{2+} in young patients with borderline hypertension. *Circulation* **82**, 384.
- Gonella, M., Calabrese, G. (1989): Magnesium status in chronically haemodialyzed patients: the role of dialysate magnesium concentration. *Magnesium Research* **2**, 259.
- Gums, J. G. (1987): Clinical significance of magnesium: a review. *Drug. Intell. Clin. Pharm.* **21**, 240.
- Harzard, R., Wurmser, L. (1932): Action de sels de magnesium sur les vasoconstricteurs renaux. *C. R. Soc. Biol.* **110**, 525.
- Heaton, F. W., Pyrah, L. N., Beresford, C. C., Bryson, R. W., Martin, D. F. (1962): Hypomagnesaemia in chronic alcoholism. *Lancet* **2**, 802.
- Henderson, D. G., Schierup, J., Schodt, T. (1986): Effect of magnesium supplementation on blood pressure and electrolyte concentration in hypertensive patients receiving long-term diuretic treatment. *Br. Med. J.* **293**, 664.
- Horton, R., Biglieri, E. G. (1962): Effect of aldosterone on metabolism of magnesium. *J. Clin. Endocrinol. Metab.* **22**, 1187.
- Hurley, L. S. (1981): Mg deficiency in pregnancy and its effects on the fetus. *Magnesium-Bull.* **3/1a**, 202.
- Imai, M. (1978): Calcium transport across the rabbit thick ascending limb of Henle's loop perfused in vitro. *Pflügers Arch.* **374**, 255.
- Kjeldsen, S. E., Sejersted, O. M., Frederichsen, P., Leren, P., Fide, J. K. (1990): Increased erythrocyte magnesium in never treated essential hypertension. *A. J. H.* **3**, 573.
- Koberlin, W., Mischell, W. (1958): Der Magnesiumgehalt des Blutserums bei der Frau während der Schwangerschaft und bei Spättoxikosen. *Zentralbl. Gynäkol.* **6**, 226.
- Leary, W. P., Reyes, A. J., Van der Byl, K., Acosta-Barrios, T. N. (1985): Effects of captopril, hydrochlorothiazide and their combination on timed urinary excretions of water and solutes. *J. Cardiovasc. Pharmac.* **7**, S56.
- MacIntyre, I., Boss, S., Troughton, V. A. (1963): Parathyroid hormone and magnesium homeostasis. *Nature (London)* **198**, 1058.
- Martindale, I., Heaton, F. W. (1964): Magnesium deficiency in the adult rat. *Biochem. J.* **92**, 119.
- Massry, S. G., Coburn, J. W., Kleeman, C. R. (1969): Renal handling of magnesium in the dog. *Am. J. Physiol.* **216**, 1460.

- McCarron, D. A. (1983): Calcium and magnesium nutrition in human hypertension. *Ann. Inter. Med.* **98**, 800.
- McCollister, R. J., Flink, F. B., Lewis, M. D. (1963): Urinary excretion of magnesium in man following the ingestion of ethanol. *Am. J. Clin. Nutr.* **12**, 415.
- McNair, P., Christiansen, C., Madsbad, S., Lauritzen, E., Faber, O., Binder, C., Transbil, I. (1978): Hypomagnesaemia, a risk factor in diabetic retinopathy. *Diabetes* **27**, 1075.
- Mordes, J. P., Wacker, W. E. C. (1977): Excess Mg. *Pharmacol. Rev.* **29**, 273.
- Morel, F., Roinel, N., Le Grimmelec, C. (1969): Electron probe analysis of tubular fluid composition. *Nephron* **6**, 350.
- Motoyama, T., Sano, H., Suzuki, H., Kawaguchi, K., Saito, K., Furuta, Y., Fukuzaki, H. (1986): Oral magnesium treatment and the erythrocyte sodium pump in patients with essential hypertension. *J. Hyperten.* **4** (Suppl. 6), S682.
- Page, E., Polimeni, P. J. (1972): Magnesium exchange in rat ventricle. *J. Physiol. (London)* **224**, 121.
- Peeronboom, H., Geldschlager, H., Keck, H., Heinen, E., Srohmeyer, G. (1980): Intestinal Mg absorption in hyperparathyroidism on animal study. *Magnesium-Bull.* **2**, 121.
- Petersen, B., Schrooll, M., Christiansen, C., Transbol, I. (1977): Serum and erythrocyte magnesium in normal elderly Danish people. *Acta Med. Scand.* **201**, 31.
- Poujbol, P., Touvy, C., Roinel, N., De Rouffignac, C. (1980): Stimulation of renal magnesium reabsorption by calcitonin in the rat. *Am. J. Physiol.* **239**, F524.
- Pritchard, J. A., Pritchard, S. A. (1975): Standardized treatment of 154 consecutive cases of eclampsia. *Am. J. Obstet. Gynecol.* **123**, 543.
- Quamme, G. A. (1978): Effect of intraluminal furosemide on calcium and magnesium transport in the loop of Henle and the role of PTH. *Kidney International* **14**, 642.
- Quamme, G. A. (1980): Effect of calcitonin on calcium and magnesium transport in the rat nephron. *Am. J. Physiol.* **238**, 573.
- Quamme, G. A., Carney, S. C., Wong, N. L. M., Dirks, J. H. (1980): Effect of PTH on renal Ca and Mg reabsorption in Mg deficient rats. *Pflügers Arch.* **386**, 59.
- Quamme, G. A., Dirks, J. H. (1980): Effect of intraluminal and contraluminal magnesium on magnesium and calcium transfer in the rat nephron. *Am. J. Physiol.* **238**, 187.
- Resnick, L. M., Laragh, J. H., Sealey, J. E., Alderman, M. H. (1983): Divalent cations in essential hypertension: relations between serum ionized calcium, magnesium and plasma renin activity. *N. Engl. J. Med.* **309**, 888.
- Rude, R. K. (1989): Physiology of magnesium metabolism and the important role of magnesium in potassium deficiency. *Am. J. Cardiol.* **63**, 31G.
- Rude, R. K., Belhune, J. E., Singer, F. R. (1980): Renal tubular maximum for magnesium in normal hyperparathyroid and hypoparathyroid men. *J. Clin. Endocrinol. Metab.* **41**, 1425.
- Ryan, M. P., Devane, J., Ryan, M. F., Counihan, T. B. (1984): Effects of diuretics on the renal handling of magnesium. *Drugs* **28** (Suppl. 1), 167.
- Sharegi, G. R., Agus, Z. S. (1982): Magnesium transport in the cortical thick ascending limb of Henle's loop of the rabbit. *J. Clin. Invest.* **69**, 759.
- Shils, M. E. (1964): Experimental human magnesium depletion. *Am. J. Clin. Nutr.* **14**, 242.
- Statopolsky, E., Weerts, C., Lopez-Hilker, S., Norwood, K., Zink M., Windus, D., Délmez, J. (1986): Calcium carbonate as a phosphate binder in patients with chronic renal failure undergoing dialysis. *N. Eng. J. Med.* **315**, 157.
- Suki, W. N., Rouse, A., Ng, R. C., Kokko, J. P. (1980): Calcium transport in the thick ascending limb of Henle. Heterogeneity of function in the medullary and cortical segments. *J. Clin. Invest.* **66**, 1004.
- Sutton, R. A. L., Watson, L. (1969): Urinary excretion of calcium and magnesium in primary hyperparathyroidism. *Lancet* **1**, 1000.

- Tillman, D. M., Semple, P. F. (1988): Calcium and magnesium essential hypertension. *Clin. Sci.* **75**, 395.
- Turlapaty, P. D., Altura, B. T., Altura, B. M. (1980): Ca^{2+} -uptake and distribution in alloxan diabetic rat arterial and venous smooth muscle. *Experientia* **36**, 1298.
- Wacker, W. E. C. (1980): *Mg and Man*. Harvard Univ. Press, Cambridge, Mass. – London, 71.
- Wen, S. F., Wong, N. L. M., Dirks, J. H. (1971): Evidence for renal magnesium secretion during magnesium infusion in the dog. *Am. J. Physiol.* **220**, 33.
- Wesson, L. G. Jr. (1962): Magnesium, calcium and phosphate excretion during osmotic diuresis in the dog. *J. Lab. Clin. Med.* **60**, 422.
- Whang, R., Oei, T. O., Hamiter, T. (1978): Frequency of hypomagnesaemia associated with hypokalaemia in hospitalized patients. *Am. J. Clin. Path.* **71**, 610.
- Whang, R., Welt, L. G. (1963): Observations in experimental magnesium depletion. *J. Clin. Invest.* **42**, 305.
- Whelton, P. K., Klag, M. J. (1989): Magnesium and blood pressure — review of the epidemiologic and clinical trial experience. *Am. J. Cardiol.* **63**, 26G.
- Wilcox, C. S. (1978): The effect of increasing the plasma magnesium concentration on renin release from the dog's kidney: Interactions with calcium and sodium. *J. Physiol.* **284**, 203.
- Wong, N. L. M., Quamme, G. A., Dirks, J. H. (1983): Tubular reabsorptive capacity for magnesium in the dog kidney. *Am. J. Physiol.* **224**, 62.
- Wong, N. L. M., Quamme, G. A., Suttun, R. A. L., Dirks, J. H. (1979): The effect of mannitol on divalent ion transport in the kidney. *J. Lab. Clin. Med.* **94**, 683.

7.4. Significance of magnesium in functioning of the nervous system

- Aikawa, J. K. (1981): *Magnesium: Its Biologic Significance*. CRC Press, Inc., Boca Raton, FA.
- Altura, B. M., Altura, B. T., Gebrewold, A., Ising, H., Günther, T. (1984): Magnesium deficiency and hypertension: Correlation between magnesium-deficient diets and microcirculatory changes in situ. *Science* **223**, 1315.
- Alvarez-Leefmans, F. J., Gamino, S. M., Rink, T. J. (1984): Intracellular free magnesium in neurones of *Helix aspersa* measured with ion-selective micro-electrodes. *J. Physiol.* (London) **354**, 303.
- Ashton, D., Willems, R., De Prins, E., Wauquier, A. (1988): Field-potential assay of antiepileptic drugs in the hippocampal slice. *Epilepsia* **29**, 321.
- Avoli, M., Drapeau, C., Louvel, J., Pumain, R., Olivier, A., Villemure, J.-G. (1991): Epileptiform activity induced by low extracellular magnesium in the human cortex maintained in vitro. *Ann. Neurol.* **30**, 589.
- Bashuk, R. G., Krendel, D. A. (1990): Myasthenia gravis presenting as weakness after magnesium administration. *Muscle Nerv.* **13**, 708.
- Bertorini, T. E., Bhattacharya, S. K., Palmieri, G. M. A., Chesney, C. M., Pifer, D., Baker, B. (1982): Muscle calcium and magnesium content in Duchenne muscular dystrophy. *Neurology* (New York) **32**, 1088.
- Bird, M. M. (1980): The morphology of synaptic profiles in explants of foetal and neonatal mouse cerebral cortex maintained in a magnesium-enriched environment. *Cell Tiss. Res.* **206**, 115.
- Birks, R. I. (1974): The relationship of transmitter release and storage to fine structure in a sympathetic ganglion. *J. Neurocytol.* **3**, 133.

- Bito, L. Z. (1969): Blood-brain barrier: Evidence for active cation transport between blood and the extracellular fluid of brain. *Science* **165**, 81.
- Blatter, L. A. (1990): Intracellular free magnesium in frog skeletal muscle studied with a new type of magnesium-selective microelectrode: Interactions between magnesium and sodium in the regulation of $[Mg^{2+}]_i$. *Pflüg. Arch. Eur. J. Physiol.* **416**, 238.
- Brorson, J. R. (1991): Magnesium suppresses seizurelike discharges in cultured neurons. *Arch. Neurol.* **48**, 677.
- Carman, J. S., Post, R. M., Teplitz, A., Goodwin, F. K. (1974): Divalent cations in predicting antidepressant response to Li. *Lancet* **2**, 1454.
- Chi, O. Z., Pollak, P., Weiss, H. R. (1990): Effects of magnesium sulfate and nifedipine on regional cerebral blood flow during middle cerebral artery ligation in the rat. *Arch. Int. Pharmacodyn. Ther.* **304**, 196.
- Chutkow, J. G. (1978): Uptake of magnesium into the brain of the rat. *Exp. Neurol.* **60**, 592.
- Classen, H. G. (1981): Stress reaction modified by Mg status. *Magnesium-Bull.* **3**, 148.
- Czeh, G., Somjen, G. (1989): Changes in extracellular calcium and magnesium and synaptic transmission in isolated mouse spinal cord. *Brain Res.* **486**, 274.
- Daus, A. T., Freeman, W. M., Wilson, J., Aponte, C. (1985): Clinical experience with 781 cases of alcoholism evaluated and treated on an inpatient basis by various methods. *Int. J. Addict.* **20**, 643.
- Del Castillo, J., Engbaek, L. (1954): The nature of the neuromuscular block produced by magnesium. *J. Physiol. (London)* **124**, 370.
- Demoliou-Mason, C. D., Barnard, E. A. (1986): Characterization of opioid receptor subtypes in solution. *J. Neurochem.* **46**, 1129.
- Dinsdale, H. B. (1988): Does magnesium sulfate treat eclamptic seizures? Yes. *Arch. Neurol.* **45**, 1360.
- Durlach, J. (1988): *Magnesium in Clinical Practice*. John Libbey Eurotext, London – Paris.
- Ellory, J. C., Flatman, P. W., Stewart, G. W. (1983): Inhibition of human red cell sodium and potassium by divalent cations. *J. Physiol. (London)* **340**, 1.
- Emser, W. (1982): Hypermagnesemic periodic paralysis. Treatment with digitalis and lithium carbonate. *Arch. Neurol.* **39**, 727.
- Flatman, P. W. (1988): The effects of magnesium on potassium transport in ferret red cells. *J. Physiol. (London)* **397**, 471.
- Glick, J. L. (1990): Dementias: The role of magnesium deficiency and a hypothesis concerning the pathogenesis of Alzheimer's disease. *Med. Hypotheses* **31**, 211.
- Goldman, R. S., Finkbeiner, S. M. (1988): Therapeutic use of magnesium sulfate in selected cases of cerebral ischemia and seizure. *New Engl. J. Med.* **319**, 1224.
- Hartzell, H. C., White, R. E. (1989): Effects of magnesium on inactivation of the voltage-gated calcium current in cardiac myocytes. *J. Gen. Physiol.* **94**, 745.
- Hasey, G. M., D'Alessandro, E., Cooke, R. G., Warsh, J. J. (1993): The interface between thyroid activity, magnesium and depression: A pilot study. *Biol. Psychiat.* **33**, 133.
- Heipertz, R., Eickhoff, K., Karstens, K. H. (1979): Magnesium and inorganic phosphate content in CSF related to blood-brain barrier functions in neurological disease. *J. Neurol. Sci.* **40**, 87.
- Herzberg, L., Herzberg, B. (1977): Mood change and magnesium. A possible interaction between magnesium and lithium? *J. Nerv. Ment. Dis.* **165**, 423.
- Huang, Q. F., Gebrewold, A., Altura, B. T., Altura, B. M. (1990): Cocaine-induced cerebral vascular damage can be ameliorated by Mg^{2+} in rat brain. *Neurosci. Lett.* **109**, 113.
- Hutter, O. F., Kostial, K. (1954): Effect of magnesium and calcium ions on the release of acetylcholine. *J. Physiol. (London)* **124**, 234.
- Janka, Z., Jones, D. G. (1982a): A morphometric study of cultured rat cerebral synapses exposed to different cationic media. *Brain Res.* **241**, 215.

- Janka, Z., Jones, D. G. (1982b): Junctions in rat neocortical explants cultured in TTX-, GABA-, and Mg^{++} -environments. *Brain Res. Bull.* **8**, 273.
- Janka, Z., Jones, D. G. (1984): Quantitative ultrastructural approaches to the analysis of synapses in culture. In: Jones, D. G. (ed.): *Current Topics in Research on Synapses*. Alan R. Liss, Inc., New York, Vol. 2, 1.
- Jones, R. S. G. (1989): Ictal epileptiform events induced by removal of extracellular magnesium in slices of entorhinal cortex are blocked by baclofen. *Exp. Neurol.* **104**, 155.
- Kaplan, P. W., Lesser, R. P., Fisher, R. S., Repke, J. T., Hanley, D. F. (1988): No, magnesium sulfate should not be used in treating eclamptic seizures. *Arch. Neurol.* **45**, 1361.
- Katz, B. (1971): Quantal mechanism of neural transmitter release. *Science* **173**, 123.
- Katz, B., Miledi, R. (1968): A study of spontaneous miniature potentials in spinal motoneurons. *J. Physiol. (London)* **168**, 389.
- Kjeldsen, S. E., Sejersted, O. M., Frederichsen, P., Leren, P., Eide, I. K. (1990): Increased erythrocyte magnesium content in essential hypertension. *Scand. J. Clin. Lab. Invest.* **50**, 395.
- Koike, T. (1983): Nerve growth factor-induced neurite outgrowth of rat pheochromocytoma PC 12 cells: Dependence on external Mg^{2+} and Ca^{2+} . *Brain Res.* **289**, 293.
- Kruse, H. D., Orent, E. R., McCollum, E. V. (1932): Studies on magnesium deficiency in animals. I. Symptomatology resulting from magnesium deprivation. *J. Biol. Chem.* **96**, 519.
- Linder, J., Brismar, K., Beck-Friid, J., Saaf, J., Wetterberg, L. (1989): Calcium and magnesium concentrations in affective disorder: Difference between plasma and serum in relation to symptoms. *Acta Psychiat. Scand.* **80**, 527.
- Lipcsey, A., Szentistványi, I., Janka, Z. (1986): *Biological Basis of Psychiatry*. Akadémiai Kiadó, Budapest. (In Hung.)
- Ludi, H., Schatzmann, H. J. (1989): Some properties of a system for sodium-dependent outward movement of magnesium from metabolizing human red blood cells. *J. Physiol. (London)* **390**, 367.
- Maguire, M. E. (1984): Hormone-sensitive magnesium transport and magnesium regulation of adenylate cyclase. *Trends Pharmacol. Sci.* **5**, 73.
- Martineau, J., Barthelemy, C., Garreau, B., Lelord, G. (1985): Vitamin B_6 , magnesium, and combined B_6 -Mg: Therapeutic effects in childhood autism. *Biol. Psychiat.* **20**, 467.
- McIntosh, T. K., Vink, R., Yamakami, I., Faden, A. I. (1989): Magnesium protects against neurological deficit after brain injury. *Brain Res.* **482**, 252.
- McKinlay, R. G., Usherwood, P. N. R. (1978): The effects of magnesium ions on the fine structure of the insect neuromuscular junction. *J. Ultrastruct. Res.* **62**, 83.
- Meltzer, S. J., Auer, J. (1905): Physiological and pharmacological studies of magnesium salts. I. General anesthesia by subcutaneous injection. *Am. J. Physiol.* **14**, 366.
- Mody, I., Lambert, J. D. C., Heinemann, U. (1987): Low extracellular magnesium induces epileptiform activity and spreading depression in rat hippocampal slices. *J. Neurophysiol.* **57**, 869.
- Nicoletti, F., Wroblewski, J. T., Costa, E. (1987): Magnesium ions inhibit the stimulation of inositol phospholipid hydrolysis by endogenous excitatory amino acids in primary cultures of cerebellar granule cells. *J. Neurochem.* **48**, 967.
- Parkinson, F. E., Fredholm, B. B. (1992): Magnesium-dependent enhancement of endogenous agonist binding to A_1 adenosine receptors: A complicating factor in quantitative autoradiography. *J. Neurochem.* **58**, 941.
- Reinhart, R. A. (1988): Magnesium metabolism. A review with special reference to the relationship between intracellular content and serum levels. *Arch. Intern. Med.* **148**, 2415.
- Riggs, J. E., Klingberg, W. G., Flink, E. B., Schochet, Jr. S. S., Balian, A. A., Jenkins, J. J. (1992): Cardioskeletal mitochondrial myopathy associated with chronic magnesium deficiency. *Neurology* **42**, 128.

- Rodriguez, F. D., Bardaji, E., Traynor, J. R. (1992): Differential effects of Mg^{2+} and other divalent cations on the binding of tritiated opioid ligands. *J. Neurochem.* **59**, 467.
- Rotevati, S., Murphy, E., Levy, L. A., Raju, B., Lieberman, M., London, R. E. (1989): Cytosolic free magnesium concentration in cultured chick heart cells. *Am. J. Physiol. Cell Physiol.* **257**, C141.
- Rugolo, M., Zoccarato, F. (1984): Magnesium transport by brain mitochondria: Energy requirement and dependence on Ca^{2+} fluxes. *J. Neurochem.* **42**, 1127.
- Sherwood, R. A., Rocks, B. F., Stewart, A., Saxton, R. S. (1986): Magnesium and premenstrual syndrome. *Ann. Clin. Biochem.* **23**, 667.
- Sibai, B. M. (1990): Magnesium sulfate is the ideal anticonvulsant in preeclampsia-eclampsia. *Am. J. Obstet. Gynecol.* **162**, 1141.
- Somogyi, J. (1987): Transport processes of neural cells. In: Magyar, K., Vizi, E. Sz. (eds): *The Essentials of Neurochemistry*. Medicina, Budapest, 90. (In Hung.)
- Sulakhe, P. V., Jagadeesh, G., Phan, N. T., Rao, T. S., Veeranjanyulu, A. (1990): $MgCl_2$ -sensitive and Gpp(NH)p-sensitive antagonist binding states of rat heart muscarinic receptors: Preferential detection at ambient temperature assay and location in two subcellular fractions. *Mol. Cell. Biochem.* **94**, 133.
- Watanabe, M., George, S. R., Seeman, P. (1985): Regulation of anterior pituitary D_2 dopamine receptors by magnesium and sodium ions. *J. Neurochem.* **45**, 1842.
- Yasui, M., Yase, Y., Ando, K., Adachi, K., Mukoyama, M., Ohsugi, K. (1990): Magnesium concentration in brain from multiple sclerosis patients. *Acta Neurol. Scand.* **81**, 197.
- Yasui, M., Yase, Y., Kihira, T., Adachi, K., Suzuki, Y. (1992): Magnesium and calcium contents in CNS tissues of amyotrophic lateral sclerosis patients from the Kii peninsula, Japan. *Eur. Neurol.* **32**, 95.
- Yoshida, S., Yano, I., Wakayama, I., Mitani, K., Yase, Y. (1990): Morphometric analysis of neurodegenerative changes induced by low calcium-magnesium and excessive aluminium intake. *Biomed. Res.* **11**, 11.

7.5. The role of magnesium metabolism in physiologic and pathologic pregnancy

- Aikawa, J. K. (1981): *Magnesium: Its Biological Significance*. CRC Press, Boca Raton, 64.
- Baltzer, G., Daume, E. (1976): Untersuchungen zum Serum-Magnesium-Spiegel in der Gravidität. *Verh. Dtsch. Ges. Inn. Med.* **82**, 880.
- Bartl, W., Riss, P. (1984): Zur Pathophysiologie und Therapie des Magnesiummangels in der Schwangerschaft. *Magnesium-Bull.* **2**, 60.
- Black, A. E., Wiles, S. M., Paul, A. A. (1986): The nutrient intake of pregnant and lactating mothers of good socio-economic status in Cambridge, UK: some implications for recommended daily allowances of minor nutrients. *Br. J. Nutr.* **56**, 59.
- Bogart, L. J., Plass, E. D. (1923): Placental transmission. I. The calcium and magnesium content of fetal and maternal blood serum. *J. Biol. Chem.* **56**, 299.
- Conradt, A., Weidinger, H., Algayer, H. (1984): Reduzierte Frequenz von Gestosen bei Beta-mimetika-behandelten Risikoschwangerschaften mit Magnesium-Zusatztherapie. *Geburtsh. Frauenheilk.* **44**, 118.
- Dorsett, L. (1926): Intramuscular injection of magnesium sulphate for control of convulsions in eclampsia. *Am. J. Obstet. Gynec.* **11**, 227.
- Doyle, W., Crawford, M. A., Wynn, A. H., Wynn, S. W. (1989): Maternal magnesium intake and pregnancy outcome. *Magnesium Research* **2**, 205.

- Dyckner, T., Wester, P. O., Widman, L. (1988): Effects of peroral magnesium on plasma and skeletal muscle electrolytes in patients on long-term diuretic therapy. *Int. J. Cardiol.* **19**, 81.
- Elliot, J. P.: Magnesium sulfate as a tocolytic agent. (1983): *Am. J. Obstet. Gynec.* **117**, 277.
- Engback, L.: Pharmacodynamics of neuromuscular blocking agents. Inhibitor ion: Magnesium (1972) In: Cheymol, J.: *Neuromuscular Blocking and Stimulating Agents*. Pergamon Press, Oxford, Vol. 1, 391.
- Fischer, B., Fischer, U. (1981): Magnesium in der inneren Medizin, Pathophysiologie und Klinik. *Magnesium-Bull.* **1**, 249.
- Holtmeier, H. J.: Das primäre und sekundäre Magnesiummangelsyndrom. In: Heilmeyer, L., Holtmeier, H. J.: *Ernährungswissenschaften*, Stuttgart, 111.
- Ising, H., Günther, T., Handrock, M., Michalek, R., Schwarzer, J., Vorman, J., Wüster, G. A. (1981): Magnesium und Lärmwirkungen. *Magnesium-Bull.* **1**, 155.
- James, M. F. M., Huddle, K. R. L., Owen, A. D., van der Veen, B. W. (1988): Use of magnesium sulphate in the anaesthetic management of phaeochromocytoma in pregnancy. *Can. J. Anaesth.* **35**, 178.
- Jaspers, V., Spätling, L., Fallenstein, F., Quakernack, K. (1981): Magnesium, Kalzium, Hä-moglobin, Hämatokrit, Östriol und HPL unter Magnesiumsubstitution in der Schwangerschaft. *Gebrutsh. u. Frauenheilk.* **50**, 628.
- Kiss, D., Szőke, B. (1975): Rolle des Mg bei der Verhütung der Frühgeburt. *Zbl. Gynäk.* **97**, 924.
- Koller, S. (1983): *Risikofaktoren der Schwangerschaft*. Springer Verlag, Berlin – Heidelberg – New York – Tokyo, 157.
- Kovács, L. (1989): Prevention of intrauterine growth retardation by magnesium substitution in pregnancy. In: Kurjak, A., Beazley, J. M.: *Fetal Growth Retardation: Diagnosis and Treatment*. CRC Press, Boca Raton, 163.
- Kovács, L., Molnár, G. B., Huhn, E., Bódis, L. (1988a): Magnesium-substitution in der Schwangerschaft. *Geburtsh. Frauenheilk.* **48**, 595.
- Kovács, L., Molnár, G. B., Huhn, E., Bódis, L. (1988b): Magnesium supplementation during pregnancy. *Magyar Nőorv. L.* **51**, 9. (In Hung.)
- Krebs, O. S., Briggs, A. P. (1923): Blood studies in normal pregnancy. *Am. J. Obstet. Gynecol.* **5**, 67.
- Kuti, V., Balázs, M., Morvay, F., Varenka, Zs., Székely, A., Szűcs, M., Hajdók, K., Halmos, K., Szabó, I., Benkő, L., Tas, M., Pázsit, L., Zmertich, A., Tüske, Zs., Bálint, I., Mélykúti, M., Csuka, J., Fodor, M., Horváth, I., Kóbor, T., Morva, L. (1982): Effects of maternal magnesium supply on the spontaneous abortion, premature birth, intrauterine development of the foetus and infant death. (An experimental epidemiological study). *Egészségtudomány* **26**, 62. (In Hung.)
- Lazard, E. M. (1925): A preliminary report on the intravenous use of magnesium sulphate in puerperal eclampsia. *Am. J. Obstet. Gynecol.* **9**, 178.
- Lim, P., Jacob, E., Dong, S., Khoo, O. T. (1969): Values for tissue magnesium as a guide in detecting magnesium deficiency. *J. Clin. Path.* **22**, 417.
- Mahran, M., Hanna, S. (1968): Magnesium level in the serum of pregnant women and in the amniotic fluid. *J. Egypt. Med. Ass.* **4**, 251.
- Michel, C. (1989): Sur la composition chimique de l'embryon et du foetus humains aux différentes périodes de la grossesse. *Compt. Rend. Soc. Biol.* **51**, 422.
- Rigó, J. Jr., Hídvégi, J., Csömör, S., Györe, I., Tölgyesi, Gy., Rigó, J. (1987): Study of correlations of serum magnesium and certain fat parameters in pregnant women. *Magyar Nőorv. L.* **50**, 150. (In Hung.)
- Ring, K., Grimm, E., Schwarz, M. (1975): Wechselwirkungen zwischen L-Aspartat und Kaliumionen beim Transport in lebenden Zellen. In: Kronschwitz, H.: Kalium-Magnesium-Zink-Aspartat, 15. Kolloquium. Frankfurt/M., 3.

- Rissmann, P. (1916): Neue Wege der Eklampsiebehandlung. *Zeitschr. Geburtsh. Gynäk.* **78**, 447.
- Rosner, F., Gorfien, P. C. (1968): Erythrocyte and plasma zinc and magnesium levels in health and disease. *J. Lab. Clin. Med.* **72**, 213.
- Seelig, M. S. (1981a): *Magnesium Deficiency in the Pathogenesis of Disease*. Plenum Press, New York – London, 38.
- Seelig, M. S. (1981b): Magnesium requirements in human nutrition. *Magnesium-Bull.* **1**, 26.
- Seelig, M. S., Berger, A. R. (1974): Range of normal serum magnesium values. *N. Engl. J. Med.*, **290**, 974.
- Sibai, B. M. (1990): Magnesium sulfate is the ideal aticonvulsant in preeclampsia-eclampsia. *Am. J. Obstet. Gynecol.* **162**, 1141.
- Sibai, B. M., Villar, M. A., Bray, E. (1989): Magnesium supplementation during pregnancy: a double-blind randomized controlled clinical trial. *Am. J. Obstet. Gynecol.* **161**, 115.
- Skajaa, K., Dorup, I., Sandström, B. M. (1991): Magnesium intake and status and pregnancy outcome in a Danish population. *Brit. J. Obstet. Gynecol.* **98**, 919.
- Spätling, L. (1981): Orale Magnesium-Zusatztherapie bei vorzeitiger Wehentätigkeit. *Geburtsh. Frauenheilk.* **41**, 101.
- Spätling, L., Disch, G., Classen, H. G. (1989): Magnesium in pregnant women and the newborn. *Magnesium Research* **2**, 271.
- Spätling, L., Kunz, P. A., Vonderschmitt, D. J., Hich, R., Huch, A. (1983): Zum Magnesiumgehalt der Uterusmuskulatur im III. Trimenon. *Arch. Gynecol.* **235**, 470.
- Spätling, L., Spätling, G. (1988): Magnesium supplementation in pregnancy. A double-blind study. *Br. J. Obstet. Gynecol.* **95**, 120.
- Staib, I., Kretzschmar, M. (1968): Messung der Elektrolytkonzentration in verschiedenen Gewebearten der Ratte nach Verabreichung von Kalium-Magnesium-Aspartat. *Arzneim. Forsch.* **18**, 342.
- Stefanini U., Vegetti, T., Lupi, G., Bianchi, F. (1968): Ricerche sulla magnesemia in casi di parto prematuro. *Ann. Obstet. Gynecol.* **90**, 59.
- Watson, K. V., Molow, C. F., Ogburn, P. L., Jacob, H. S. (1986): Magnesium sulfate: Rational for its use in preeclampsia. *Proc. Natl. Acad. Sci. USA* **83**, 1075.
- Wilkins, I. A., Goldberg, J. D., Phillips, R. N., Bacall, Ch. J., Chervenak, F. A., Berkowitz, R. L. (1986): Long-term use of magnesium sulfate as a tocolytic agent. *Obstet. Gynecol.* **67**, 389.
- Wischnik, A., Mandler, N., Heimisch, W., Schroll, A., Weidenbach, A. (1982): Das kardiale Risiko bei Tokolyse und Möglichkeiten zu dessen Antagonisierung. II. Mitteilung: Kardioprotektion durch Magnesiumsubstitution. *Geburtsh. Frauenheilk.* **4**, 537.
- Wischnik, A., Weidinger, H. (1985): Magnesiumaspartat und Magnesiumsulfat in der Geburtshilfe. *Magnesium-Bull.* **3**, 96.

7.6. Magnesium and biliary tract motility

- Becker, J. M., Moody, F. G., Zinsmeister, A. R. (1982): Effect of gastrointestinal hormones on the biliary sphincter of the opossum. *Gastroenterology* **82**, 1300.
- Behar, J., Biancani, P. (1980): Effect of cholecystokinin and the octapeptide of cholecystokinin on the feline sphincter of Oddi and gallbladder. Mechanism of action. *J. Clin. Invest.* **66**, 1231.
- Berry, H., Flower, R. J. (1971): The assay of endogenous cholecystokinin and factors influencing its release in the dog and cat. *Gastroenterology* **60**, 409.

- Brotschii, E. A., La Morte, W. W., Williams, L. F. Jr. (1984): The role of extracellular calcium ion in gallbladder contractility. *Gastroenterology* **86**, 1036.
- Chen, Y. F., Chey, W. F., Chang, T. M., Lee, K. Y. (1985): Duodenal acidification releases cholecystokinin. *Am. J. Physiol.* **249**, G29.
- Chen, S. T., Peikin, S. R. (1982): Role of calcium as a mediator of guinea pig gallbladder contraction caused by ACh and CCK-OP. *Gastroenterology* **82**, 1253.
- Crochelt, R. F., McCallion, M. A., Peikin, I. R. (1984): Correlation of ⁴⁵Calcium influx with contractility in guinea pig gallbladder strips. *Gastroenterology* **86**, 1350.
- Fried, G. M., Ionue, K., Wiener, I., Watson, L. C., Thompson, J. C. (1981): Effect of divalent cations on the release of cholecystokinin and gastrin. *Surg. Forum* **32**, 209.
- Harada, T., Katsuragi, T., Furukawa, T. (1986): Release of acetylcholine mediated by cholecystokinin receptor from the guinea pig sphincter of Oddi. *J. Pharmacol. Exp. Therap.* **239**, 554.
- Harvey, R. F., Dowsett, L., Hartog, M., Read, A. E. (1973): A radioimmunoassay for cholecystokinin-pancreozymin. *Lancet* **11**, 826.
- Harvey, R. F., Ederla, A., Vantini, I., Scuro, L. A., Oliver, J. M., Read, A. E. (1978): Secretion and clearance rate of cholecystokinin pancreozymin. *Ital. L. Gastroenterol.* **10**, 100.
- Inoue, K., Wiener, I., Fagan, C. J., Watson, L. C., Thompson, J. C. (1981): Effect of oral magnesium sulfate on gallbladder contraction and cholecystokinin release in man. *Gastroenterology* **80**, 1181.
- Ivy, A. C. (1934): The physiology of the gallbladder. *Physiol. Rev.* **14**, 102.
- Ivy, A. C., Oldberg, E. (1928): A hormone mechanism for gallbladder contraction and evacuation. *Am. J. Physiol.* **86**, 599.
- Lilja, P., Fagan, C., Wiener, I., Inoue, K., Watson, L. C., Thompson, J. C. (1981): Disappearance half-time of CCK-99% correlated with gallbladder volume in man. *Gastroenterology* **80**, 1213.
- Lilja, P., Fagan, C., Wiener, I., Inoue, K., Watson, L. C., Rayford, P. L., Thompson, J. C. (1982): Infusion of pure CCK in humans: Correlation between plasma concentrations of CCK and gallbladder size. *Gastroenterology* **83**, 256.
- Lin, T. M. (1975): Actions of gastrointestinal hormones and related peptides on the motor function of the biliary tract. *Gastroenterology* **69**, 1006.
- Lonovics, J. (1989): Calcium antagonists and the gastrointestinal tract. *Orvosképzés* **64**, 213. (In Hung.)
- Lonovics, J., Hajnal, F., Mara, P., Szabó, I., Varró, V. (1979): Investigation of cholecystokinin-octapeptide splitting enzyme in dog kidney. *Acta Hepato-Gastroent. (Stuttgart)* **26**, 222.
- Lonovics, J., Hajnal, F., Suddith, R. L., Rayford, P. L., Thompson, J. C. (1980a): Metabolism of different molecular forms of cholecystokinin. *Proc. XXVIII. Int. Union of Phys. Sci. Budapest* **14**, 183.
- Lonovics, J., Guzman, S., Devitt, P. G., Hejtmancik, K. E., Suddith, R. L., Rayford, P. L., Thompson, J. C. (1980b): Release of pancreatic polypeptide in human by infusion of cholecystokinin. *Gastroenterology* **79**, 817.
- Lonovics, J., Hajnal, F., Suddith, R. L., Rayford, P. L., Thompson, J. C. (1981): Metabolism of different molecular forms of cholecystokinin. *Adv. Physiol. Sci. Nutrition. Digestion. Metabolism* **12**, 383.
- Lonovics, J., Hajnal, F., Varró, V., Thompson, J. C. (1985a): Humoral regulation of the biliary tract motility. I. Gallbladder. *Kísérl. Orvostud.* **37**, 588. (In Hung.)
- Lonovics, J., Varró, V., Thompson, J. C. (1985b): The effect of cholecystokinin and substance P antagonists on cholecystokinin and substance P-stimulated gallbladder contraction. *Gastroenterology* **88**, 1480.
- Lonovics, J., Varró, V., Thompson, J. C. (1985c): The role of calcium and cAMP in cholecystokinin (CCK)-stimulated rabbit gallbladder contraction. *Gastroenterology* **88**, 1480.

- Lonovics, J., Penke, B., Rayford, P. L., Thompson, J. C. (1986): Cholecystokinin-destroying activities of canine tissue homogenates. *Hepatogastroenterology* **33**, 27.
- Lonovics, J., Németh, J., Hulesch, H., Bálint, G. A., Varró, V., Thompson, J. C. (1988a): Both calmodulin and cyclic nucleotides participate in the cholecystokinin (CCK) and substance P (SP) induced gallbladder (GB) contraction. *Gastroenterology* **94**, 270.
- Lonovics, J., Németh, J., Hulesch, H., Bálint, G. A., Varró, V., Penke, B. (1988b): The role of calmodulin and cyclic nucleotide system in the cholecystokinin induced gallbladder contraction. In: Penke, B., Török, A. (eds): *Peptides. Chemistry, Biology, Interaction with Proteins*. Walter de Gruyter, Berlin – New York, 185.
- Lonovics, J., Lénárt, Zs., Velösy, B., Németh, J., Thompson, C. J., Varró, V. (1988c): Differences in the mechanism of cholecystokinin, substance P and vasoactive intestinal polypeptide induced Oddi-sphincter relaxation in dogs. In: Penke, B., Török, A. (eds): *Peptides. Chemistry, Biology, Interaction with Proteins*. Walter de Gruyter, Berlin – New York, 171.
- Lonovics, J., Németh, J., Varró, V., Greeley, G. H. Jr., Thompson, C. J. (1990a): Hormonal mechanism in gallbladder motility. In: Thompson, J. C. (ed.): *Gastrointestinal Endocrinology. Receptors and Post-Receptor Mechanisms*. Academic Press, San Diego – New York, 491.
- Lonovics, J., Greeley, G. H. Jr., Thompson, J. C. (1990b): *In vitro* effects of gastrointestinal hormones on rabbit sphincter of Oddi. *Gastroenterology* **98**, 254.
- Lonovics, J., Németh, J., Greeley, G. H. Jr., Varró, V., Thompson, C. J. (1990c): Proposed mechanism for cholecystokinin (CCK)-, substance P (SP)-, and morphine (MO)-induced sphincter of Oddi (SO) contraction in rabbits. *Gastroenterology* **98**, 507.
- Lonovics, J., Velösy, B., Lénárt, S., Greeley, G. H. Jr., Thompson, J. C. (1990d): Species differences in Oddi-sphincter responses to brain-gut peptides. *Dig. Dis. Sci.* **35**, 6.
- Lonovics, J., Gomez, G. (1991a): The role of gastrointestinal hormones and neuropeptides in the regulation of gallbladder motility. Cellular basis of peptide action. *The Regulatory Peptide Letter* **3**, 65.
- Lonovics, J., Jakab, I., Lénárt, Zs., Velösy, B., Varró, V., Greeley, G. H. Jr., Thompson, J. C. (1991b): Pharmacomechanical coupling in the isolated sphincter of Oddi (RSO) during cholecystokinin (CCK), substance P (SP) and morphine (MO) stimulation. *Gastroenterology* **100**, A465.
- Lonovics, J., Jakab, I., Lénárt, S., Velösy, B. (1991c): Cyclic nucleotide level changes in the rabbit sphincter of Oddi (RSO) during vasoactive intestinal polypeptide (VIP), nitroglycerine (NG), nifedipine (NIF), isoproterenol (IPR), and aminophyllin (APH) stimulation. *Zeitschr. Gastroenterol.* **29**, 193 (A).
- Lonovics, J., Lénárt, Zs., Várkonyi, T. T., Jakab, I., Velösy, B., Varró, V. (1991d): Mechanism of magnesium sulfate- and nifedipine-induced gallbladder and sphincter of Oddi relaxation in rabbits. *Eur. J. Gastroenterology and Hepatology* **3**, (Suppl. 1), S47 (A).
- Marx, M., Gomez, G., Lonovics, J., Thompson, J. C. (1987): Cholecystokinin. In: Thompson, J. C., Greeley, G. M. Jr., Rayford, P. L., Townsend, C. M. Jr. (eds): *Gastrointestinal Endocrinology*. McGraw-Hill Book Company, New York, 212.
- Meyer, J. H. (1975): Release of secretin and cholecystokinin. In: Thompson, J. C. (ed.): *Gastrointestinal Hormones*. University of Texas Press, Austin, 475.
- Owyang, C. Ng, P., Go, W. L. W. (1976): Cholecystokinin: Metabolic clearance and tissue distribution. *Gastroenterology* **70**, 925.
- Owyang, C., Go, W. L. W., DiMagno, E. P., Miller, L. J., Brennan, L. A. (1977): Alteration of serum gastrointestinal (GI) hormone levels in renal insufficiency. *Gastroenterology* **72**, 1110.
- Rayford, P. L., Fender, H. R., Ramus, N. I., Reeder, D. D., Thompson, J. C. (1975): Release and half life of CCK in man. In: Thompson, J. C. (ed.): *Gastrointestinal Hormones*. University of Texas Press, Austin, 301.
- Reeder, D. D., Villar, H. V., Brandt, E. N. Jr., Rayford, P. L., Thompson, J. C. (1974): Radio-

- immunoassay measurement of the disappearance half-time of exogenous cholecystokinin. *Physiologist* **17**, 319.
- Ryan, J. P. (1981): Motility of the gallbladder and biliary tree. In: Thompson, L. R. (ed.): *Physiology of the Gastrointestinal Tract*. Raven Press, New York, 473.
- Ryan, J. P. (1985): Calcium and gallbladder smooth muscle contraction in the guinea pig: effect of pregnancy. *Gastroenterology* **89**, 1279.
- Stasiewicz, J., Wormsley, K. G. (1974): Functional control of biliary tract. *Acta Hepato-Gastroenterol.* **21**, 450.
- Thompson, J. C., Fender, H. R., Ramus, N. I., Villar, H. V., Rayford, P. L. (1975): Cholecystokinin metabolism in man and dogs. *Ann. Surg.* **182**, 496.
- Varró, V., Lonovics, J. (1988): Sphincter of Oddi dyskinesia: pathology and clinical aspects. In: Bianchi Porro, G. (ed.): *Topics in Digestive Disease*. Raven Press, New York, 357.
- Wiener, I., Inoue, K., Fagan, C. J., Lilja, P., Watson, L. C., Thompson, J. C. (1981): Release of cholecystokinin in man: Correlation of blood levels with gallbladder contraction. *Ann. Surg.* **194**, 321.
- Wiley, J. W., O Dorisio, T. M., Owyang, C. (1988): Vasoactive intestinal polypeptide mediates cholecystokinin-induced relaxation of the sphincter of Oddi. *J. Clin. Invest.* **81**, 1920.

7.7. The role of magnesium in urolithiasis

- Andersen, D. A. (1962): The nutritional significance of primary bladder stones. *Brit. J. Urol.* **34**, 160.
- Bach, D. (1984): *Einfluß der Ernährung auf lithoge und inhibitorische Substanzen im Urin*. Cantor, Aulendorf.
- Berg, W., Hesse, A., Schneider, H. J. (1976): Zum Einfluss des Magnesiums auf die Litholyse und Kristallisationsrate von Kalzium-Oxalat. In: Schneider, H.-J., Anke, M. (eds): *Magnesiumstoffwechsel*. Friedrich Schiller-Universität, Jena, 131.
- Brautbar, N., Gruber, H. E. (1986): Magnesium and bone disease. *Nephron* **44**, 1.
- Briellmann, Th., Hering, F., Seiler, H. L., Rutishauser, G. (1988): Neuere Untersuchungen mit dem Oxaltoleranztest. In: Gasser, G., Vahlensieck, W. (eds): *Pathogenese und Klinik der Harnsteine XIII*. Steinkopff, Darmstadt, 79.
- Brundig, P., Börner, R.-H., Schulz, E., Pirlich, W. (1985): Über die Beeinflussung des Harnsteinbildungsrisikos durch Veränderungen der Magnesium- und Calciumkonzentration im Urin unter Streßbedingungen. *Z. Urol. Nephrol.* **78**, 245.
- Carmona, P., Bellanato, J., Cifuentes Delatte, L. (1980): Trimagnesium orthophosphate in renal calculi. *Invest. Urol.* **18**, 151.
- Cifuentes Delatte, L., Carmona, P., Bellanato, J., Santos, M., Hidalgo, A. (1977): Trimagnesium phosphates in renal calculi. In: Gasser, G., Vahlensieck, W. (eds): *Pathogenese und Klinik der Harnsteine V*. Steinkopff Verlag, Darmstadt, 196.
- Durak, I., Yasar, A., Yurtarslan, I., Akpoyraz, M., Tasman, S. (1988): Analysis of magnesium and trace elements in urinary calculi by atomic absorption spectrophotometry. *Brit. J. Urol.* **62**, 203.
- Ebisuno, S., Morimoto, S., Yoshida, T. et al. (1987): Effect of dietary calcium and magnesium on experimental renal tubular deposition of calcium oxalate crystal induced by ethylene glycol administration and its prevention with phytin and citrate. *Urol. Int.* **42**, 330.
- Elliot, J. S., Ribeiro, M. (1973): The effect of varying concentrations of calcium and magnesium upon calcium oxalate solubility. *Invest. Urol.* **10**, 295.
- Ettinger, B., Citron, J. T. (1988): Chlorthalidone reduces calcium oxalate calculous recurrence but magnesium hydroxide does not. *J. Urol.* **139**, 679.

- Fries, W., Meister, R., H., Berger, I. H., Schwille, P. O. (1990): Tissue calcium, magnesium and phosphorus in the rat kidney: influence of gastric resection. In: Vahlensieck, W., Gasser, G., Hesse, A., Schoeneich, G. (eds): *Urolithiasis*. Excerpta Medica, Amsterdam, 28.
- Gershoff, S. N. (1985): Treatment of type I primary hyperoxaluria. *N. Eng. J. Med.* **313**, 959.
- Grases, F., Genestar, C., Conte, A., March, P., Costa-Bauza, A. (1989): Inhibitory effect of pyrophosphate, citrate, magnesium and chondroitin sulphate in calcium oxalate urolithiasis. *Brit. J. Urol.* **64**, 235.
- Hallson, P. C., Rose, G. A., Sulaiman, S. (1982): Magnesium reduces calcium oxalate crystal formation in human whole urine. *Clin. Sci.* **62**, 17.
- Hallson, P. C., Rose, G. A. (1988): Reduction of the urinary risk factors of urolithiasis with magnesium and tartarate mixture: a new treatment. *Brit. J. Urol.* **61**, 382.
- Hammarsten, G. (1929): On calcium oxalate and its solubility in the presence of inorganic salts. *C. R. Lab. Carlsberg* **17**, 1.
- Hesse, A. (1984): *Diagnostik von Risikofaktoren des Kalziumoxalat-Steinleidens*. Albrecht Hesse, Bonn.
- Jacobs, M. G., Bowsher, W. G., Whitfield, H. N. (1990): Beware of antacids! *Brit. J. Urol.* **66**, 661.
- Jensen, A. T., Rowles, S. L., (1957): Lattice constants and magnesium contents of some naturally occurring whitlockites. *Nature* **179**, 912.
- Johansson, G., Backman, U., Danielson, B. G., Fellström, B., Ljunghall, S., Wikström, B. (1981): Prophylactic treatment with magnesium hydroxide in renal stone disease. In: Smith, L. H., Robertson, W. G., Finlayson, B. (eds): *Urolithiasis*. Plenum Press, New York, 267.
- Johansson, G., Backman, U., Danielson, B. G., Fellström, B., Ljunghall, S., Wikström, B. (1981): Magnesium metabolism in renal stone formers. In: Smith, L. H., Robertson, W. G., Finlayson, B. (eds): *Urolithiasis*. Plenum Press, New York, 885.
- Kavanagh, J. P., Rao, P. N. (1990): The application of supersaturation indices to stone prophylaxis. In: Vahlensieck, W., Gasser, G., Hesse, A., Schoeneich, G. (eds): *Urolithiasis*. Excerpta Medica, Amsterdam, 118.
- King, R. G., Stanbury, S. W. (1970): Magnesium metabolism in primary hyperparathyroidism. *Clin. Sci.* **39**, 281.
- Klemperer, G., Trischler, F. (1902): Untersuchungen über Herkunft und Löslichkeit der im Urin ausgeschiedenen Oxalsäure. *Zschr. klin. Med.* **44**, 337.
- Knappwost, A. (1977): Physikalisch-chemische und physiologische Grenzen der Möglichkeiten zur Litholyse von Oxalatkonkrementen des Harns mit peroral aufgenommenen Magnesiumsalzen. In: Gasser, G., Vahlensieck, W. (eds): *Pathogenese und Klinik der Harnsteine*. V. Steinkopff Verlag, Darmstadt, 370.
- Knappwost, A., Matouschek, E. (1975): Zur Beeinflussung der Zitrat Ausscheidung im Harn. *Fortschr. Urol. Nephron.* **5**, 85.
- Koghri, K., Garside, J., Blacklock, N. J., (1988): The role of magnesium in calcium oxalate urolithiasis. *Brit. J. Urol.* **61**, 107.
- Kohri, K., Kodama, M., Ishikawa, Y. (1989): Magnesium-to-calcium ratio in tap water, and its relationship to geological features and the incidence of calcium-containing urinary stones. *J. Urol.* **142**, 1275.
- McLean, R. J. et al. (1990): A simple technique for studying struvite crystal growth in vitro. *Urol. Res.* **18**, 39.
- Leskovar, P., Huber, J., Piendl, A., Heid, T., Meschik, M., Nachbar, F. (1988): Verbesserte Differenzierung zwischen Steinkranken und Steingesunden. In: Gasser, G., Vahlensieck, W. (eds): *Pathogenese und Klinik der Harnsteine* XIII. Steinkopff Verlag, Darmstadt, 53.
- Li, M. K., Blacklock, N. J., Garside, J. (1985): Effects of magnesium on calcium oxalate crystallization. *J. Urol.* **133**, 123.

- Lyon, E. S., Borden, T. A. et al. (1966): Calcium oxalate lithiasis produced by pyridoxine deficiency and inhibition with high magnesium diets. *Invest. Urol.* **4**, 133.
- Martinez, M. E., Salinas, M., Miguel, J. L. et al. (1987): Magnesium excretion in idiopathic hypercalciuria. *Nephron* **40**, 446.
- Meema, H. E., Oreopulos, D. G., Rapoport, A. (1987): Serum magnesium level and arterial calcification in end-stage renal disease. *Kidney Int.* **32**, 388.
- Melnick, I., Landes, R. R., Hoffman, A. A. (1971): Magnesium therapy for recurring calcium oxalate urinary calculi. *J. Urol.* **105**, 119.
- Del Moral, A., Rivadeneyra, M. A., Roldan, E., Perez-Garcia, I., Ramos-Cormenzana, A., Garcia-Cervigon, A. (1989): Formation of bobierite (magnesium phosphate) crystal aggregates by bacteria from human urine and renal calculi. *Urol. Int.* **44**, 222.
- Mukai, T., Howard, J. E. (1963): Some observation on the calcification of rachitic cartilage by urine. *Bull. Johns Hopkins Hosp.* **112**, 279.
- Mulvaney, W. P. (1959): A new solvent for certain urinary calculi. *J. Urol.* **82**, 546.
- Neithercut, W. D. (1989): Effect of calcium, magnesium and sodium ions on in vitro nucleation of human gall bladder bile. *Gut* **30**, 665.
- Neumann, L., Jensen, B. G. (1989): Osteomalacia from Al and Mg antacids. *Acta Orthop. Scand.* **60**, 361.
- Ogilviet, H., Butler, D. G., Gartley, C. J., Dohoo, I. R. (1983): Magnesium oxide induced metabolic alkalosis in cattle. *Can. J. Comp. Med.* **47**, 108.
- Oreopulos, D. G., Soyannwo, M. A. O., McGeown, M. G. (1968): Magnesium/calcium ratio in urine of patients with renal stones. *Lancet* **420**.
- Ponder, S. W., Brouhard, B. H., Travis, L. B. (1990): Hyperphosphaturia and hypermagnesiuria in children with IDDM. *Diabetes Care* **13**, 437.
- Prien, E. L., Gershoff, St. F. (1974): Magnesium oxide-pyridoxine therapy for recurrent calcium oxalate calculi. *J. Urol.* **112**, 509.
- Rayssiguier, Y. (1984): Role of magnesium and potassium in the pathogenesis of arteriosclerosis. *Magnesium* **3**, 226.
- Resnick, M. I., Munday, D., Boyce, W. H. (1982): Magnesium excretion and calcium oxalate urolithiasis. *Urology* **20**, 385.
- Respondek, P., Leskovar, P., Stöhrer, M., Mandalka, B., Nachbar, F., Heid, T., Meschik, M. (1988): Einige steinrelevante Harnmeßgrößen bei immobilisierten Patienten. In: Gasser, G., Vahlensieck, W. (eds): *Pathogenese und Klinik der Harnsteine XIII*. Steinkopff Verlag, Darmstadt, 105.
- Revúsová, V., Perníková, D., Polakovičová, D., Breza, J. (1989): Blood lymphocyte magnesium in kidney stone formers. *Int. Urol. Nephrol.* **21**, 375.
- Roca, P., Conte, A., Rera, T., Grases, F. (1990): Can a relationship reflect the risk of calcium oxalate urolithiasis? *Int. Urol. Nephrol.* **22**, 215.
- Rosemary, L., Ryal, Villis, R. Maarshall (1981): The effect of urine and other inhibitors on the growth and aggregation of calcium oxalate crystals in vitro. In: Smith, L. H., Robertson, W. G., Finlayson, B. (eds): *Urolithiasis*. Plenum, New York, 631.
- Rude, R. K., Oldham, S. B., Sharp, C. F., Singer, F. R. (1978): Parathyroid hormone secretion in magnesium deficiency. *J. Clin. Endocrinol. Metab.* **47**, 800.
- Salinas, M., Martinez, M. E., Miguel, J. I. et al. (1985): Magnesium excretion in idiopathic hypercalciuria. *Nephron* **40**, 446.
- Salvarani, C., Baricchi, B. R., Capozzoli, R., Castellani, N. (1989): Bartter's syndrome and chondrocalcinosis: a possible role for hypomagnesemia in the deposition of calcium pyrophosphate dihydrate (CPPD) crystals. *Clin. Exp. Rheumatol.* **7**, 415.
- Schamschula, R. G., Sugár, E., Un, P. S. H., Duppenmthaler, J. L., Tóth, F., Barmes, D. E. (1988): Aluminium, calcium and magnesium content of Hungarian foods and dietary intakes by children aged 3, 9 and 14 years. *Acta Physiol. Hung.* **72**, 237.

- Schneider, H.-J., Horn, G. (1968): Trinkkuren mit Meerwasser. *Z. Urol.* **61**, 753.
- Schneider, H.-J., Anke, M. (Eds) (1976): *Magnesiumstoffwechsel*. Friedrich-Schiller-Universität, Jena, 97–117.
- Schneider, H.-J., Röhrborn, C., Ruggendorff, E. W. (1983): A gel model for measuring crystallization inhibitor activities in calcium oxalate lithiasis. *World J. Urol.* **1**, 131.
- Schwille, P. O., Rümenapf, G., Köhler, R., Weippert, J. H. (1987): Fasting gastrinemia and elevated supersaturation with hydroxyapatite of fasting urine — observations in renal calcium stone patients and controls. *Urol. Res.* **15**, 99.
- Strohmaier, W. L., Bichler, K.-H., Kalchauer, M., Schreiber, M. (1988): Harnalkalisierung mit Mineralwasser bei Kalziumoxalatsteinpatienten. In: Gasser, G., Vahlensieck, W. (eds): *Pathogenese und Klinik der Harnsteine XIII*. Steinkopff Verlag, Darmstadt, 2436.
- Sutor, D. J. (1968): Newberyite — its formation in human urinary calculi. *Nature* **218**, 195.
- Takasaki, E. (1972): The magnesium: calcium ratio in the concentrated urines of patients with calcium oxalate calculi. *Invest. Urol.* **10**, 147.
- Takasaki, E., Shimano, E. (1967): The urinary excretion of oxalic acid and magnesium in oxalate urolithiasis. *Invest. Urol.* **5**, 303.
- Tarttelin, M. F. (1987): Feline struvite urolithiasis: factors affecting urine pH may be more important than magnesium levels in frog. *Vet. Rec.* **121**, 227.
- Terhorst, B., Lübke, W. (1971): Untersuchungen über den Serum- und Urinspiegel von Magnesium bei Harnsteinkranken. *Zschr. Urol.* **64**, 649.
- The Magnesium Ion — Clinical Aspects* (1982): Proceedings of a symposium at the annual meeting of the Swedish Society of Medical Sciences. Stockholm, 1981. Dec. *Acta Med. Scand.* (Suppl.) **661**, 1.
- Thomas, W. C. Jr. (1976): *Renal Calculi: A Guide to Management*. C. C. Thomas Publisher, Springfield 134.
- Tischmann, K., Achilles, W., Ulshöfer, B., Rodeck, G. (1988): Der Einfluß unterschiedlicher, oral verabreichter Magnesiumpräparate auf das Kristallwachstum von Kalziumoxalat und andere Parameter im menschlichen Harn. In: Gasser, G., Vahlensieck, W. (eds): *Pathogenese und Klinik der Harnsteine XIII*. Steinkopff Verlag, Darmstadt, 230.
- Ulmann, A., Hadi, S., Lacour, B., Bourdeau, A., Bader, C. (1985): Renal magnesium and phosphate wastage in a patient with hypercalciuria and nephrocalcinosis: effect of oral phosphorus and magnesium supplements. *Nephron* **40**, 83.
- Unger, G. (1976): Möglichkeiten der Beeinflussung des intermediären Oxalsäurestoffwechsels durch Magnesium. In: Schneider, H.-J., Anke, M. (eds): *Magnesiumstoffwechsel*. Friedrich-Schiller-Universität, Jena, 156.
- Vermeulen, C. W., Lyon, E. S., Miller, G. H. (1958): Calcium phosphate solubility in urine as measured by a precipitation test. *J. Urol.* **79**, 596.
- Willis, J. B. (1961): The determination of calcium and magnesium in urine by atomic absorption spectroscopy. *Anal. Chem.* **33**, 556.

8. Magnesium supplementation

8.1. Magnesium-containing drugs.

Pharmacotechnological aspects of the most important magnesium compounds

Magnesium is an essential element for the living world. It is especially important for the human organism, in which it often has to be supplemented. Such supplementation may be carried out with certain dietary foods, natural substances or magnesium-containing drugs. This section surveys the latter group.

The most important magnesium preparations used for therapeutic purposes (medicinal substances and magistral, galenic and registered pharmaceutical preparations) will first be listed, and the utilization of magnesium compounds as auxiliary materials in the production of the various forms of drugs will then be discussed. The magnesium ion itself, together with its physiological, pharmacological and clinical aspects, is dealt with, among others, in the works of Simon (1967), Vaughan et al. (1979), Peerenboom and Keck (1980), Picciano et al. (1981), Mutschler and Völger (1982), Günther (1983), Kroll and Elin (1985), Classen (1986), Gums (1987), Durlach (1988), Ackermann (1989), Hollifield (1989) and Aden (1990). Since the above topic is also covered by other sections of this book, it is not discussed here.

Magnesium compounds used for therapeutic purposes

According to the definition of the *Pharmacopoeia Hungarica* (1986), a substance may be regarded as a drug if it is employed to influence the living organism, or is introduced into the living organism for diagnostic purposes. The prevention of a disease is also regarded as a therapeutic purpose.

The Pharmacopoeia makes a distinction between medicinal substances and medicinal preparations. Medicinal substances are chemical substances, volatile and non-volatile oils, and also fatty and waxy substances, used as drugs. Medicinal preparations are drugs having a particular pharmaceutical formulation, usually composed of several constituents; they may be magistral, galenic or registered pharmaceutical preparations. The immunobiological and blood preparations are considered to be medicinal preparations.

Medicinal substances

In the Hungarian Pharmacopoeia currently in force, there are 6 magnesium compounds which are used for therapeutic purposes:

Magnesium carbonicum hydroxydatum,
Magnesium oxydatum,
Magnesium trisilicicum,
Magnesium chloratum,
Magnesium sulfuricum,
Magnesium sulfuricum siccatum.

The first three of these are "non-systemic antacids", i.e. their cations form insoluble carbonates in the intestine, are excreted with the stool as basic salts, and do not upset the acid-base equilibrium of the organism, even if administered permanently.

Magnesium carbonate hydroxide is a snow-white, light powder or an easily pulverizable, loose mass. It is odourless and tasteless. It is practically insoluble in water and alcohol. It dissolves with effervescence in acids. Its aqueous suspension is alkaline. Its usual single dose is 0.25–4.0 g, while its usual daily dose is 0.75–12.0 g.

Magnesium oxide is a snow-white, very light, fine loose powder. Its is odourless. It has an alkaline taste. It is practically insoluble in water and alcohol. It dissolves in acids to form salts. Its aqueous suspension is alkaline. Its usual single dose is 0.25–4.0 g, its usual daily dose is 0.75–12.0 g.

Magnesium trisilicate is a white, fine, loose powder. It is odourless and tasteless. It is practically insoluble in water and alcohol. It is only weakly soluble in mineral acids. Its aqueous suspension is neutral or slightly alkaline. Its usual single dose is 0.50–1.0, and its daily dose is 1.50–3.0 g.

Magnesium chloride has a rather broad sphere of indication, but its main field of application is electrolyte-substitution therapy. It exists as white or colourless, hygroscopic crystals. It is odourless. Its taste is bitter-salty. It dissolves very readily in water, and readily in alcohol. Its aqueous solution is neutral.

The final two compounds are "saline purgatives". When administered in concentrated solution, the non-absorbable salts (such as magnesium sulphate itself) increase the osmotic pressure of the intestinal content considerably; the concentrated solution is rapidly diluted by the digestive juices, which pour in and restore the isotonia.

Magnesium sulphate exists as colourless, prism-shaped or needle-shaped crystals or a white, crystalline powder. It is odourless. Its taste is bitter-salty. In dry air, it crumbles. It dissolves readily in water, while it is practically insoluble in alcohol. In hot water, it dissolves extremely readily. Its aqueous solution is neutral. Its usual single dose is 5.0–25.0 g orally, 2.0–4.0 g i.m.; its usual daily dose is 5.0–25.0 g orally, or 6.0–12.0 g, i.m.

Anhydrous magnesium sulphate is a fine, white, hygroscopic powder. It is odourless. Its taste is bitter-salty. It dissolves readily in water, while it is practically insoluble in alcohol. Its aqueous solution is neutral. Its usual single and daily dose is 2.0–10.0 g. Anhydrous magnesium sulphate is used for the preparation of powder mixtures, even if hydrated magnesium sulphate is prescribed.

Some magnesium compounds will now be mentioned, which, though not official in the current Pharmacopoeia, are employed as medicinal substances in several prescriptions. These are:

Magnesium asparticum,
Magnesium hydroxydatum,

Magnesium peroxydatum 25%,
Magnesium citricum,
Magnesium salicylicum,
Magnesium hydrogenphosphoricum,
Magnesium gluconicum.

Magnesium aspartate is used in the adjuvant therapy of cardiac arrhythmias. The hydroxide and peroxide are components of antacids and remedies for coating the gastric mucosa. Magnesium citrate is applied for the replacement of magnesium ions, for nephrolitholysis and for adjustment of the urinary pH. Magnesium salicylate is used in choleretics and nephrolitholytics, while magnesium hydrogenphosphate is a component of enzymatic digestives. The gluconate is a vehicle for intravenous oxytetracycline preparations (Tetran, Tetranetta).

Medicinal preparations

Depending on their composition, preparation and control, medicinal preparations may be magistral drugs prepared according to the individual prescriptions of the physician, drugs prepared according to the *Formulae Normales* (1987), galenic preparations or registered pharmaceutical preparations.

Magistral and galenic preparations

There are only two official medicinal preparations which contain magnesium: *Solutio pro dialysi peritoneale I* and *II*. One of the differences between the two preparations is that the latter contains potassium chloride; it is essential that the physician should be able to select between a potassium-free and a potassium-containing dialysate, depending on the ionogram of the patient (hypo-, normo- or hyperkalaemia). Nevertheless, the two preparations contain the same amount of magnesium chloride.

As opposed to the Pharmacopoeia, the number of magnesium-containing preparations included in the *Formulae Normales* (1987) is somewhat larger:

Gran. magnesii trisilicici,
Pulv. alcalinus cum belladonna,
Pulv. aluminii antacidus,
Pulv. antacidus,
Pulv. antacidus cum belladonna,
Pulv. digestivus,
Pulv. neutracidus,
Spars. antisudoricum,
Spars. infantum.

It may be seen that the majority of these as antacids, while the two dusting powders (*Sparsorium*) are used as dermatologicals. The first five of these preparations contain (among others) magnesium oxide or magnesium silicate (the silicate granulate contains both), while *Pulv. digestivus* and *Pulv. neutracidus* contain magnesium carbonate hydroxide, the former containing anhydrous magnesium sulphate, too. It

should be borne in mind that, if administered together with tetracyclines (Tetran, etc.) and/or iron preparations, all the above preparations reduce the desired therapeutic effect of the tetracycline or iron by disturbing their absorption.

One of the components of the two dusting powders is magnesium carbonate hydroxide.

Magnesium-containing preparations may also be found in large numbers among the prescriptions of the *Formulae Normales Veterinariae* (1973):

Magn. sulfuricum cryst.,
Inj. magnesii sulfurici 50%,
Inf. narcotica,
*Sol. ad exterminationem**,
Pulv. antidiarrhoicus,
Pulv. kalii bromati comp.,
Inf. calcii et magnesii chlorati,
Inf. glucosi c. calcio et magnesio,
Inf. glucosi polysalina,
Antidot. arsenici et zinci.

Crystalline magnesium sulphate should be applied as an *ex tempore* solution or mixed with the fodder of the animal. The next three preparations also contain crystalline magnesium sulphate, whereas anhydrous magnesium sulphate is used in the two powder mixtures. One of the components of the three infusions is crystalline magnesium chloride, and the antidote contains magnesium carbonate hydroxide. The preparation denoted by an asterisk may never be applied in human medicine: administered intravenously or intracardially, it serves for the extermination of animals. Five further magnesium-containing preparations which contain crystalline magnesium chloride, magnesium sulphate, magnesium trisilicate or magnesium carbonate hydroxide have been suggested for inclusion in the 3rd edition of *Formulae Normales Veterinariae*.

The picture would be incomplete without mention of the 43 magnesium-containing prescriptions included in the *Manuale pharmaceuticum* (1986). These are mainly antacids and electrolyte supplements, but also include antidotes, nephrolitholytics, roborants, dermatologics, biocosmetics, etc.; moreover, in some prescriptions magnesium is present as auxiliary material. Instead of a lengthy list of all these prescriptions, the magnesium compounds found in them are given below, in the sequence of their incidence (indicated by the number following them):

<i>Magn. chloratum</i>	15
<i>Magn. carb. hydroxyd.</i>	6
<i>Magn. oxydatum</i>	5
<i>Magn. stearinicum</i>	5
<i>Magn. sulfuricum</i>	4
<i>Magn. trisilicicum</i>	3
.....	
<i>Magn. citricum</i>	3
<i>Magn. peroxydatum</i> 25%	2
<i>Magn. asparticum</i>	1

Only the compounds below the dashed line have not been incorporated in the Pharmacopoeia.

The magnesium-containing compounds included in the *Kórházi Gyógyszerészeti Manuális* (Hospital Pharmaceutical Manual, 1989) must also be mentioned. The primary aim of this publication is to support the work of hospital pharmacists. The drugs included in it therefore serve only for the treatment of in-patients in hospitals and nursing homes. It details more than 50 prescriptions which contain magnesium compounds. Most of these are dietetics (infusions, dialysates, etc.), which are prepared with crystalline magnesium chloride or a 50% solution of magnesium chloride. Magnesium chloride is also found in the cardioplegic solutions "Kardiostop I" and "Kardiostop II", which are used to produce hypothermic cardiac arrest, and should therefore be prepared with close attention to the rules pertaining to the preparation of infusions. There are also several perfusions among the prescriptions. The "Dehydrating solution", "Artificial saliva", "Synthetic saliva", "Otologic solution" and "Haldane-Amenfeld powder" contain magnesium chloride among other components.

There are many antacids, stomachics and spasmolytics, which contain mainly magnesium oxide, magnesium carbonate or magnesium silicate as one of their components. These preparations are employed as powders or suspensions. The "Dental powder" and "Powder for hyperhydrosis of the foot" contain magnesium carbonate hydroxide, and the "Universal antidote" magnesium oxide. The manual also includes prescriptions for 8 tablets containing magnesium stearate as auxiliary material.

Registered pharmaceutical preparations

Those magnesium-containing pharmaceutical preparations will be listed here which are distributed in Hungary, and are therefore included in the *Útmutató a gyógyszerkészítmények rendelésére* (Guide for the Prescription of Medicinal Products) published by the National Institute of Pharmacy in 1988, in Hungarian. The registered name of the preparation is followed by the name of the producing company in parentheses:

Almagel and Almagel A suspensions (Pharmachim),

Cholagol solution (Galena),

Cystenal solution (Galena),

Lukullin dragée (EGIS),

Magurlit granulate (Chinoin),

Nilacid tablet (Chinoin),

Panangin dragée and injection (Gedeon Richter),

Tetran intravenous injection (Chinoin),

Tetranetta intravenous injection (Chinoin),

Tisacid tablet and suspension (Alkaloida),

Vicalin tablet (Medexport).

One of the components of the suspensions *Almagel* and *Almagel A* is magnesium hydroxide. The suspensions are used as antacids and adsorbents in the treatment of gastric and duodenal ulcer, acute and chronic gastritis, hyperacidity, etc. *Almagel A*

differs from Almagel in that it also contains benzocaine. In cases in which the patient complains of nausea, vomiting or considerable pain, therefore, the treatment is started with Almagel A; then, after cessation of the acute complaints, it is continued with Almagel. Their administration together with tetracyclines and iron preparations is contraindicated because of complex formation. They also inhibit the absorption of several other drugs (e.g. cardiac glycosides and barbiturates), and there should therefore be an interval of at least 1–2 hours between the administration of the latter and Almagel.

Cholagol solution contains, among others, magnesium salicylate. It is administered in the treatment of cholelithiasis, chronic cholecystitis, following surgery of the biliary tract, and in cirrhosis for mitigation of the subjective complaints. Patients susceptible to heartburn should take it during or after meals. It does not substitute the specific treatment of the underlying disease.

Cystenal solution also contains magnesium salicylate. It is used as a nephrolitholytic in the prevention and therapy of nephrolithiasis, primarily in those cases in which spontaneous passage of the calculi may be expected. Its sphere of indication includes incrustational processes of the renal pelvis and the bladder, urate diathesis and secondary infections of the urinary tract. It may cause heartburn as a side-effect, which may usually be relieved if it is taken during meals.

One of the active constituents of *Lukullin* dragée is magnesium hydrogenphosphate. The product was employed as an enzymatic digestive in dyspepsia, achylia, meteorism and flatulence due to maldigestion. The tablets are provided with an intestinosolvent coating because of their enzyme content. The dragées should therefore be swallowed whole, immediately following meals.

One of the components of *Magurlit* granulate is magnesium citrate. Similarly to the above-mentioned Cystenal solution, it is used as a nephrolitholytic, and in cases of radiolucent calculi and permanently acidic ($\text{pH} < 5.5$) urine. In cases involving infected, alkaline urine or in cardiovascular insufficiency, it is contraindicated because of its high sodium and potassium contents. Its dosage should be individually determined. The granulate should be taken without crushing, with liquids. The dosage should be set so that the pH of the fresh urine excreted before the usual times of ingestion (morning, noon and evening) is not more than 6.2–6.7. The pH should be monitored daily by comparing the coloration of the indicator paper enclosed in the package with the colour scale. As adverse reactions, gastrointestinal disturbances may occur, but these are usually only temporary and disappear even without suspension of the therapy.

Nilacid tablet contains magnesium trisilicate and magnesium oxide. Similarly to Almagel suspension Nilacid is used, as an antacid and adsorbent in cases of hyperacidity, hypersecretion, heartburn, reflux oesophagitis, and gastric and duodenal ulcer. It should be swallowed after chewing, with a small amount of water. The frequent ingestion of large doses may have a laxative effect. Its administration together with oral tetracyclines is contraindicated, because it inhibits their absorption by chelate formation. It may also reduce the absorption of other drugs (e.g. iron salts, cardiac glycosides and barbiturates) by inhibiting their absorption or by modifying the gastric pH. In renal insufficiency, the permanent administration of large doses may cause hypermagnesaemia.

Panangin dragée and injection contain magnesium and potassium aspartates. They are employed as cardioprotectives in the complementary therapy of angina pectoris. The indications include the adjuvant therapy of the arrhythmias accompanying and following myocardial infarction, and the treatment of ventricular arrhythmias caused by digitalis toxicity. They are contraindicated in acute and chronic renal insufficiency. The injection should be diluted with a 5% glucose solution, and administered as a slow intravenous injection or drip. It is also suitable for combined treatment.

The active agent of the *Tetran* intravenous injection is oxytetracycline chloride (as pyrrolidine methyloxytetracycline); the vehicles of its powder ampoule are magnesium glyconate and ascorbic acid. It is a broad-spectrum antibiotic, which is used in several bacterial infections, according to the antibiotic sensitivity, and in penicillin allergy. It is contraindicated in tetracycline hypersensitivity, pregnancy and myasthenia gravis (in the latter because of its magnesium content). If possible, it should be avoided in children below the age of 8 years (because of its damaging effect on the bones and teeth). The solution for injection should be reconstituted immediately before administration (*ex tempore*) with distilled water for injection; its injection should take 1 minute. It may also be administered intrapleurally, intraperitoneally and intraarticularly. It may have several adverse effects, such as gastrointestinal symptoms, cutaneous lesions, allergic reactions and haematologic side-effects. Its administration together with penicillin preparations and drugs impairing the hepatic function is contraindicated, while together with anticoagulants it should be carefully controlled. During treatment, the patient should avoid direct sunshine; if cutaneous lesions appear, the treatment must be suspended.

Tetranetta intravenous injection differs from the above preparation only in that its solution contains a smaller amount of active agent and auxiliary materials. It is used in the treatment of children. Its indications, adverse reactions, etc. are the same as those of *Tetran* injection.

The active agent of *Tisacid* tablet and suspension is a complex compound: aluminium magnesium hydroxide carbonate hydrate. It is used as an antacid and adsorbent in the treatment of hyperchlorhydria, acute and chronic gastritis, gastric and duodenal ulcer and heartburn. It should be swallowed whole or after chewing, with a small amount of water. Its side-effects may be constipation and eructation. Its administration together with tetracyclines is contraindicated, since the antibiotic effect might be reduced by chelate formation. Because of the modification of the gastric pH, it is advisable to introduce an interval of 1 hour between the administration of other drugs and the ingestion of *Tisacid* tablet.

Vicalin tablet contains, among others, magnesium carbonate hydroxide. It is used as an antacid and adsorbent in gastric and duodenal ulcers. Its components have astringent, antimicrobial, mild laxative, tonizing, spasmolytic and anti-inflammatory effects, and additionally they decrease the capillary permeability. As a side-effect, frequent stools may occur; this ceases on reduction of the dose. Another side-effect is the black or green coloration of the stool. During *Vicalin* therapy, the administration of atropine or other secretion inhibitors is contraindicated.

Among the infusions and peritoneal dialysates produced by the Institute for Serobacterial Production and Research "Human", there are 12 preparations which include magnesium chloride among their components, namely:

Balansol S-5,
Infusamin S-5,
Infusamin X-5,
Peridisol 1-D,
Peridisol 1-DK,
Peridisol 2-D,
Peridisol 2-SK,
Rehydrosol S-5,
Rindex 5,
Rindex 10,
Ringer-acetate S-5,
Ringer-lactate.

The above preparations are used as dietetics for parenteral nutrition, salt and sugar supplementation, and plasma replacement. Besides magnesium, they usually contain sodium, potassium and calcium ions as well, in sterile, pyrogen-free solutions. Their administration is indicated in every condition in which the enteral supplementation of the daily salt and water requirement is completely or partly inhibited or contraindicated (e.g. major operations and trauma). They may also be indicated in hypertonic dehydration and isotonic dehydration (water and salt loss).

They may be administered only intravenously; their paravenous application leads to local tissue injury. Only absolutely clear solutions may be used. It is forbidden to store the opened solutions for later usage. No other product may be added to the solution (because of the risk of hidden incompatibility).

The production of the peritoneal dialysates (Peridisol 1-D, 1-DK, 2-D, 2-SK), and the requirements concerning them (sterility and exception of pyrogens), are the same as for infusions; there is an essential difference only in the mode of their administration. They are usually indicated in the following cases: acute and chronic renal insufficiency; disturbances of the salt, water and acid-base metabolism; prevention of uraemia in the perioperational treatment of patients with impaired renal function; and in peritonitis for lavage of the peritoneum.

In recent years, a fairly large number of preparations have been made commercially available for the supplementation of causal therapy, i.e. as adjuvants. Most of them are qualified as therapeutic products. Just to mention a few examples: "Andrews medicinal salt", applied as an acid binder and laxative, contains magnesium sulphate; *Milk of magnesia*, in the form of tablets or suspension, contains magnesium hydroxide and is used for indigestion and bilious complaints; *Mil-Par* emulsion, applied as a laxative, likewise contains magnesium hydroxide.

Magnesium 250 mg Pharmavit is an effervescent tablet used in the prevention and therapy of magnesium deficiency; it contains magnesium oxide in addition to ascorbic acid.

One of the active ingredients of *Digestif Rennie* tablets is magnesium carbonate. The preparation is used as a remedy for indigestion. *Tovita* is commercially available both as tablet and powder; in addition to a great amount of calcium, it contains essential trace elements, including magnesium.

Multivitamin M effervescent tablet may prevent or improve metabolic disorders caused by various vitamin and mineral deficiencies; besides several vitamins, it contains magnesium, iron, copper and zinc.

Multicomp tablet contains magnesium in the form of a basic magnesium polygalacturonate complex, together with four other metal ions (iron, manganese, zinc and copper); it may be applied very effectively in the prevention and therapy of conditions elicited by a deficiency of essential metals.

Magnesium-containing pharmaceutical preparations are used not only in human therapy, but also in veterinary medicine. *Polycalcit* injection contains magnesium chloride, *Tetran combinatus pulvis* contains anhydrous magnesium sulphate, and *Septiol* solution contains magnesium silicate. In *Reseptyl* tablet and *Superboryl* dusting powder, magnesium stearate is present as vehicle. Among the medicated premixes *Galactovit* contains magnesium sulphate, and *Ásványpremix (Mineralpremix) AP-18* magnesium oxide.

There are also a great many magnesium-containing products among the pharmaceutical preparations produced abroad. Only the most important preparations will be mentioned here. For example, *Magnorbin* injection is a 10% solution of magnesium ascorbate, used for vasospasmolysis, and in osmotherapy and narcosis. The majority of the antacid tablets *Magaldrate*, *Neutrolac*, *Acinormal*, *Syntrogen*, *Trevidal*, etc. contain magnesium silicate and other magnesium compounds. Further preparations are *Biomagnesin*, a lozenge containing magnesium hydrogenphosphate and magnesium citrate, which is administered in hypomagnesaemia, and the lozenges *Mg5-Longoral* and *Magnesium-Diasporal*, which contain magnesium citrate and magnesium laevulinate, respectively. In *Magnetrans Forte*, a preparation used for magnesium supplementation, magnesium oxide is filled in a soft gelatine capsule.

The active ingredient of *Magnerot* tablet is magnesium orotate. This product too is used for supplementation of the magnesium ion and in the adjuvant therapy of functional disturbances of the cardiovascular system. Some of the *Isopaque* preparations contain magnesium metrizoate as components. Finally, mention should be of *Magnesium Verla N*, which may be applied in various cases of magnesium deficiency or increased magnesium requirements (arrhythmias, pregnancy, sural cramps, tetany, etc.). The product is commercially available in three forms: the dragée contains magnesium L-hydrogen glutamate and trimagnesium dicitrate, the injection contains magnesium L-hydrogen glutamate, while the granulate, which is to be dissolved in water, contains magnesium L-hydrogen aspartate.

Magnesium compounds used as auxiliary materials

A considerable number of magnesium compounds are used not (or not only) for therapeutic purposes, but rather as auxiliary materials in the production of various drug formulations. The modern auxiliary materials should meet the following essential pharmacotechnological requirements: (1) The auxiliary material should not have an independent pharmacological effect. (2) It should influence the effect of the

pharmacon according to the desired therapeutic purpose. (3) It should be compatible with the active agent. (4) Its microbiological purity should meet the necessary requirements. (5) It should usually be odourless, tasteless and colourless. (6) It should be readily available and relatively cheap.

The above requirements are generally met by the magnesium-containing auxiliary materials.

The list of magnesium-containing auxiliary materials is too long to be presented here, the more so since these products are often distributed often under different registered names. The most recent, 3rd edition of the book by Fiedler (1989), one of the best-known experts on this topic, enumerates magnesium-containing auxiliary materials commercialized under almost 30 different names.

Only those auxiliary materials will be mentioned here which are most often used in the Hungarian pharmaceutical industry. The most important of these is *magnesium stearate*, which is official in the Hungarian Pharmacopoeia.

As concerns its composition, magnesium stearate is in fact a mixture of the magnesium salts of fatty acids — mainly palmitic acid and stearic acid. It is a white, light, fine powder, fatty to the touch. It is almost tasteless, and has a mild, characteristic odour. It is practically insoluble in water, alcohol and ether. It may be dissolved in benzene. Its loss on drying is 6% at most. It practically does not absorb water, even in an environment of high relative humidity.

It is employed in several fields of pharmaceutical formulation. For example, it is used as an antiadhesive agent in a proportion of 0.1–1.0% in tablet pressing.

Selmeczi and Kedvessy (1981) reported that in higher proportions it has an unfavourable effect on the disintegration time, it may also reduce the rate of dissolution of the active agent, and it decreases the mechanical stability of the tablets. Magnesium stearate is incompatible with substances giving acidic reactions, substances sensitive to alkalis (e.g. acetylsalicylic acid and isonicotinic hydrazide) and iron salts.

Another frequently used auxiliary material is *talcum* (*Alumen plumosum*), which is also official in the Hungarian Pharmacopoeia. It is a mixture of purified and pulverized natural magnesium silicates.

It is a white or off-white, very fine powder, fatty to the touch. It is odourless and tasteless. It hardly becomes wet in water. It is insoluble in water, acids and organic solvents. It is partly dissolved by alkaline bases. Its aqueous suspension is neutral. Its moisture content is < 1%. It practically does not adsorb water, even in an environment of high relative humidity.

It is frequently highly contaminated with aerobic microorganisms (bacteria). It is commercially available in very diverse qualities. Its chemical purity is 93–98%. Its most frequent pollutants are calcium silicates, aluminium and iron oxides, calcium carbonate and asbestos.

In pharmaceutical formulation, it is employed in tablet pressing, in coating syrups, as an elementary substance of dusting powders, etc. In tablet pressing, it is normally used as a glidant, in a proportion of 5% or less. The Hungarian Pharmacopoeia usually gives 3% as the employable limit. In most cases, it is used in tablet pressing in a 9:1 combination with magnesium stearate.

Bentonite is employed in the production of several drug forms. Its main mass is a clay mineral consisting of montmorillonite, in which various amounts of magnesium, calcium and iron are present besides aluminium oxide.

It is a light-grey, greenish or yellowish, odourless, very fine powder with a slightly characteristic taste. 90% of the particles have a size of 200 nm. Its tendency to gelation is greatly increased even by small amounts of substances giving alkaline reactions (e.g. magnesium oxide), while it is decreased by acids. In organic solvents, it is insoluble and does not swell. It is highly hygroscopic.

It is employed as binder substance, in a concentration of 2–5%, in the production of granulates. It may bind some pharmaca by adsorption, and hence may inhibit release of the active agent. It is incompatible with electrolytes and acids. For pharmaceutical purposes, only activated and sterilized bentonite may be used.

*

To summarize, magnesium has important roles in drug therapy and in the production of medicinal preparations.

8.2. The magnesium content of herbs and their therapeutic use

The elimination of civilizational, adaptational, chronic degenerative, psychosomatic and chronic noncontagious diseases imposes increasing demands on the society and the individual, on medicine and health care.

To preservation of health involves maintenance of dynamic equilibrium between the numerous interactions of the organism and its environment. If the necessary amounts of essential materials are not supplied by nutrition, even a genetically faultless system will experience difficulties. These may be transient, but may also become prolonged and severe, and a certain point the quantitative changes may result in qualitative alterations. The elements making up the human body are usually classified according to their importance. There are those which are essential for survival of the living organism. Magnesium is one of these macroelements (Vahora, 1981).

Research on this element, which is now coming more and more into the focus of attention, began with the observation of the favourable effect of mineral waters with high magnesium content. Already, last century, magnesium was well known as a laxative and a spasmolytic agent, but intensive research on magnesium has been performed only within the past 20 years.

Although magnesium salts, and particularly magnesium sulphate, have long been used in the treatment of certain chronic diseases, and were later administered intravenously with very good results, in life-threatening conditions (eclampsia and tetanus). It is only in the past few years that research has started on the detailed mechanism of action of magnesium and on its role in maintaining homeostasis. Kuti (1978) considers that the modern diet does not supply magnesium in sufficient amounts. Indeed, it can be declared that practically the entire population of Hungary is endangered by nutritional magnesium deficiency. Neither is the magnesium content of our drinking water sufficient: it even shows a decreasing tendency. When water supply systems are constructed, soft water with a low magnesium content is preferred due to technological considerations. Magnesium extracted from the top soil layer by intensive cul-

tivation is supplemented by natural, but not by chemical fertilization. Moreover, potassium introduced with chemical fertilizers also impairs the magnesium uptake of plants (Loch, 1978).

The number and intensity of the negative environmental effects brought about by urbanization are therefore increasing, furthering the possibility of magnesium deficiency states. The most common conditions with increased daily magnesium requirements are growth and development; reconvalescence; pregnancy and lactation; physical and intellectual work; psychic stress; infectious diseases; poisoning; surgery; administration of vitamin D; increased protein synthesis; alcohol consumption; diuretics.

The role of magnesium in the human organism

The magnesium content of the human organism (average body-weight 70 kg [155 lb]) is ca. 25 g, approximately 60% of which is located in the skeleton. Three-quarters of this 60% readily mobilized (Williams, 1971; Simon, 1976). The remaining 40% of the magnesium content is concentrated in other tissues, primarily in skeletal and cardiac muscle and in the liver. The brain, the thyroids and the kidneys also contain significant amounts of magnesium. Of the magnesium in the plasma, 55% is present as the free ion, 32% is protein-bound, 3% exists as magnesium phosphate and 4% is in the form of magnesium citrate, while the remaining 6% is complexed (Blaxter, 1956). The extracellular magnesium content is a mere 1%. The magnesium concentration of the blood is a very important parameter: below 2 and over 2.2 mg per 100 cm³ is considered to be pathological (Hársing, 1973).

Only about 30–40% of the magnesium taken up from food is resorbed. It is excreted nearly exclusively via the kidneys, which is why magnesium therapy is contraindicated in renal insufficiency. The daily amount of magnesium excreted in the urine is 0.17–0.28 g. In certain cases, the amount of magnesium excreted in the faeces may be twice as much as that in the urine, this is magnesium that was not absorbed from food.

Magnesium is a bioelement of vital importance, essential for maintaining normal life functions such as growth, development and reproduction. It plays a key role in a great number of basic biochemical processes, the undisturbed progress of which is possible only in a very narrow range of magnesium concentrations (Table 8.1; Bíró and Lindler, 1988).

Magnesium is a cofactor in all ATP-dependent enzyme reactions. It is indispensable in the production, storage and liberation of energy. Stored energy is liberated in mitochondria in the course of oxidative phosphorylation; magnesium is the most im-

Table 8.1. Magnesium contents (mg/100 g)

Vegetables	9– 87
Fruits	10– 60
Fruit products	18– 130
Nuts, oil seeds	140– 970
Legumes	1260–3600

portant activator of this process and is therefore an essential participant of energy production (Aikawa, 1963).

Magnesium forms a complex with the three phosphate groups of ATP, and only the complex Mg-ATP complex bind to the substrate binding site of ATPases. When the intracellular magnesium concentration decreases, energy release becomes limited, which leads to difficulties in the formation and conduction of impulses and contraction problems in the heart (Kohler, 1966; Hidas, 1980). Sufficient magnesium levels are indispensable also for the activity of other enzymes, e.g. the magnesium-dependent enzymes of carbohydrate and lipid metabolism.

Magnesium therapy has come to play a very significant role in the treatment of *cardiac and vascular* diseases. Magnesium dilates the coronaries and thereby increases the amount of blood passing through the heart. By relaxing the smooth muscles of the peripheral resistance veins, it is able to decrease blood pressure (Kota, 1969). In a state of chronic magnesium deficiency, a process of calcification starts up in cardiac muscle, resulting in damage or even atrophy of the cardiac muscle cells (Rigó, 1965).

A magnesium deficiency in the heart may have the following consequences: cardiac muscle necrosis; increased calcium influx into cardiac muscle cells; myofibrillar troubles in myocardium enhanced efflux of catecholamines; and coronary spasms.

During the initial period of intrauterine life, the foetus takes up very large amounts of magnesium, the rate of uptake greatly exceeding that of mass increase.

The magnesium content of the foetal blood exceeds that of the maternal blood. From the 8th intrauterine month on, only the amount of magnesium necessary for physiological growth is stored. If magnesium is administered to a pregnant woman, most of it is absorbed by the placenta, but part is rapidly passed on to the foetus so that there is always enough magnesium available for fast growth. Excessive magnesium intake may also lead to serious problems since the permeability of the placenta may easily endanger the foetus, which is unable to eliminate all the magnesium flooding its organism above a certain limit (Ludmény, 1978).

A magnesium deficiency, however, is even more dangerous for the foetus. The inappropriate development of the offspring of magnesium-deficient mothers has been proved by reproducible animal experiments (Bachem et al., 1980). Stillbirth and in certain cases abortion are likewise common occurrences (Kiss, 1975; Kuti, 1978).

Magnesium also plays a significant role in DNA, RNA and protein synthesis. The antithrombic effect of magnesium citrate has been demonstrated experimentally: its effects in surgery and childbirth are more powerful than those of the usual anticoagulants (Durlach et al., 1967).

The antistress, neuromuscular and calcium-antagonist effects of magnesium are also worth mentioning (Csányi, 1976).

The magnesium content of herbs

Very few data are available in this field. In their pioneering work, Rác et al. (1978) analyzed the magnesium contents of 41 herbal species in the summer and in the autumn and found the summer values to be higher without exception, which correlates well with the intensity of assimilation and also the autumn breakdown of chlorophyll.

Table 8.2. Daily magnesium needs (mg/kg body mass) according to Bíró and Lindler (1988)

Adults	6–10
Expectant and nursing mothers	8–15
Infants and young children	15–30

The highest magnesium content, 6.6 g/kg, was measured in the leaves of *Rheum undulatum* (Chinese rhubarb), that part has not yet been introduced into the therapy, followed by 4.4 g/kg in the leaves of *Atropa belladonna* (deadly nightshade), 3.5 g/kg in *Levisticum officinale* (lovage) leaves and 3.0 g/kg in *Ribes nigrum* (black currant) leaves.

The daily magnesium requirements are easily supplied by a reasonable diet (Table 8.2). Nevertheless, it may happen that magnesium has to be administered in order to supply enough magnesium to the body. Appropriate herbal mixtures containing other active ingredients in addition to magnesium may prove extremely useful.

Herbal teas have been developed for the prevention of heart attacks and for foetal protection.

Herbal teas

In the planning of herbal teas for the prevention of heart attacks and for foetal protection, the main considerations were to find herbs with appropriate active ingredients and high magnesium content (Table 8.3).

Commercial drugs prepared for analysis are lysed in a mixture of nitric acid and perchloric acid, and the magnesium content is determined by atomic absorption spectrophotometry.

For other active ingredients, plants containing flavonoids and procyanidins were selected for both herbal mixtures, since these are spasmolytic and cardiac restorative compounds that also improve circulation. Their amounts in the herbal mixtures are measured spectrophotometrically according to the Hungarian Pharmacopoeia (7th edition, 1986; flavonoids) and Krawczyk (1990). Flavonoids are determined in a complex with $AlCl_3$ at 375 nm, and procyanidins at 620 nm as anthocyanins after acid hydrolysis.

The composition of two herbal mixtures and the pertinent data in the scientific literature are as follows:

Herbal tea for prevention of heart attacks:

The herbal mixture is made from 5 pharmacopoeal or freely distributed plants:

Howthorn (*Crataegi summitas*) flowers

Indications: cardiac problems, relating to neurosis, or old age; strengthening cardiac musculature; improving oxygen supply

Black-currant (*Ribes nigri folium*) leaves

Indications: mild diuretic and saluretic, suppresses potassium excretion

Table 8.3. Magnesium contents of plants selected for herbal infusions

Name of plant		Plant part	Magnesium content (mg/100 g)
Latin	English		
<i>Agrimonia eupatoria</i>	agrimony	herba	293.7
<i>Agropyron repens</i>	wheat-grass	rhizoma	69.5
<i>Calendula officinalis</i>	calendula	flos	200.0
<i>Coriandrum sativum</i>	coriander	fructus	247.9
<i>Crataegus monogyna (oxyacantha)</i>	hawthorn	summitas	304.0
<i>Equisetum arvense</i>	common horsetail	herba	231.5
<i>Foeniculum vulgare</i>	fennel	fructus	295.0
<i>Fragaria vesca</i>	wild strawberry	folium	278.0
<i>Juglans regia</i>	common walnut-tree	folium	512.3
<i>Matricaria recutita</i>	chamomile	anthodium	181.3
<i>Melissa officinalis</i>	balm	folium	563.1
<i>Mentha piperita</i>	peppermint	folium	600.9
<i>Pulmonaria officinalis</i>	lungwort	folium	145.2
<i>Ribes nigrum</i>	black-currant	folium	693.0
<i>Rosa canina</i>	hedge-rose	pseudofruct.	332.0
<i>Rubus fruticosus</i>	blackberry	folium	352.0
<i>Sambucus nigra</i>	blackelder	flos	352.0
<i>Taraxacum officinale</i>	dandelion	folium	498.5
<i>Tilia cordata</i>	little-leaf linden	flos	391.7
<i>Urtica dioica</i>	stinging nettle	folium	499.6
<i>Vaccinium myrtillus</i>	huckleberry	folium	250.9
<i>Zea mays</i>	corn silk	stigma	239.5

Balm (*Melissae folium*) leaves

Indications: mild sedative; promotes digestion

Walnut (*Juglandis folium*) leaves

Indication: slightly lowers blood pressure

Dandelion (*Taraxaci folium*) leaves

Indications: diuretic and liver-protecting effect.

From the drugs making up the herbal mixtures, *Crataegi summitas*, *Melissae folium* and *Juglandis folium* are listed in the official Hungarian Pharmacopoeia (7th edition), while *Taraxaci folium* and *Ribes nigri folium* are freely distributed.

Crataegi summitas increases the working capacity of the cardiac muscle, improves the blood flow of the coronaries and, when administered together with *Melissae folium*, reduces cardiac problems of neurotic origin.

Ribes nigri folium lowers blood pressure and has a diuretic effect. Its active ingredients (mostly flavonoids) prevent the vasopressor effect of vasoconstrictor substances produced in the body or introduced with medicines, and also sedate the central nervous system. The preparation Hiporib developed by Rácz et al. (1982) to decrease blood pressure is based on this herb.

The active ingredients of *Melissae folium* have sedative and spasmolytic effect and well complement the beneficial effect of *Crataegi summitas* on the heart (Braun, 1974).

Juglandis folium contains hydroquinone derivatives, tannin and ascorbic acid. It is remarkably rich in mineral salts, especially magnesium ions. It is listed in the 7th Hungarian Pharmacopoeia.

The most important substances in dandelion *Taraxaci folium* are triterpene-saponins, flavonoids and the essential oil. It is administered in subacute and chronic nephritis, where its significant diuretic effect is utilized (Petri et al., 1989). This material also protects the liver (Braun, 1974).

Table 8.4. Magnesium contents of herbal tea mixture and of its components for the prevention of heart attacks

Name of plant	Mass of plant (g)	Magnesium content (mg)
<i>Crataegi summitas</i>	30	85.20
<i>Ribes nigri folium</i>	20	94.00
<i>Melissae folium</i>	20	76.20
<i>Juglandis folium</i>	20	56.80
<i>Taraxaci folium</i>	10	21.20
	100	333.40

Table 8.5. Procyanidin (PC) contents of herbal tea mixture and of its components for the prevention of heart attacks

Name of plant	PC (%)	Mass of plant (g)	PC content (g)
<i>Crataegi summitas</i>	2.59	30	0.77
<i>Ribes nigri folium</i>	2.00	20	0.40
<i>Melissae folium</i>	0.18	20	0.04
<i>Juglandis folium</i>	1.63	20	0.33
<i>Taraxaci folium</i>	0.15	10	0.01
		100	1.55

Table 8.6. Flavonoid contents of herbal tea mixture and of its components for the prevention of heart attacks

Name of plant	Flavonoid (%)	Mass of plant (g)	Flavonoid content (g)
<i>Crataegi summitas</i>	0.70	30	0.21
<i>Ribes nigri folium</i>	0.85	20	0.17
<i>Melissae folium</i>	0.48	20	0.10
<i>Juglandis folium</i>	1.45	20	0.29
<i>Taraxaci folium</i>	1.70	10	0.17
		100	0.94

The therapeutic effects of the herbal mixture are enhanced by the considerable magnesium contents of the listed plants (300–500 mg/100 g).

Directions for use: One heaped tablespoonful (3–4 g) of herbal mixture is kept in 300 cm³ of boiling water for a few seconds, then covered and left to cool for 15 minutes. It is next strained, flavoured to taste and consumed in 2–3 portions daily.

Application: It is advised to use the herbal mixture to eliminate cardiac problems of nervous origin, to increase the working capacity of the cardiac muscle, to lower pathologically high blood pressure and to prevent arteriosclerosis.

The active ingredients of the herbal mixture are listed in *Tables 8.4, 8.5 and 8.6.*

Herbal tea for foetal protection:

Rose-hips (*Cynosbati pseudofructus*) source of vitamin C

Balm (*Melissae folium*) sedative

Peppermint (*Menthae piperitae folium*) helps cholerrhagia and digestion

Nettle (*Urticae folium*) leaves activate the metabolism

Howthorn (*Crataegi summitas*) flowering tips, cardiac restorative.

The plants making up this herbal mixture are used in official and traditional medical practice for consumption as a refreshing drink, and as infusions to supply vitamins and to promote digestion. With the exception of *Urticae folium*, these plants are listed in the 7th Hungarian Pharmacopoeia. The most important active ingredients of *Cynosbati pseudofructus* are ascorbic acid, water-soluble bioflavonoids (vitamin P), pectin, organic acids and mineral salts. It may serve as an additional source of vitamin C, primarily during pregnancy. It is especially advantageous to administer vitamin C in its natural form, accompanied by bioflavonoids, for in this material the bioflavonoids complement the effect of ascorbic acid and inhibit its breakdown. The significant amounts of pectins and organic acids in this material lend it a mild diuretic and laxative effect, which helps to eliminate indigestion, so frequently occurring during pregnancy (Tyler, 1985; Petri et al., 1989; *Tables 8.7, 8.8 and 8.9*).*

Table 8.7. Magnesium contents of herbal tea mixture and of its components for foetal protection

Name of plant	Mass of drug (g)	Magnesium content (mg)
<i>Cynosbati pseudofructus</i>	30	174.0
<i>Melissae folium</i>	30	114.3
<i>Menthae piperitae folium</i>	20	114.0
<i>Urticae folium</i>	10	41.4
<i>Crataegi summitas</i>	10	28.4
	100	472.1

* Flavonoid, procyanidin and vitamin C contents listed in the Tables were determined by Zoltán Pálfi; and magnesium contents by László Lelik (University for Horticulture and Nutrition).

Table 8.8. Procyanidin contents of herbal tea mixture and of its components for foetal protection

Name of plant	Procyanidin (g)	Mass of plant (g)	Procyanidin content (%)
<i>Cynosbati pseudofructus</i>	0.66	30	0.20
<i>Melissae folium</i>	0.18	30	0.05
<i>Menthae piperitae folium</i>	0.29	10	0.06
<i>Urticae folium</i>	0.29	10	0.03
<i>Crataegi summitas</i>	2.59	10	0.26
		100	0.60

Table 8.9. Flavonoid contents of herbal tea mixture and of its components for foetal protection

Name of plant	Flavonoid (%)	Mass of plant (g)	Flavonoid content (g)
<i>Cynosbati pseudofructus</i>	0.014	30	0.004
<i>Melissae folium</i>	0.480	30	0.144
<i>Menthae piperitae folium</i>	1.180	20	0.240
<i>Urticae folium</i>	1.000	10	0.100
<i>Crataegi summitas</i>	0.700	10	0.070
		100	0.558

The sedative, relaxing and spasmolytic effects of *Melissae folium* are beneficial in alleviating anxiety, often experienced in pregnancy, and in giving a sense of well-being. Its main fields of administration are heart problems, insomnia and indigestion of nervous origin (Weiss, 1982; Koch-Heitzmann and Schultze, 1984).

Of the active ingredients of *Urticae folium*, provitamin A and vitamin K are not extracted into water; it therefore provides primarily chlorophyll, an antiseptic and significant amounts of mineral salts, mostly the magnesium ion (Braun, 1987).

The active ingredients of *Menthae piperitae folium* help to relieve indigestion, and the nausea that often accompanies pregnancy. Fields of therapeutic application for this material are dyspepsia and cholecystopathy (Duke, 1987).

The therapeutic effects of *Crataegi summitas* are to increase the working capacity of the cardiac muscle, to improve the blood flow of the coronaries and, when administered together with *Melissae folium*, to reduce cardiac problems of neurotic origin (Rácz et al., 1982). These positive effects on the heart help to maintain the optimal oxygenation of both mother and foetus. The relatively high magnesium content of this drug (302.2 mg/100 g) is also to be noted.

The magnesium ion content of the herbal tea mixture composed in our Institute is the following:

<i>Cynosbati pseudofructus</i>	200.0 mg/100 g
<i>Melissae folium</i>	590.7 mg/100 g
<i>Menthae piperitae folium</i>	538.8 mg/100 g
<i>Urticae folium</i>	504.8 mg/100 g
<i>Crataegi summitas</i>	302.2 mg/100 g

Directions for use: A heaped tablespoonful (2.5–3 g) of the herbal mixture into 300 cm³ of boiling water, preferably in a glass container, is left to stand covered for 10 minutes, then strained, flavoured to taste, preferably with honey, and consumed in 2–3 cups a day. For straining, the simultaneous use of gauze and cotton wool is recommended.

Application: This herbal tea mixture is composed of five herbs, four of which are accepted in officinal medicine and one freely distributed. It helps to supplement the increased needs for vitamins and minerals in pregnancy, and exerts mild sedative and digestive effects. Prolonged administration (as a cure for several weeks) is recommended.

Neither of the two infusions has any deleterious side-effects, as proved in animal experiments. Clinical tests are in progress.

By means of such products, magnesium naturally bound in plants, together with the other active ingredients accompanying it, will effectively serve therapeutic aims, and the long-term propagation of phytotherapy will also be promoted.

Summary

The author investigated some important medicinal plants for their magnesium contents, and selected the bests for (1) prevention of heart attack, and (2) for foetal protection.

The active ingredients as flavonoids procyanidines and vitamin C content were determined and standardized beside the magnesium content and releases from the tea mixtures. The tea mixtures do not have any side effects and are suitable for a long-term application of naturally bound magnesium completing with other high effective, active plant ingredients.

8.3. Magnesium substitution in dietary treatment

Attention was called to the possible importance of magnesium in dietary treatment by data which revealed a 6.9% (Whang et al., 1985) and an 11% (Wong et al., 1983) incidence of hypomagnesaemia in hospitalized patients. Whang et al. (1985) reported that hypomagnesaemia was especially frequent in conjunction with other electrolyte disturbances: hypomagnesaemia was found in 42% of hypokalaemia, 29% of hypophosphataemia, 23% of hyponatraemia and 22% of hypocalcaemia cases.

Magnesium therapy via dietary treatment may be needed in magnesium depletion, and in cases where magnesium therapy is the goal. Alcoholism and chronic liver diseases (cirrhosis) belong among the conditions of magnesium depletion. The magnesium deficiency of chronic alcoholics is a well-known consequence of regular alcohol consumption, which gives rise to a magnesium loss (alcohol increases magnesium excretion, even when administered parenterally). There are many similarities between the symptoms of hypomagnesaemia and the neuromuscular excitation following acute alcohol withdrawal. The magnesium status of most alcoholics can be simply restored by a normal magnesium intake. In most liver cirrhotic patients a magnesium deficiency can be demonstrated (Lieber, 1988).

A low serum magnesium level is frequently found in diseases and pathological conditions where malabsorption develops, mostly as a consequence of the increased magnesium loss. In these cases, the elevated amount of fatty acids in the intestine produces non-soluble magnesium soap substances, and the excretion of these with the faeces results in the magnesium loss. Consequently dietary fat reduction in malabsorption has a favourable effect on the magnesium nutrition (Booth et al., 1963). The danger of magnesium depletion must be taken into consideration in different infections, and primarily those involving vomiting, diarrhoea and increased perspiration (this can be responsible for 10–15% of the total daily magnesium loss). Wound healing increases the magnesium requirements, since magnesium is a cofactor of the enzymes promoting protein synthesis. In these cases, the magnesium requirements of the body are especially high if a significant magnesium loss develops due to previous severe diarrhoea or intestinal fistula (Goodson and Hunt, 1988).

Magnesium depletion can arise after severe burning injuries, in part as a result of osmotic diuresis and in part in connection with the nitrogen excretion (Bessey and Wilmore, 1988).

A significant magnesium depletion can occur in cases of severe protein energy malnutrition, especially in forms accompanied by vomiting and diarrhoea, mainly in children in countries with an insufficient magnesium supply. Nichols et al. (1978) found hypomagnesaemia in 50% of children hospitalized in South America because of malnutrition, with a magnesium deficiency in the musculature. Publications on children suffering from malnutrition on hospitalization are not rare, and this calls attention to the incidence of magnesium deficiency.

In cases of poorly controlled diabetes, the danger of the development of magnesium depletion, due in particular to the urinary loss of magnesium, must be taken into consideration (Shils, 1990), and the risk of development of a magnesium deficiency exists in diabetes of both Types 1 and 2. Sjögren et al. (1988) found not only a decreased magnesium content in the muscles and the serum in patients with diabetes of Type 2, but also an increased urinary magnesium loss. Clinical studies have led to speculations on a potential link between the magnesium deficit and most of the diabetic complications, e.g. angiopathy, including retinopathy (Garland, 1992).

The possibility of the development of a magnesium deficiency is suggested in all cases where the diet is limited in quantity and/or quality e.g. extremely restricted and unprofessional slimming diets, insufficient nutrition of elderly people or diets advised by nutritional extremists.

A magnesium depletion can develop after parathyroidectomy performed because of hyperparathyroidism (Jones et al., 1973) and in hyperthyroidism, and in primary and secondary hyperaldosteronism (Wester, 1987).

A magnesium-deficient status may be observed in some renal diseases and/or during the use of medicines which influence the renal function. In chronic renal diseases, the limited diet, and the magnesium loss caused by vomiting, diarrhoea, malabsorption, and the use of diuretics and/or a magnesium-deficient dialysate can cause a magnesium depletion. An increased magnesium loss may be experienced in post-obstructive nephropathies, chronic glomerular nephritis and acute tubulo-interstitial nephritis (Shils, 1990).

The effects of drugs that increase magnesium excretion are well known in the aetiology of magnesium depletion (e.g. chlorothiazide, hydrochlorothiazide, ethacrynic acid, ammonium chloride and mercury-containing diuretics). The diuretic effect and hence the magnesium-excreting action of alcohol are likewise well known. The magnesium-discharging effect of laxatives and drugs causing steatorrhoea should similarly be taken into consideration. Long-term digoxin treatment can result in a magnesium deficiency by decreasing magnesium reabsorption (Gums, 1987).

There are cases when magnesium substitution can become necessary, e.g. in the treatment of ventricular extrasystole emerging as a consequence of long-term digoxin and diuretic therapy, and a low magnesium content of the myocardium may be supposed, leading to a decreased intracellular potassium concentration, which can result in ventricular arrhythmia. Oral or parenteral administration of magnesium can result in a rapid and significant improvement in these cases (Dyckner and Wester, 1979).

Since the 1960s, there have been data on the beneficial effect of magnesium therapy on the serum lipids, and the relationship between magnesium intake and serum lipids was recently studied by Davis et al. (1981): 17.92 mmol magnesium chloride was administered daily for 118 days to 16 patients with hypercholesterolaemia in whom the LDL-C and VLDL-C levels were elevated, and the HDL-C level was low. At the end of the study period, the TC and VLDL-C levels of all the patients were reduced significantly, there was a great improvement in the LDL-C level too, and the HDL-C level was increased. Magnesium supplementation was suggested as the first therapeutic choice for the treatment of atherosclerosis. Orimo and Ouchi (1990) found that an increased amount of dietary magnesium in cholesterol-fed rabbits suppressed the development of atherosclerotic lesions in the aorta, without affecting the plasma TC and HDL-C levels, but with a slight decrease in the TG level (Ouchi et al., 1990). Decreases in the serum TC and TG levels and a marked attenuation of the atherosclerotic process was demonstrated in cholesterol-fed rabbits treated with magnesium aspartate (Altura et al., 1990).

Dyckner and Wester (1983) applied magnesium aspartate hydrochloride supplementation for 6 months in the therapy of 39 patients treated with diuretics. The blood pressure of the patients was decreased at the end of the treatment, but the serum magnesium level was not changed. These results were not confirmed by Henderson et al. (1986), who administered magnesium oxide (each dose contained 301 mg magnesium) to 20 patients with hypertension for 6 months and the results were then compared with those on 20 placebo-treated controls. All patients received potassium-

excreting diuretics, and at the end of the study period there was no difference between the blood pressures in the magnesium and placebo-treated groups. Other, similarly controversial data do not facilitate the assessment of the question, and do not permit the definite recommendation of magnesium supplementation in the treatment of hypertension. Oral magnesium supplementation (1 g MgO/day) was administered for 4 weeks to 21 outpatients with uncomplicated essential hypertension and a significant blood pressure decrease was found (Motoyama et al., 1989). It was concluded that an appropriate oral magnesium intake might be effective as non-pharmacological treatment for essential hypertension. Whelton and Klag (1989) came to the same conclusion, but suggested large, well-controlled studies before magnesium treatment can be recommended in all forms of hypertension. Magnesium supplementation did not seem to have an additive blood pressure-decreasing effect in mild hypertensive patients on a reduced sodium intake (Nowson and Morgan, 1989). Singh et al. (1989) found that magnesium therapy can prevent the development of resistant hypertension, and reduce the blood pressure by 10/5 mm Hg, and they concluded that magnesium supplementation may be suggested for hypertensive patients treated with diuretics. Kesteloot (1991) considered that dietary magnesium probably has a slight blood pressure-lowering effect, but more data are needed to evaluate the importance of this.

The role of magnesium supplementation in pregnancy has not yet been decided unanimously. In pregnancy-induced hypertension, magnesium administration increased the birthweight and the placental weight significantly in 18 women (Rudnicki et al., 1990), and it was concluded that magnesium supplementation could have a beneficial effect on foetal growth in pregnancy-induced hypertension. McGarvey et al. (1991) found an inverse relationship between the maternal prenatal magnesium intake and the systolic blood pressure of the infants at the age of 6 months. In a randomized double-blind study on 568 pregnant women, the outcome of pregnancy was significantly improved in the magnesium-treated group: fewer maternal hospitalizations, a reduction in preterm deliveries, and the less frequent referral of the newborns to the neonatal intensive care unit (Jaspers et al., 1990). In the large study by Skajaa et al. (1991), the magnesium intake seemed adequate, and pre-eclampsia and preterm labour did not seem to be associated with a low dietary magnesium intake. Accordingly, they did not recommend routine magnesium supplementation during pregnancy in populations with a relatively good socio-economic status.

Hypomagnesaemia and a low erythrocyte magnesium content have been described in non-insulin-dependent diabetes mellitus. Paolisso et al. (1989) studied the effect of magnesium supplementation in 8 elderly, moderately obese non-insulin-dependent diabetics and concluded that magnesium administration may be a useful adjuvant to the common hypoglycaemic agents in the therapy of such patients. Both experimental and clinical examinations suggest that increased urinary magnesium excretion is the major factor resulting in the magnesium-deficient nutritional status in diabetes caused by a specific renal tubular magnesium reabsorption failure, and osmotic diuresis is the other factor (Garland, 1992).

The treatment of magnesium depletion is not too difficult, since the absorption is very efficient in such cases. In parallel with the improvement in the magnesium status, the absorption will gradually decrease until 60% of the magnesium intake is excreted. During magnesium administration, the hardness of the drinking water should be taken into consideration, since very hard water can contain even 400 mg magne-

Table 8.10. Magnesium contents of foods in Hungary (Bíró and Lindner, 1988)

> 500 mg/100 g	50–25 mg/100 g	< 25 mg/100 g
Beans (2170)	Semolina (40)	Pearl barley (20)
Split peas (1260)	Rye flour (25)	Maize flour (7)
Lens (1340)	Bread crumbs (35)	Rice, rice flour (13)
Soy bean (3600)	White bread (48)	Noodles, with 2 eggs (23)
Poppy seed (506)	Sweet bread (28)	Noodles, with 4 eggs (22)
Sunflower seed (620)	Crescent, salty (43)	Bread, rye (24)
Pumpkin seed (970)	Crescent, with milk (42)	Milk, goat (13)
	Roll of bread (41)	Breast milk (3)
	Ewe cheese (42)	Skimmed milk (18)
<u>500–100 mg/100 g</u>	Cheese, Ementhaler (30)	Curd, medium fat (6)
Oatmeal (110)	Veal (25)	Sour milk cream (14)
Soy flour (240)	Chicken breast (30)	Kefir, yogurt (15)
Graham bread (400)	Mutton (25)	Pork cheese (22)
Milk powder (110)	Horsemeat (39)	Cabbage (24)
Walnut (256)	Beef (36)	Lettuce (24)
Peanut (290)	Pork, fatty (29)	Green pepper (16)
Hazel-nut (368)	Pork, medium fat (41)	Apple (11)
Almond (140)	Pork, low fat (42)	Lemon (20)
Cocoa powder (200)	Poultry meat (30)	Cantaloupe (20)
Tea (250)	Beef liver (34)	Cherry (16)
	Beef tongue (37)	Gooseberry (15)
<u>100–50 mg/100 g</u>	Pork liver (38)	Water-melon (15)
Cheeses (56–66)	Ham, smoked (44)	Apricot (14)
Sausage (high fat) (57)	Ham (25)	Raspberry (24)
Beetroot (87)	Liver paste (27)	Orange (22)
Spinach (53)	Low-fat sausages (Viennese) (32)	Peach (14)
Green peas (64)	Carp (30)	Plum (16)
Banana (60)	Tuna (28)	Grape (14)
Chocolate, black (65)	Potato (28)	Cake, fine (22)
	Kohlrabi (32)	Tomato juice (16)
	Cauliflower (31)	
	Haricot bean (29)	
	Coffee (40)	
	Raisin (43)	
	Chestnut (48)	

sium/dm³, but soft water as little as 6 mg/dm³. The physician must know the average local magnesium intake, i.e. the amount of the magnesium in the diet of the population. The magnesium content of the food is the basis of dietary planning (Table 8.10).

In such planning, attention must be paid to the factors influencing the intestinal absorption and the utilization of the magnesium, and to the loss of magnesium during the cooking processes.

The food industry makes widespread use of inorganic polyphosphates as stabilizers against rancidity. These substances increase the solubility of magnesium (and other) salts and consequently presumably promote the absorption of magnesium, and therefore the better utilization of magnesium from the food (Rao and Rao, 1984).

The glucose polymer (which breaks down to glucose in the body) produced from maize starch significantly increases magnesium absorption, as demonstrated in 8 healthy subjects by Bei et al. (1986). This glucose polymer was suggested for therapy and

also to increase the efficiency of diets planned for magnesium supplementation. The effect of dietary fibres on the absorption of minerals, including magnesium, is well known. The effect of refined cellulose was studied by Slavin and Marlett (1980) in 7 healthy adult women. The addition of 16 g refined cellulose to the diet resulted in increased urinary and faecal magnesium excretion at the end of the one-month period of the experiment. This revealed that even a moderate cellulose supplementation increases the magnesium loss.

A negative magnesium balance was found on the addition of 10 and 20 g of cellulose and hemicellulose to the diet in adolescent boys and girls (McHale et al., 1979). This obviously can not mean that cellulose and hemicellulose should be avoided in the diet, but draws attention to an increased concern as to the effects of dietary fibres.

The role of the dietary fibres in magnesium utilization can be modified by different factors (Drews et al., 1979). The inclusion of 14.2 g hemicellulose in the diet of 8 adolescent boys increased the magnesium excretion more efficiently than did the same quantity of cellulose, but the magnesium loss was least increased by pectin. In animal experiments in which diets supplemented with high pectin-containing apples were administered, changes suggestive of a magnesium deficiency could not be demonstrated, and it was considered that well-balanced diets do not involve the danger of a negative magnesium balance (Sablé-Amplis et al., 1986).

The use of different animal or vegetable proteins in the diet (casein, beef protein or soy protein) did not lead to significant changes in magnesium utilization (Lo et al., 1980).

It is proved and accepted that in animal experiments calcium and magnesium mutually influence the absorption of the other, a decreased intake of one of them being accompanied by the increased absorption of the other, but this mutual influence is less apparent in humans. Consequently, the effect of magnesium supplementation in this respect does not always meet expectations. An increased calcium intake in man can decrease the magnesium absorption and plasma magnesium level, and even the urinary magnesium excretion (Clarkson et al., 1967), while an increased magnesium intake can result in a decreased faecal magnesium level and an increased urinary magnesium content (Heaton and Parson, 1961). Other observations indicate that long-term magnesium administration does not influence the calcium balance. No data are available on the influence of naturally calcium-rich (but not fortified) diets on the magnesium status of the body. The difference between the mineral contents of the traditional balanced nutrition and an extreme nutritional diet presumably does not have an unfavourable influence on the mutual effect of the two electrolytes. In non-vegetarian balanced nutrition, the calcium and magnesium contents may be 700–800 and 300–400 mg/day, in the diet of lacto-ovo-vegetarians they are around 1200 and 640 mg/day, and in the diet of strict vegetarians (vegans) they are 660 and 540 mg/day (Holtmeier, 1988).

In the practice of dietary magnesium supplementation, the administration of magnesium-containing mineral waters (in Hungary: "Balfi", "Fonyódi" and "Harmatvíz") and special mineral waters with therapeutic effect (in Hungary: "Ferenc József", "Hunyadi János", "Igmándi", "Jódaqua" and "Mira") can be included insofar as these waters contain mineral salts capable of being absorbed. The possible consequences of the simultaneous use of magnesium-containing medicines (e.g. antacids) must be taken into consideration.

8.4. Magnesium supplementation with acidic polysaccharides

Most of the magnesium ion requirements of human and various animal organisms come from magnesium chemically bound to components of the food (acidic polysaccharides [APS], proteins and amino acids, nucleic acids, nucleotides and nucleosides, etc.). In order to supply a subacute, but usually chronic, latent magnesium deficiency, which is very often brought about by an insufficient, one-sided nutrition poor in magnesium, organic Mg(II) compounds of *natural origin*, or their semisynthetic derivatives obtained by chemical modification and enriched with magnesium ions, are much more suitable than inorganic or synthetic Mg(II) compounds (Sigel and Sigel, 1990).

When the former type of compounds are administered orally, the organism ensures a higher degree of absorption, more effective utilization, more appropriate storage and safer excretion, i.e. all in all a more satisfactory *magnesium homeostasis* than when the latter type of inorganic and synthetic Mg(II)-compounds are used (e.g. chloride, citrate, EDTA), which may also cause unpleasant or deleterious side-effects such as diarrhoea and the elimination of essential trace metal ions.

Dehydrated APS, proteins, amino acids, nucleic acids, nucleotides and nucleosides bind the magnesium ion in inner sphere chemical complexes. The charge of the central magnesium ion is neutralized by the negative charges of $-\text{COO}^-$, $-\text{O}-\text{SO}_3^-$ and $-\text{O}-\text{PO}_3^{2-}$ groups and the remaining need for shielding of ionized magnesium, whose coordination number is six, is satisfied by further oxygen (e.g. ring and glycoside oxygen and/or hydroxyl group) or nitrogen atoms (e.g. amino or substituted amino groups). In the *hydrated* state, however, outer sphere complex bond may also be formed. The magnesium ion is coordinated by six water molecules in a regular octahedral arrangement in the inner (first) sphere, whereby the aqua ion $[\text{Mg}(\text{H}_2\text{O})_6]^{2+}$ is formed. In this arrangement, the anions neutralizing the charge are in the outer (second) sphere, binding to the water molecules of the inner sphere via hydrogen bridge bonds and van der Waals forces. In the hydrated state, another type of inner sphere complex bond may also be established, where the inner sphere of the central magnesium ion contains not only water molecules, but also highly polarizable anions capable of neutralizing charges of magnesium ions and neutral atoms or atomic groups. The elucidation of these bonding conditions made it possible to interpret why APS in general bind magnesium ions more weakly than do proteins and amino acids, nucleic acids, nucleotides and nucleosides (Martin, 1990).

Hydrated Mg(II)-APS complexes introduced into the organism in a natural way, i.e. orally, via the intestinal tract, come into contact with the brush border membranes of the intestinal cells and villi. A proportion of the calcium ions bound to the sialic acid constituents, phospholipids and glycoproteins of these membranes are exchanged for the magnesium ions of the ingested APS. The formed calcium complexes of APS are then excreted with the faeces (Barta-Bedó et al., 1973), while the magnesium ions that enter via contact ion-exchange are carried on along their well-known transport route (Hardwick et al., 1991):

a) by passive diffusion not requiring energy, characterized by a linear dependence on the magnesium ion concentration, and by a water influx, which is then gradually inhibited by significant increases in magnesium ion concentration, decreasing the membrane permeability; and

b) energy-dependent facilitated diffusion that follows a saturation curve.

Due to the contact Mg^{2+} - Ca^{2+} ion-exchange mechanism, the effectivity of absorption of the magnesium ion is proportional to the value of the *ion-selectivity coefficient* for Mg^{2+} and Ca^{2+} of carrier APS, where

$$K_{\text{Mg}}^{\text{Ca}} = \frac{(\text{Ca}^{2+})_{\text{gel}}}{(\text{Mg}^{2+})_{\text{gel}}} : \frac{(\text{Ca}^{2+})_{\text{solution}}}{(\text{Mg}^{2+})_{\text{solution}}}$$

(Haug and Smidsrød, 1970; Smidsrød, 1973).

The $K_{\text{Mg}}^{\text{Ca}}$ values determined *in vitro* (Table 8.11) show that these coefficients depend on several structural factors. They depend primarily on the polarizing power of the cations, $\text{Pb}^{2+} > \text{Cu}^{2+} > \text{Zn}^{2+} > \text{Co}^{2+} > \text{Mn}^{2+} > \text{Sr}^{2+} > \text{Ca}^{2+} > \text{Mg}^{2+} > \text{K}^{+}$, on the mole fraction ($X_{\text{Ca}^{2+}}$) of the participating ions in the gel phase (in Table 8.12, this value is identical for the two ions), and on the polarizability of APS.

Table 8.11. Cation selectivity coefficients of APS (Haug and Smidsrød, 1970; Smidsrød, 1973)

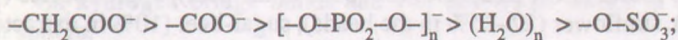
Acidic group	APS polymer ($X_{\text{Mg}} = 0.5$)	$K_{\text{Mg}}^{\text{Ca}}$	$K_{\text{Mg}}^{\text{Sr}}$	$K_{\text{Ca}}^{\text{Cu}}$
-COOH	Polyguluronate (90%), $n = 50$	40	150	8
	Polyguluronate (90%), $n = 50$ ($X_{\text{Ca}} = 0.2$)	30	(250)	-
	Polyguluronate (90%), $n = 50$ ($X_{\text{Ca}} = 0.2$)	100	(600)	-
	Polyguluronate (38%), $n = 20$	3.3	(2.7)	-
	Polyguluronate (38%), $n = 20$	3.4	-	-
	Polymannuronate (90%), $n = 26$	1.8	1.2	12
	Polymannuronate (90%), $n = 26$	2.1	-	-
	Alginate (92% mannuronate)	1.6	1.4	11
	Acetylated polyguluronate	1.0	1.0	12
	Polygalacturonate (90%)	7.0	9.6	32
	Polygalacturonate (90%), ($X_{\text{Ca}} = 0.2$)	30 (100)	-	-
	Oxidized cellulose (β -D-glucuronate)	1.1	1.5	11
	Oxidized starch (α -D-glucuronate)	1.2	-	-
	Carboxymethyl cellulose	1.4	1.3	17
	Carboxymethyl dextrane	1.8	1.4	10
	Hyaluronic acid	0.9	-	3.0
-COOH and -SO ₃ H	Chondroitine sulphate	1.1	0.95	2.4
-SO ₃ H	Carrageen	1.2	1.4	1.2
	Fucoidane	1.3	1.6	1.5
	Dextrane sulphate	1.1	2.0	0.9
	Pectic acid disulphate	1.0	-	-
-OP(OH) ₂ O	Dextrane polyphosphate	0.9	1.1	8.0

Table 8.12. Average magnesium levels in serum and whole blood (based on observations of acute 4-hour magnesium absorption in 10 healthy volunteers)

Orally administered magnesium preparation (100 mg/dose)	Serum magnesium level (mmol/l)			Total blood magnesium level (mmol/l)			Significant level
	fasting	after 4 hours	increasing	fasting	after 4 hours	increasing	
Basic magnesium-polygalacturonate (HOMgPG) in fruit jelly	0.952	1.042	0.09	1.568	1.780	0.212	p = 0.01
Neutral magnesium-polygalacturonate (KMgPG) in fruit jelly	0.862	0.883	0.021	1.296	1.463	0.167	p = 0.01
Magnesium oxide (MgO) in fruit jelly	0.871	0.921	0.05	1.361	1.431	0.070	p = 0.01

The latter is in turn determined by the following structural factors:

a) the polarizability of the negatively charged functional groups of APS relative to the water molecules of the hydration shell:



b) the number and distance of the functional groups within the APS polymer chain;

c) the structure of the monomer rings building up the APS chain, the configuration of their glycoside linkages and the flexibility of the polymer chain formed, which result in the following sequence: polyguluronate > polygalacturonate > polymannuronate > polyglucuronate;

d) in heteropolymers with several kinds of uronic acids or neutral monosaccharide components, their various distributions: (atactic, syndiotactic, isotactic);

e) the chain length determined by the degree of polymerization (n): when these increase, the *stability constants* of the APS-metal (Ca and Mg) complexes increase according to a saturation curve (Kohn, 1971; Kohn and Larsen, 1972; Kohn, 1975; Kohn and Maloviková, 1981). The Mg(II) complexes of the monomers are therefore hardly suitable for the introduction of magnesium, in view of their low stability constants. Even the bacteria residing in the human or animal colon are capable of liberating only very little monomer or oligomers ($n = 2, 3, 4$) from APS polymers during their transit time; thus, these are negligible as regards magnesium absorption. In contrast, the stability constants of the metal complexes of APS with intermediate degrees of polymerization ($n \sim 50$) are larger than those of monomers and oligomers, but lower than the corresponding values for amino acids and nucleotides (Martin, 1990), and they are therefore suited for magnesium intake. APS with very high degrees of polymerization are in turn used for the removal of toxic or radioactive metal ions (Pb^{2+} , $^{90}\text{Sr}^{2+}$ and Cd^{2+}) from the body (Tanaka and Skoryna, 1971).

The value of $K_{\text{Mg}}^{\text{Ca}}$ is significantly affected by the structure of metal APS complexes formed by natural metal ions or bound calcium ions intermolecular linking together the polymer chains, where the value of $K_{\text{Mg}}^{\text{Ca}}$ increases significantly at low

values of $[Ca^{2+}]$ as compared with those measured at intermediate values ($X_{Ca} \sim 0.4-0.5$). Acetylation of the OH groups decreases the values of the stability and selectivity coefficients for steric reasons (Kohn, 1975).

The APS in nutrients, which also serve as magnesium sources, may be of plant, or animal origin.

Mg(II) complexes of acidic polysaccharides of vegetal origin

Some of the Mg(II)-APS complexes of plant origin which may be considered for magnesium supplementation in practice are natural, e.g. pectin, pectic acid, alginic acid, carrageenan, fucoidan and mastics, while others are semisynthetic, e.g. pectic acid dinitrate and disulphate and the oxidized, sulphate ester and phosphate derivatives of starch.

Pectin, pectic acid and their derivatives

The most abundant APS in the plant kingdom is pectin, the structural material building up cell walls (Kertész, 1951; Fishman and Jen, 1985), the highest amounts of which are found in Citrus species (30–35% in the peel), apple species (15–20% in the pomace), sunflower (22–25% in the heads), sugar-beet (10% in extracted beetroot slices) and hedge rose (7.5–10.8% in rose-hips) and which is also extracted from these sources. Pectin is a heteropolymer: its chain molecules ($n = 25-2000$) are built up of *D-galacturonic acid* monomers linked by $\alpha(1-4)$ -D-glycoside linkages. Some of the carboxyl groups of the monomers (50–95%) are methyl-esterified, while others form mixed salts with macro metal ions (Ca^{2+} , Mg^{2+} , K^+ and Na^+). Additionally, pectin also contains neutral monosaccharides (10–20%), L-rhamnose as L-rhamnogalacturonan chain sections in the "elbows" of the chains, L-arabinogalactan and D-xyloglucan side-chains, and D-xylose, 2-O-methyl-D-xylose, L-fucose, 2-O-methyl-D-fucose and D-apiiose branches. L-Arabinogalactan chains are also bound by glycoside linkages to the cell-wall glycoproteins, which are rich in proline and also contain serine, alanine and threonine (Albersheim, 1973).

Finally, the sugar hydroxyl groups may be partially acetylated, as in the case of sugar beet, sunflower, potato, pear and peach pectin, while in sugar beet ferulic acid esters are also to be found (Fishman and Jen, 1985).

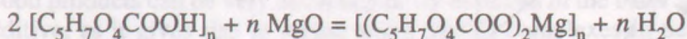
Pectin with a high polymerization degree is utilized for the removal of toxic Pb^{2+} , Cd^{2+} and Sr^{2+} from living organisms (Tanaka and Skoryna, 1971; Paskins-Hurlburt et al., 1977).

The base, acid or enzyme-catalysed hydrolysis of pectin (Kertész, 1951; Worth, 1967; BeMiller, 1985; Thibault and Rinaudo, 1985), often performed in the presence of calcium chelators such as EDTA or polyphosphate, results in *pectic acid* or *oligo* and *polygalacturonic acid* or *polygalacturonate* (PGA), the Mg(II) complexes of which are suitable for oral magnesium supplementation in living organisms (Lakatos et al., 1976; 1988).

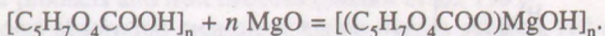
Pectin is demethylated, deacetylated, deferulated and deproteinated by the most practicably applied base or acid hydrolysis, thereby making all the carboxyl and sugar

hydroxyl groups free, which greatly increases the capacity of the newly-formed PGA to bind the magnesium ion and the value of the selectivity coefficient K_{Mg}^{Ca} (Kohn and Furda, 1967). On the other hand, because of the splitting of the pectin chains, hydrolysis considerably decreases the chain length down to the polymer or oligomer level ($n = 10-250$) and the "ballast", i.e. neutral carbohydrate and protein content of the pectin is also decreased. The magnesium ion binding capacity of PGA and the strength of the magnesium polygalacturonate (MgPG) bond are therefore increased.

Hydrolysis of pectin and pectic acid with MgO in aqueous solution results in two kinds of *MgPG complexes*, one *neutral*:

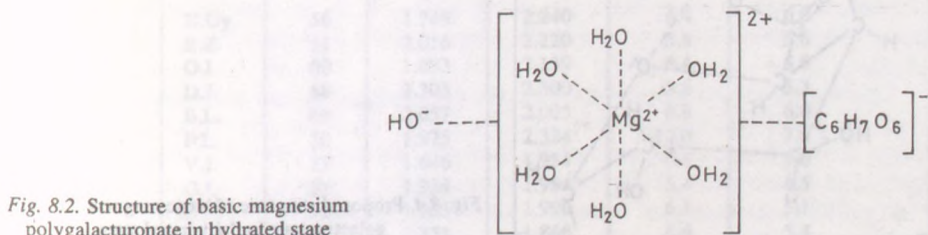
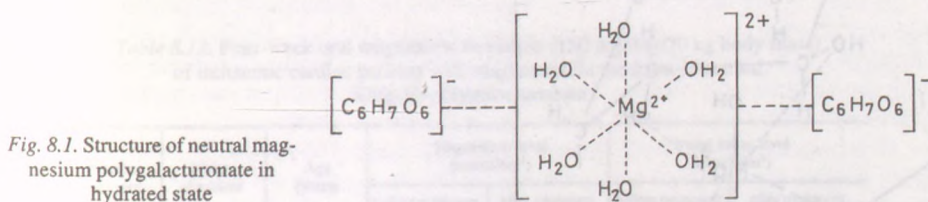


and one *basic*:



In both cases, a hydrated complex of outer-sphere type in the gel state is formed (Figs 8.1 and 8.2), where in the neutral complex two PG^- anions and in the basic complex one PG^- anion and one OH^- ion, or possibly one HCO_3^- anion resulting from the reaction $OH^- + CO_2 = HCO_3^-$, are linked to the water molecules of the aqua ion $[Mg(H_2O)_6]^{2+}$ via hydrogen bridge bonds and van der Waals forces in the second coordination sphere.

In contrast, under conditions of dehydration, there is a significant structural difference between neutral and basic Mg(II) complexes. In the neutral complex, the central magnesium ion is coordinated by six oxygen atoms, forming an inner sphere complex in a distorted octahedral configuration such that the two carboxylate anions acting as unidentate ligands neutralize the two positive charges of the central metal ion, while two ring oxygen atoms and two glycoside oxygen atoms satisfy the coordination number of six by dative bonds (Fig. 8.3; Lakatos et al., 1983a, b). In basic Mg(II) complexes,



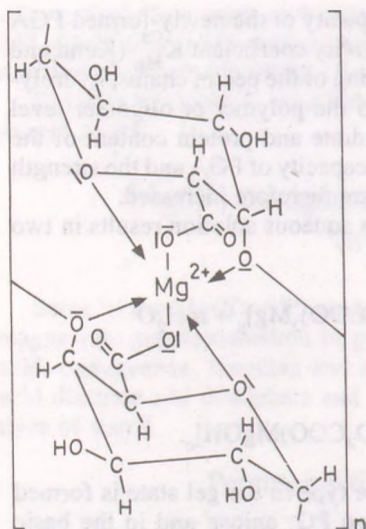


Fig. 8.3. Structure of neutral magnesium polygalacturonate in dehydrated state

however, one of the positive charges of the magnesium ion is neutralized by an OH^- (or a HCO_3^-) ion rather than a second polygalacturonate chain, two sugar hydroxyl groups of which probably satisfy the magnesium ion coordination number of six by means of weaker bonds (Schweiger, 1966; Fig. 8.4).

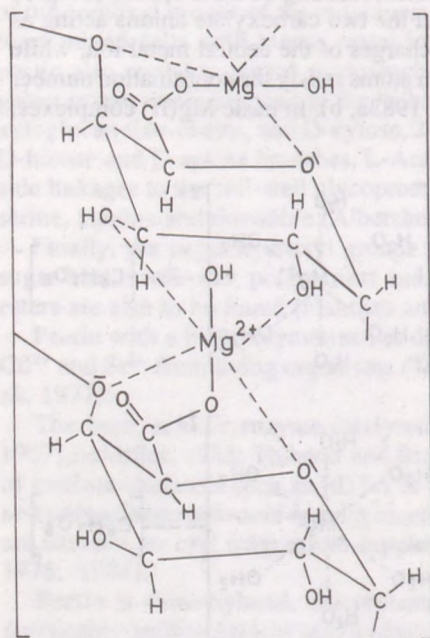


Fig. 8.4. Proposed structure of basic magnesium polygalacturonate in dehydrated state

The looser structure of the basic complex and the weaker bond between the chains (as opposed to the more compact structure of the neutral complex joined by bridge linkages involving the magnesium ion) in contact interaction with the membranes of the intestinal cells initially ensure an easier and faster magnesium and calcium ion exchange, since at $X_{Ca} < 0.4$ the value of the selectivity coefficient K_{Mg}^{Ca} falls between 50 and 100, while at $X_{Ca} > 0.4$ it is between 3 and 10. As the exchange proceeds, however, the increasing calcium ion concentration promotes the formation of more and more inter-chain calcium bridge linkages, whereby the structure approaches that of the neutral complex.

Many food products can be very advantageously enriched in the basic Mg(II) complex as additive, as it gives rise to mixed anion Mg(II) complexes in neutralization reactions with the acidic components of foodstuffs: APS, amino acids and fruit acids. These are highly suitable for magnesium supplementation, and they often improve the texture of food products and fruit nectares (Sándor et al., 1991).

Acute (4-hour) absorption measurements on human subjects (10 cases) revealed that neutral and basic Mg(II)PG corresponding to a magnesium dose of 100 mg, administered in sour cherry jelly, resulted in a significantly higher magnesium level in total blood (Table 8.12) than did the MgO used for comparison as a control, and the highest level was obtained with basic MgPG (Bodrogi et al., 1988).

For comparative purposes, albino rats were fed neutral KMg(II)PG and KMg(II)-aspartate (6 mg Mg/100 g body mass/day) in chocolate filling (50 mg Mg/25 g) in an appropriate constant premix and food containing the physiologically necessary amount of vitamins and trace elements (metal-PG) but no magnesium for 7 weeks. After this treatment, the magnesium content of the left cardiac chamber was approximately 3 times higher than that of the right one; the maximal level was obtained with KMg(II)PG (Zelles, 1978).

In 10 patients with ischaemic cardiac disease, the oral administration for 4 weeks of neutral KMg(II)PG (150 mg Mg/day/70 kg body mass) supplemented with the necessary vitamins (B₆, C and E) and constant trace elements (metal-PG), together

Table 8.13. Four-week oral magnesium treatment (150 mg/day/70 kg body mass) of ischaemic cardiac patients with magnesium in the form of neutral KMg(II)-polygalacturonate

Number of cases	Name of patient	Age (years)	Magnesium level (mmol/dm ³)		Blood sugar level (mmol/dm ³)	
			before treatment	after treatment	before treatment	after treatment
1.	N.Gy.	56	1.749	2.240	6.4	6.0
2.	B.Z.	51	2.016	2.220	5.8	5.6
3.	O.I.	60	1.893	2.139	6.4	5.8
4.	D.J.	68	2.303	2.300	5.6	5.3
5.	B.L.	66	2.057	2.005	6.8	6.0
6.	P.L.	50	1.975	2.324	10.0	7.8
7.	V.J.	57	1.646	1.954	6.8	5.0
8.	G.I.	57	1.934	1.954	5.4	4.5
9.	D.S.	51	1.255	1.996	6.1	5.1
10.	Gy.I.	41	1.851	1.866	6.6	5.4

Table 8.14. Magnesium and potassium levels of lymphocytes of ischaemic and hyperlipaemic cardiac patients before and after a one-week oral magnesium treatment (200 mg/day)

	Patient No. 1 (B.I.) age 41		Patient No. 2 (V.L.) age 53	
	magnesium	potassium	magnesium	potassium
	(10 ⁶ mg/cell)		(10 ⁶ mg/cell)	
Initial value	0.2132	0.0861	0.2001	0.0952
After taking neutral KMgPG	1.1526	21.0078	21.5240	3.3874
Before taking Panangin (KMg-aspartate)	0.1891	2.8320	0.1969	3.5842
After taking Panangin	0.2893	2.7098	0.3968	5.0774

with a low calcium diet (no milk or milk products), resulted in a significant increase in the magnesium level in the whole blood, a decrease in blood sugar level (Table 8.13) and the alleviation of ischaemia, anginal attacks and arrhythmia (Fülöp et al., 1986).

Two male patients (41 and 53 years of age), similarly with ischaemic cardiac disease, were given neutral KMg(II)PG (200 mg Mg/day/70 body mass) orally for one week. Blood samples and lymphocytes were then taken, and they were kept on a diet poor in magnesium and calcium for 2 weeks. They finally received KMg(II)-aspartate again for one week. The results of repeated determination of the potassium and magnesium levels in their lymphocytes (Table 8.14) showed that the increase in magnesium level was significantly higher (10- and 6-fold) after the administration of KMg(II)PG than after MgK(II)-aspartate (Fülöp, 1986).

After oral administration of neutral KMg(II)PG (7 g/day/70 kg), 3 hours after a glucose load of 50 g, the blood sugar levels of five asthenic, mildly diabetic patients were significantly decreased (50% on average) as compared to the control (Simončič et al., 1983).

In work initiated by Kiss and Melles (1972), the anaemia of 62 pregnant women was corrected by orally supplied constant vitamins (C, A, E, B₁, B₃, B₆ and B₉), trace elements (metal-PG) and neutral and basic Mg(II)PG (200 mg/day/70 kg body mass), with the achievement that the haemoglobin level and the serum iron parameters were practically unimpaired during the pregnancy (Lakatos, 1988).

18 premature infants were treated orally with neutral Mg(II)PG corresponding to a daily magnesium dose of 3 mg, together with the necessary vitamins and trace elements (metal-PG) from the age of 10 days to 30 days. The infants exhibited a significant increase in body mass (25 g/day on average), in contrast with the control group, who received magnesium in the form of KMg(II)-aspartate (21 g/day) (Frank, 1978).

Sulphation, nitration and phosphatization of pectin or pectic acid result in the semi-synthetic poly(oligo)galacturonic acid disulphate, dinitrate and diphosphate, respectively, in which two OH groups of the monomer are disubstituted. In aqueous sodium hydroxide solutions of all three compounds, in the presence of magnesium chloride, NaMg(II)-PG-disubstituted complexes are formed, which are water-soluble. The disulphate is mostly used as a food additive (Schweiger and Andrew, 1972), while the

dinitrate is suitable for the parenteral introduction of magnesium and iron (Lakatos et al., 1979a). Magnacomp tablet contains basic PG complex of Mg, vitamins B₁ and B₆, and L-arginin; the Multicomp tablet contains basic PG-complexes of Mg, Fe, Zn, Mn and Cu, and Ferrocomp tablet contains basic PG complexes of Fe, Co, Cu, Zn, Mn and vitamins C and B₉.

Alginic polysaccharides

Large quantities of alginic acid (Alg) are found in maritime brown algae, in the form of mixed salts (14–40%) of macro metal ions (Ca²⁺, Mg²⁺, Na⁺ and K⁺) (Muzzarelli, 1973; Muzzarelli et al., 1974). Alg is a heteropolymer ($n = 300\text{--}1000$) made up of β -D-mannuronic acid and α -L-guluronic acid in $\alpha(1\text{--}4)$ and $\beta(1\text{--}4)$ linkages, respectively. Uronic acid monomers join to form long-chain molecules in ratios depending upon the algal source (6.5–0.1). Their ion selectivities largely depend on the ratio of the two types of monomers (Haug and Smidsrød, 1965; Patrick, 1967; Smidsrød and Haug, 1968). MgAlg (Algicon) combined with antacids is used as an anti-reflux in reflux diseases of the stomach and the oesophagus (Lambert et al., 1990). Alg liberated by gastric acid exerts its protecting effect on the stomach and oesophagus lining, and at the same time magnesium ions are generated. Due to its high n value, however, this polymer is more suited for the removal of radioactive ⁹⁰Sr²⁺ from the body (Tanaka and Skoryna, 1971), but it also increases the excretion of Fe²⁺, Cu²⁺, Zn²⁺ and Ca²⁺ in the faeces (Hodgkinson et al., 1967).

The higher the guluronic acid content of alginates, the larger is their capacity to bind Sr²⁺, Ca²⁺ and transition metal ions (see Table 8.11).

Maritime red algae contain *carrageenan*, which consists mostly of D-galactose-6-sulphate or 2,6-disulphate linked by $\alpha(1\text{--}3)$ - and $\beta(1\text{--}4)$ -glycoside linkages, and also *fucoidan*, which is poly- α -L-fucopyranose and its 4-sulphate, with $\alpha(1, 2)$ linkages (Tanaka and Skoryna, 1971; Weiner, 1991). Mg²⁺ and Ca²⁺-carragenates are used as gelatinizing agents to improve the texture of certain beverages and foodstuffs. Because of the $-\text{OSO}_3^-$ groups, the selectivity constant $K_{\text{Mg}}^{\text{Ca}}$ is low (see Table 8.11) as is the complex stability, and it is therefore of hardly any use for magnesium supplementation, just like the semi-synthetic dextran sulphate (Gekko and Noguchi, 1979).

Gum acidic polysaccharides of plant origin

Vegetal gums, such as *gum arabic*, contain considerable amounts of poly-D-glucuronic acid. Similarly, the semi-synthetic products oxidized starch and oxidized cellulose contain poly(oligo)- α -D-glucuronic acid (Lakatos et al., 1979b) and poly(oligo)- β -D-glucuronic acid (Jacopian, 1974), respectively; both have been tested for the intravenous and oral intake of magnesium and iron.

Acidic polysaccharides of animal origin

Of the acidic mucopolysaccharides of animal origin, *hyaluronic acid* and *chondroitin-4- and 6-sulphate* also contain poly-D-glucuronic acid.

These molecules have a large cation-exchange capacity, and they therefore also participate in extracellular ion transport. They bind the calcium ion weakly, but selectively (Hunter et al., 1988), and thus their magnesium "salts" are used (Valle et al., 1988). The iron complexes of chondroitin sulphates have been used for intravenous injection (Nakanishi and Kishi, 1970).

References to Chapter 8

8.1. Magnesium-containing drugs

- Ackermann, M. (1989): Magnesium — Eine körpereigene Substanz und ein bedeutsames Pharmakon. *Therapiewoche Suppl.* **39**, 1791.
- Aden, G. D. (1990): Magnesium — Ein lebenswichtiges Mineral. *PTA Heute* **4**, 492.
- Classen, H.-G. (1986): Magnesiumsalze in der Humantherapie: Grundlagen zum Verständnis von Wirkungsweise und Indikationen. *VitaMinSpur* **1**, 5.
- Durlach, J. (1988): *Magnesium in Clinical Practice*. John Libbey Eurotext Ltd., London — Paris.
- Fiedler, H. P. (1989): *Lexikon der Hilfsstoffe für Pharmazie, Kosmetik und angrenzende Gebiete*. Cantor, Aulendorf.
- Formulae Normales* (1987). Editio VI. Medicina, Budapest.
- Formulae Normales Veterinariae* (1973). Editio II. Mezőgazdasági Kiadó, Budapest.
- Gums, J. G. (1987): Clinical significance of magnesium: A review. *Drug Intell. Clin. Pharm.* **21**, 240.
- Günther, T. (1983): Fötaler und maternaler Magnesium — Stoffwechsel: Einfluß von Mg-Mangel und Wirkung von Isoproterenol. In: *Magnesium und Schwangerschaft*. Ed. Weidinger, H. Bayreuther Gespräch. 63.
- Hollifield, J. W. (1989): Thiazide Treatment of Systemic Hypertension: Effects on Serum Magnesium and Ventricular Ectopic Activity. *Am. J. Cardiol.* **63**, 226.
- Kórházi Gyógyszerészeti Manuális (1989): 2nd ed. MGYT Kórházi Gyógyszerészeti Szervezete, Budapest.
- Kroll, M. H., Elin, R. J. (1985): Relationships between magnesium and protein concentrations in serum. *Clin. Chem.* **31**, 244.
- Manuale pharmaceuticum* (1986). MGYT, Budapest.
- Mutschler, E., Völger, K.-D. (1982): Die Bedeutung von Magnesium in der Therapie. *Z. Allg. Med.* **58**, 677.
- Peerenboom, H., Keck, E. (1980): Die Bedeutung des Magnesiums in der Medizin. II. *Münch. med. Wschr.* **122**, 1328.
- Pharmacopoeia Hungarica* (1986): Editio VII. Medicina, Budapest.
- Picciano, M. F., Calkins, E. J., Garrick, J. R., Deering, R. H. (1981): Milk and mineral intakes of breastfed infants. *Acta Paediatr. Scand.* **70**, 189.

- Selmecezi, B., Kedvessy, Gy. (1981): *The Tableting Technology*. Medicina, Budapest. (In Hung.)
- Simon, K. H. (1967): *Magnesium. Physiologie — Pharmakologie — Klinik*. Wissenschaftliche Verlagsgesellschaft mbH, Stuttgart.
- Directive for Prescription of Pharmaceutical Products*. (1988). Medicina, Budapest. (In Hung.)
- Vaughan, L. A., Weber, C. W., Kemberling, S. R. (1979): Longitudinal changes in the mineral content of human milk. *Am. J. Clin. Nutr.* **32**, 2301.

8.2. The magnesium content of herbs and their therapeutic use

- Aikawa, J. K. (1963): *The Role of Magnesium in Biological Processes*. C.C.Thomas Publisher, Springfield, I. 11.
- Bachem (1980): 3. Hohenheimer Magnesium-Symposium, *Therapie-Woche* **3V**, 3073.
- Bíró, Gy., Lindler, K. (1988): *Table of Nutrients*. Medicina, Budapest. (In Hung.)
- Blaxter, K. L. (1956): *The Magnesium Content of Bone in Hypomagnesaemic Disorders of Livestock*. CIBA Foundation Symp. on Bone Structure and Metabolism, Boston, 1955.
- Braun, H. (1974): *Heilpflanzenlexikon für Ärzte und Apotheker*. (4. Aufl.) Fischer Verlag, Stuttgart.
- Csányi, V. (1976): *Cell Biology*. Gondolat, Budapest. (In Hung.)
- Duke, J. A. (1987): *CRC Handbook of Medicinal Herbs*. CRC Pr. Inc., Boca Raton, FL.
- Durlach, J. (1967): The effect of magnesium on blood coagulation. *Coeur et Méd. Int.* **7**, 218.
- Hársing, L. (1973): *Physiology and Pathophysiology*. Medicina, Budapest. (In Hung.)
- Hidas, I. (1980): The role of magnesium in the ion. *Medicus Universalis* **13/1**, 48.
- Hungarian Pharmacopoeia* (7th ed., 1986). I–III. Medicina, Budapest.
- Kiss, D. (1975): *Centralbl. Gynecol.* **15**, 924–929.
- Koch-Heitzmann, I., Schultze, W. (1987): *Melissa Officinalis L.: Die neue therapeutische Wirkung einer alten Heilpflanze*. *Dtsch. Apoth. Ztg.* **124**, 2137.
- Kochler, V. (1966): *Electrolytes in Cardiovascular Diseases*. Vol. 2. S. Karger, Basel, 395.
- Kota, J. (1969): *Cardiology* **9**, 120, 121.
- Krawczyk, U. (1990): *Study and Research on Analytical Methods for Determination of Flavonoids, Procyanidins and Anthocyanins in Some Plant Preparations*. Semmelweis Med. Univ., Budapest. Ph. D. Thesis.
- Kuti, V. (1978): Experimental epidemiological study of the correlation of premature delivery and magnesium deficiency. *Med. Univ.* **11/11**, 13. (In Hung.)
- Loch, J. (1978): The magnesium supply in Hungarian soils. *Med. Univ.* **11/11**, 3. (In Hung.)
- Loch, J. (1985): Characterization of the magnesium status of soils by means of the EUF–Mg fractions. *Plant and Soil* **83**, 77.
- Ludmény, K. (1978): The biological significance of magnesium in ontogenesis. *Med. Univ.* **11/11**, 25. (In Hung.)
- Petri, G., Mikita-Nyiredi, K., Nyiredi, Sz. (1989): *Modern Therapeutical Application of Medicinal Herbs*. Medicina, Budapest. (In Hung.)
- Rácz, G. (1978): Chemotaxonomical and biochemical observations in the course of the determination of the mineral content of 41 plant species. *Herba Hung.* **17**, 2, 43. (In Hung.)
- Rácz, G., Bodon, J., Tölgyesi, Gy. (1982): *Modern Use of Medicinal Herbs*. Dacia Publishing House, Cluj–Napoca (Contemporary Series, 1). (In Hung.)
- Rigó, J. (1965): *Vitalstoffe. Zivilisationskrankheiten* **10**, 16.
- Rude, R. K. (1989): Physiology of magnesium metabolism and the important role of magnesium in potassium deficiency. *A. Journ. of Cardiol.* **63**, 31.
- Simon, K.H. (1966): *Vitalstoffe* **11**, 202.

- Tyler, V.E. (1985): *The Honest Herbal: A Sensible Guide to Herbs and Related Remedies*. George F. Stichley Company, Philadelphia.
- Vohora, S.B. (1981): Is the Human Body a Microcosm? *Handard Nagar* (New Delhi) **61**, 85.
- Weiss, R. F. (1982): *Lehrbuch der Phytotherapie*. Hippokrates Verlag, Stuttgart.
- Williams, D.R. (1971): *The Metals of Life*. Von Nostrand Reinhold, London.

8.3. Magnesium substitution in dietary treatment

- Altura, B. T., Brust, M., Bloom, S., Barbour, R. L., Stempak, J. G., Altura, S. T. (1990): Magnesium dietary intake modulates blood lipid levels and atherogenesis. *Proc.Natl. Acad. Sci. USA* **87**, 1840.
- Bei, L., Wood, R. J., Rosenberg, I. H. (1986): Glucose polymer increases jejunal calcium, magnesium, and zinc absorption in humans. *Am. J. Clin. Nutr.* **44**, 244.
- Bessey, P. Q., Wilmore, D. W. (1988): The burned patient. In: *Nutrition and Metabolism in Patient Care*. (Eds: Kinney, J. M., Jeejeebhoy, K. N., Hill, G. L., Owen, O. E.). W. B. Saunders Co., Harcourt Brace Jovanovics, Inc., Philadelphia 672.
- Booth, C. C., Barbouris, N., Hanna, S., MacIntyre, I. (1963): Incidence of hypomagnesemia in intestinal malabsorption. *Br. Med. J.* **2**, 141.
- Clarkson, B. M., Warren, R. L., McDonald, S. J., De Wardener, H. E. (1967): The effect of high intake of calcium on magnesium metabolism in normal subjects and in patients with chronic renal failure. *Clin. Sci.* **32**, 11.
- Davis, W. H., Leary, W. P., Reyes, A. J., Olhaberry, J. V. (1984): Monotherapy with magnesium increases abnormally low high density lipoprotein cholesterol: a clinical assay. *Curr. Ther. Res.* **36**, 341.
- Drews, L. M., Kies, C., Fox, H. M. (1979): Effect of dietary fiber on copper, zinc, and magnesium utilization by adolescent boys. *Am. J. Clin. Nutr.* **32**.
- Dyckner, T., Wester, P. O. (1979): Ventricular extrasystoles and intracellular electrolytes before and after magnesium infusion in patients on diuretic treatment. *A. Heart. J.* **97**, 12.
- Dyckner, T., Wester, P. O. (1983): Effect of magnesium on blood pressure. *Br. Med. J.* **286**, 1847.
- Garland, H. O. (1992): New experimental data on the relationship between diabetes mellitus and magnesium. *Magnesium Research* **5**, 193.
- Goodson, W. H., Hunt, T. K. (1988): Wound healing. In: *Nutrition and Metabolism in Patient Care*. (Eds: Kinney, J. M., Jeejeebhoy, K. N., Hill, G. L., Owen, O. B.). W. B. Saunders Co., Harcourt Brace Jovanovich, Inc., Philadelphia, 635.
- Gums, J. G. (1987): Clinical significance of magnesium: a review. *Drug Intell. Clin. Pharm.* **21**, 240.
- Heaton, F. W., Parson, F. M. (1961): The metabolic effect of high magnesium intake. *Clin. Sci.* **21**, 273.
- Henderson, D. G., Schierup, J., Schødt, T. (1986): Effect of magnesium supplementation on blood pressure and electrolyte concentrations in hypertensive patients receiving long-term diuretic treatment. *Br. Med. J.* **293**, 664.
- Holtmeier, H. J. (1988): *Praktische Ernährungslehre*, IV. Vegetabile Diäten. Georg Thieme Verlag, Stuttgart - New York, 284.
- Jaspers, V., Spatling, L., Fallenstein, F., Quackernack, K. (1990): Magnesium, Kalzium, Hämoglobin, Hämatokrit, Östriol und HPL unter Magnesiumsubstitution in der Schwangerschaft. *Geburtshilfe Frauenheilkd.* **50**, 628.
- Jones, C. T., Sellwood, R. A., Evanson, J. M. (1973): Symptomatic hypomagnesaemia after

- parathyroidectomy. *Br. Med. J.* **3**, 391.
- Kesteloot, H. (1991): Relationship between dietary cations and blood pressure. *Ann. Nutr. Metab.* **35**, Suppl. 1, 109.
- Lieber, Ch. S. (1988): The influence of alcohol on nutritional status. *Nutr. Rev.* **46**, 241.
- Lo, G. S., Steinke, F. H., Hopkins, D. T. (1980): Effect of isolated soybean protein on magnesium bioavailability. *J. Nutr.* **110**, 829.
- McGarvey, S. T., Zinner, S. H., Willett, W. C., Rosner, B. (1991): Maternal prenatal dietary potassium, calcium, magnesium, and infant blood pressure. *Hypertension* **17**, 218.
- McHale, M., Kies, C., Fox, H. M. (1979): Calcium and magnesium nutritional status of adolescent humans fed cellulose or hemicellulose supplements. *J. Food. Sci.* **44**, 1412.
- Motoyama, T., Sano, H., Fukazaki, H. (1989): Oral magnesium supplementation in patients with essential hypertension. *Hypertension* **13**, 227.
- Nichols, B. L., Avarado, J., Hazlewood, C. F., Viteri, F. (1978): Magnesium supplementation in protein-caloric malnutrition. *Am. J. Clin. Nutr.* **31**, 176.
- Nowson, C. A., Morgan, T. O. (1989): Magnesium supplementation in mild hypertensive patients on a moderately low sodium diet. *Clin. Exp. Pharmacol. Physiol.* **16**, 299.
- Orimo, H., Ouchi, Y. (1990): The role of calcium and magnesium in the development of atherosclerosis. Experimental and clinical evidence. *Ann. N. Y. Acad. Sci.* **598**, 444.
- Ouchi, Y., Tabata, R. E., Stergiopoulos, K., Sato, F., Hattori, A., Orimo, H. (1990): Effect of dietary magnesium on development of atherosclerosis in cholesterol-fed rabbits. *Atherosclerosis* **10**, 732.
- Paolisso, G., Passariello, N., Pizza, G., Marrazzo, G., Giunta, R., Sgambato, S., Varricchio, M., D'Onofrio, F. (1989): Dietary magnesium supplements improve beta-cell response to glucose and arginine in elderly non-insulin dependent diabetic subjects. *Acta Endocrinol.* **121**, 16.
- Rao, K. S., Rao, B. S. N. (1984): Studies on the effect of inorganic polyphosphates on dietary ionisable iron and the solubility of other minerals in vitro. *Nutr. Rep. Int.* **29**, 941.
- Rudnicki, M., Junge, J., Frolich, A., Ornvold, K., Fischer-Rasmussen, W. (1990): Magnesium supplement in pregnancy-induced hypertension. A clinicopathological study. *APMIS* **98**, 1123.
- Sablé-Amplis, R., Sicart, R., Reynier, B. (1986): Increased net apparent retention of magnesium in hamsters fed a fruit-enriched diet. *Nut. Rep. Int.* **34**, 501.
- Shils, M. E. (1990): Magnesium. In: *Present Knowledge in Nutrition*. (Ed.: Brown, M. L.). International Life Sciences Institute, Nutrition Foundation, Washington, 224-232.
- Singh, R. B., Rastogi, S. S., Mehta, P. J., Cameron, E. A. (1989): Magnesium metabolism in essential hypertension. *Acta Cardiol.* **44**, 313.
- Sjögren, A., Floren, C. H., Nilsson, A. (1988): Magnesium, potassium and zinc deficiency in subjects with Type II diabetes mellitus. *Acta Med. Scand.* **224**, 461.
- Skajaa, K., Dorup, I., Sandstrom, B. M. (1991): Magnesium intake and status and pregnancy outcome in a Danish population. *Brit. J. Obstet. Gynecol.* **98**, 919.
- Slavin, J. L., Marlett, J. A. (1980): Influence of refined cellulose on human bowel function and calcium and magnesium balance. *Am. J. Clin. Nutr.* **33**, 1932.
- Whang, R., Oei, T. O., Aikawa, J. K., Watanabe, A., Wannata, J. (1985): Predictors of clinical hypomagnesemia, hypokalemia, hypophosphatemia, hyponatremia, and hypocalcemia. *Arch. Intern. Med.* **144**, 1794.
- Wester, P. O. (1987): Magnesium. *Am. Clin. Nutr.* **45**, 1305.
- Whelton, P. K., Klag, M. J. (1989): Magnesium and blood pressure: review of the epidemiologic and clinical trial experience. *Am. J. Cardiol.* **63**, 26G.
- Wong, E. T., Rude, R. K., Singer, F. R., Shaw S. T. Jr. (1983): A high prevalence of hypomagnesemia and hypermagnesemia in hospitalized patients. *Am. J. Clin. Pathol.* **79**, 348.

8.4. Magnesium supplementation with acidic polysaccharides

- Albersheim, P. (1973): The structure of plant cell walls I-III. *Plant Physiol.* **51**, 158, 174, 188.
- Barta-Bedő, M., Lakatos, B., Meisel-Ágoston, J. (1973): Intestinal absorption and utilization of iron from iron biopolymer complexes in rats. *Europ. Nutr. Conf.* (Cambridge) **42**.
- BeMiller (1985): An introduction to pectins: structure and properties. *ACS Symp. Ser.* **310**, 2.
- Bodrogi, L., Büki, B., Horváth, E. (1988): Personal communication. SOTE, I. Belgyógy. Klinika, Budapest.
- Fishman, L., Jen, J. (1985): Chemistry and function of pectins. *ACS Symp. Ser.* **310**, 1.
- Frank, K. (1978): Personal communication. OTKI Gyermekklinika, Budapest.
- Fülöp, T. (1986): Personal communication. DOTE 1. Belklinika, Debrecen.
- Fülöp, T., Valenta, B., Meisel, J., Patvaros, I., Lakatos, B. (1986): Treatment of ischemic heart disease with Mg-, K- and metal-polygalacturonates (PG-s). *Proc. Intern. Symp.* (New result in the research of hardly known trace elements and the analytical problems of trace element research.) Akadémiai Kiadó, Budapest, 215.
- Gekko, K., Noguchi, H. (1979): Selective interaction of calcium and magnesium ions with ionic dextran derivatives. *Carbohydr. Res.* **69**, 323.
- Hardwick, L. L., Jones, M. R., Brautbar, N., Lee, D. B. N. (1991): Magnesium absorption: mechanisms and the influence of vitamin D, calcium and phosphate. *J. Nutr.* **121**, 13.
- Haug, A., Smidsrod, O. (1965): The effect of divalent metals on the properties of alginate solutions. *Acta Chem. Scand.* **19**, 341.
- Haug, A., Smidsrod, O. (1970): Selectivity of some anionic polymers for divalent metal ions. *Acta Chem. Scand.* **24**, 843.
- Hodgkinson, A., Nordin, B. B. C., Hambleton, J., Oxby, C. B. (1967): Radiostrontium absorption in man: suppression by calcium and by sodium alginate. *Can. Med. Ass. J.* **97**, 1139.
- Hunter, G. K., Wong, K. S., Kim, J. (1988): Binding of calcium to glycosaminoglycans: an equilibrium dialysis study. *Archiv Biochem. Biophys.* **260**, 161.
- Jacopian, V. (1974): Enrichment of food with minerals. *Ger. (East)* **111**, 794 (Cl. A231), 12 Mar 1975, Appl. 178-183, 29 Apr. (1974) cf. CA. **84**, 149, 556.
- Kertész, Z. I. (1951): *The Pectic Substances*. Intersci. Publ. Inc. New York - London.
- Kiss, A. S., Melles, Z. (1972): The correlation of infant and childhood anaemia with the concentration of magnesium ions in red blood cells. *Gyermekgyógyászat* **23**, 517. (In Hung.)
- Kohn, R. (1971): The activity of calcium ions in aqueous solutions of the lower calcium oligogalacturonates. *Carbohydr. Res.* **20**, 351.
- Kohn, R. (1975): Ion binding on polyuronates, alginate and pectin. *Pure Appl. Chem.* **42**, 371.
- Kohn, R., Furda, I. (1967): Interaction of calcium and potassium ions with carboxyl groups of pectin. *Coll. Czechoslov. Chem. Comm.* **32**, 4470.
- Kohn, R., Larsen, B. (1972): Preparation of water-soluble polyuronic acids and their calcium salts, and the determination of calcium ion activity in relation to the degree of polymerization. *Acta Chem. Scand.* **26**, 2455.
- Kohn, R., Maloviková, A. (1981): Intramolecular binding of calcium ions to L-gulonate and D-galacturonate. *Coll. Czech. Chem. Comm.* **46**, 1701.
- Lakatos, B. et al. (1988): A procedure for the direct production of pure polygalacturonic acid from agricultural by-products and waste containing pectin. Patent No. 206 730. (In Hung.)
- Lakatos, B., Meisel, T., Varjú, M. (1976): A process for production of the complexes of oligo- and polygalacturonic acids with essential metal ions. Patent No. 172 831 1. (In Hung.)
- Lakatos, B., Holly, S., Meisel, J. (1983): Infrared spectroscopic study on metal pectates. 1st Int. Conf. Bioinorg. Chem. Florence (1983). *Inorg. Chim. Acta* **79**, 270.

- Lakatos, B., Mády, Gy., Meisel, T., Ötvös, L., Varjú, M. (1979a): *A process for production of the metal complexes of oligo- and polygalacturonic acid dinitrates*. Patent No. 177 118 1. (In Hung.)
- Lakatos, B., Mády, Gy., Meisel, T., Varjú, M., Vinkler, P. (1979b): *A process for production of the complexes of oligo- and poly- α -D-glucuronic acids*. Patent No. 179 527 1. (In Hung.)
- Lakatos, B., Meisel, I., Rockenbauer, A., Simon, P., Koretz, L. (1983): EPR and Mössbauer spectroscopic studies on metal complexes of pectic acids and their derivatives. 1st Int. Conf. Bioinorg. Chem. Florence (1983). *Inorg. Chim. Acta* **79**, 269.
- Lakatos, B., Sándor, Z., Tölgyes, M., Kovács, Zs., Vinkler, P., Kröel-Dulay, N. (1988): *A process for production of the basic metal complexes of acidic oligo- and polysaccharides*. Patent No. 203 365 1. The commercial products are: Magnacomp, Multicomp and Ferrocamp tablets. (In Hung.)
- Lambert, J. R., Korman, M. G., Nicholson, L., Chan, J. G. (1990): In-vivo anti-reflux and raft properties of alginates. *Aliment. Pharmacol. Therap.* **4**, 615.
- Martin, R. B. (1990): Bioinorganic Chemistry of Magnesium. *Metal Ions Biol. Syst.* **26**, 1.
- Muzzarelli, R. A. A. (1973): *Natural Chelating Polymers*. Inter. Ser. Monogr. Anal. Chem. Pergamon Press, New York.
- Muzzarelli, R. A. A., Nicoletti, C., Rocchetti, R. (1974): Interactions of metal ions with alginic acid, polygalacturonic acid, carboxymethylcellulose and cutin. *Ion Exch. Membr.* **2**, 67.
- Nakanishi, Y., Kishi, M. (1970): Studies on iron-chondroitin-sulfate colloid for intravenous injection IV. *Yakugaku Zasshi* **90** (2) 120.
- Paskins-Hurlburt, A. J., Tanaka, Y., Skoryna, S. C., Moore, W., Stara, J. F. (1977): The binding of lead by a pectic polyelectrolyte. *Environm. Res.* **14**, 128.
- Patrick, G. (1967): Inhibition of strontium and calcium uptake by rat duodenal slices: Comparison of polyuronides and related substances. *Nature* **216**, 815.
- Sándor, Z., Tölgyes, M., Lakatos, B. (1991): Magnesium and trace element enriched fruit drinks and jams. VIIIth Conf. on Food Science, Hung. Budapest. *Acta Aliment.* **20**, 9.
- Schweiger, R. G. (1966): Metal chelates of pectate and comparison with alginate. *Kolloid Z.* **208**, 28.
- Schweiger, R. G., Andrew, R. (1972): Polysaccharide sulfates. II. Sulfuric acid esters of glycuronans having various degrees of substitution. *Carbohydr. Res.* **21**, 275.
- Sigel, H., Sigel, A. (ed.) (1990): Compendium on Magnesium and its Role in Biology, Nutrition, and Physiology. *Metal Ions Biol. Syst.* Vol. 26. Marcel Dekker, Inc. New York – Basel.
- Simončič, R., Rigó, J., Kopeč, Z., Chrváthová, V., Ovečka, M. (1983): Der Einfluß von Magnesiumpektinate auf die metabolischen Änderungen nach der Nahrungsmittelbelastung bei Diabetikern. *Hungarian Itinerary Congress on Dietetics*, Budapest.
- Smidsrød, O. (1973): Some physical properties of alginates in solution and in the gel state. *Norw. Inst. Seaweed Res. Report* **34**, 1.
- Smidsrød, O., Haug, A. (1968): Dependence upon uronic acid composition of some ion-exchange properties of alginates. *Acta Chem. Scand.* **22**, 1989.
- Tanaka, Y., Skoryna, C. (1971): Organic macromolecular binders of metal ions. In: Skoryna, S. C., Waldron-Edward, D. (eds): *Intestinal Absorption of Metal Ions, Trace Elements and Radionuclides*. Pergamon Press, Oxford – New York, 101.
- Thibault, J. F., Rinaudo, M. (1985): Interactions of counterions with pectins studied by potentiometry and circular dichroism. *ACS Symp. Ser.* **310**, 61.
- Valle, F. O., Romeo, A., Lorenzi, S. (1988): *Process for preparing salt of hyaluronic acid with a pharmaceutically active substance*. US Patent 4,736,024.
- Weiner, M. L. (1991): Toxicological properties of carrageenan. *Agents and Actions* **32**, 46.
- Worth, H. G. J. (1967): The chemistry and biochemistry of pectic substances. *Chem. Rev.* **67**, 465.
- Zelles, T. (1978): Personal communication. SOTE, Kórélettani Intézet, Budapest.

9. Magnesium analysis

Magnesium determination methods are partly classical (gravimetry and titrimetry) and partly instrumental analytical (spectrophotometry, emission methods and atomic absorption spectrometry).

In the process of gravimetric analysis, which is a method not really suited for complicated series of analyses, magnesium is separated in the form of a precipitate of MgNH_4PO_4 . After ignition, the residual mass is measured. From the mass of the precipitate (the quantity of starting material being known), its magnesium content can be calculated.

Of the volumetric analytical titrimetric methods, complexometric titration can be used to determine magnesium content. In the process of complexometric (chelatometric) titration, the magnesium ion and the titrant disodium dihydrogen ethylenediamine-tetraacetic acid (Komplexon III) react to form a complex.

Komplexon III forms stable complexes with both calcium and magnesium ions at $\text{pH} = 10$, but at $\text{pH} > 12$ stable complex formation occurs only with calcium.

The end-point of complexometric titration can be indicated with metal indicators. The end-points of calcium and magnesium determinations can be indicated with Eriochrome black T as indicator. Eriochrome black T and the magnesium ion form a red complex, which becomes blue at the equivalence point. (Blue is the colour of the indicator.) The end-point of calcium determination can be indicated with Murexide as indicator. Murexide and the calcium ion yield an orange-red complex, which becomes red-violet at the titration end-point. Magnesium content can be calculated from the difference in volume between the two titrations (Pataki and Zapp, 1972).

The basis of spectrophotometric methods is the light absorption of a coloured molecule formed in a reaction between the magnesium to be determined and a complex-forming compound. For magnesium determination in soil and plant samples, the titanium yellow method is commonly used (Schachtschabel and Isermeyer, 1954) whereas in biological substances the xylydyl blue method is applied (Mann and Yoe, 1956).

Emission methods are based on element excitation. When the excitation ceases, the excited atoms regain their basic states and emit the energy they have absorbed. The wave number of the emitted energy is characteristic of the element to be determined, and the intensity of the emitted radiation is proportional to its concentration.

Of the emission methods, plasma emission spectrometry ICP (inductively coupled plasma) is nowadays used for magnesium determination. For ICP, argon plasma is generally applied (Buzás, 1988).

The most commonly used method of magnesium determination is atomic absorption spectrometry. This is an analytical method based on the absorbing ability of free atoms. The principle of the measurement is that the free atoms of the target element in the ground state absorb emission resonance radiation and the extent of the absorption is proportional to the concentration of the free atoms. Resonance radiation can be produced with hollow cathode lamps, whose cathode is made of the target element and radiates a linear spectrum. The light of the radiation source passes through the atomizer (usually a flame), where the free atoms of the element absorb the radiation to an extent depending on their concentration. In the case of flame atomizing, the solution is sprayed into a flame of appropriately high temperature, where the solution evaporates and the compound of the element is decomposed into its atoms. Through a monochromator, the light of reduced intensity is directed into a light detector (usually a photoelectronmultiplier), whose signals are recorded in a suitable way (digital display, printer or screen) (Price, 1977).

9.1. Magnesium determination in soil samples

In the soil, magnesium is present in readily soluble, exchangeable and reserve forms. Plants can directly utilize only the readily soluble and exchangeable magnesium.

In practice, these two forms are determined simultaneously. To determine readily soluble and exchangeable magnesium, the soil sample is shaken in dilute salt solution, whereby solution and exchange take place until equilibrium is achieved. The amount of magnesium in the soil extract depends on the nature and concentration of the solution and on the method of extraction (shaking rate, time, etc.). Magnesium content is most commonly determined by the atomic absorption spectrometric method.

Atomic absorption measurement of magnesium

With this method, low magnesium concentrations can be determined reliably. The optimum range of magnesium concentration for measurement is $0.2\text{--}2.0\text{ }\mu\text{g}/\text{cm}^3$, which makes soil extract dilution necessary prior to measurement. During dilution, strontium chloride is added, which prevents the formation of thermally stable magnesium compounds (e.g. magnesium phosphate), which would otherwise result in a reduced absorption. Strontium can be replaced by lanthanum sulphate or lanthanum chloride.

Measurement is made at 282.5 nm. The optimum air/acetylene ratio, slit width and burner height depend on the type of the apparatus; test experiments must be made to check application instructions.

When calibration solution series are prepared, composition of the soil extract must be considered. If the extracting agent contains considerable amounts of salt, or other substances affecting viscosity, appropriate concentrations of these must be added to

the calibration solution. Failure to do so may result in an optical matrix effect, and variations in viscosity will change the vaporizing conditions, which will interfere with the measuring accuracy.

Calibration and supplementary standard solutions

Reagents:

Magnesium carbonate (MgCO_3),

Concentrated hydrochloric acid (HCl),

Strontium chloride ($\text{SrCl}_2 \cdot 6\text{H}_2\text{O}$), each of analytical purity.

Standard magnesium solution (A): 3.4683 g anhydrous magnesium carbonate is suspended in a small amount of distilled water to which 80 cm³ hydrochloric acid is added gradually. When the magnesium carbonate is fully dissolved, it is diluted to 1000 cm³ by the addition of distilled water.

Concentration: 1000 mg Mg/dm³; 1 cm³ contains 1 mg magnesium.

Diluted standard magnesium solution (B): 100 cm³ standard solution A is diluted with distilled water to 1000 cm³. 1 cm³ of the solution contains 0.1 mg magnesium.

Strontium chloride solution: 40.32 g of $\text{SrCl}_2 \cdot 6\text{H}_2\text{O}$ is dissolved in 500 cm³ distilled water, and the solution is made up to 1000 cm³ in a volumetric flask with distilled water. The standard solution contains 10 mg Sr/cm³. It is diluted 10-fold when used.

Determination of readily soluble magnesium

In foreign countries, the Schachtschabel method is most commonly used. Hungarian laboratories use a 1 mol/dm³ potassium chloride extract to determine magnesium.

Magnesium soluble in calcium chloride

In the method of Schachtschabel (1954), a soil extract is obtained from a mixture of soil and 0.0125 mol/dm³ calcium chloride extracting solution in a ratio of 1:10, and the magnesium content of the extract is determined with an atomic absorption spectrophotometer.

Reagent:

0.0125 mol/dm³ calcium chloride solution

Procedure. 5 g soil in 50 cm³ 0.0125 mol/dm³ calcium chloride is shaken for 2 hours. The extract is filtered through a high-quality, magnesium-free, fluted filter paper (e.g. Schleicher-Schüll Nr. 0790-1/2-15). If the initial filtrate is opaline, it must be refiltered to obtain a crystal-clear solution.

For atomic absorption measurements, sandy soil extracts are diluted 10-fold, whereas loam and clay soil extracts are analysed at 100 or 200-fold dilutions, respectively. Depending on the degree of dilution, 10, 1 or 0.5 cm³ soil extract and 10 cm³ strontium chloride solution are pipetted into a 100 cm³ volumetric flask. Distilled water is added to the mark and the contents are thoroughly shaken (Table 9.1).

Table 9.1. Supply limit values (ppm) of various soils
(0.0125 mol/dm³ CaCl₂ extracts)

Supply	Soil mechanical composition		
	sandy	loam	clay
Poor	≤ 25	≤ 35	≤ 60
Fair	26–50	36–70	61–120
Good	≥ 51	≥ 71	≥ 121

Calibration solution preparation procedure. 0, 1, 2, 3, 4, 5, 6, 8, 10, 15 and 20 cm³ aliquots of diluted standard magnesium solution are pipetted into 1000 cm³ volumetric flasks, and 100 cm³ strontium chloride is added to each flask. Because of the high dilution, calcium supplementation can be omitted. Distilled water is added to the mark and the contents are thoroughly shaken. The magnesium concentrations of the members of the series are 0, 0.1, 0.2, ..., 2.0 µg Mg/cm³, while their strontium contents are the same as those of the diluted soil extracts.

Magnesium soluble in potassium chloride

In Hungarian soil laboratories, 1 mol/dm³ potassium chloride is applied as an extracting agent. The magnesium contents of the extracts are determined with an atomic absorption spectrophotometer or with an ICP apparatus.

Extracting solution: 1 mol/dm³ potassium chloride

74.56 g potassium chloride is dissolved and made up to 1000 cm³. Care should be taken that the potassium chloride is free of magnesium.

Procedure. 20 g soil is shaken for 1 hour in 50 cm³ 1 mol/dm³ potassium chloride. Soil extracts are filtered through good-quality, magnesium-free, fluted filter papers (e.g. Schleicher Schüll, Nr. 0790–1/2–15). If the initial filtrate is opaline, it must be refiltered to obtain a clear solution.

For atomic absorption measurements sandy soil extracts are diluted 10-fold, whereas loamy and clayey soil extracts are diluted 100 and 200-fold, respectively. 10, 1 and 0.5 cm³ soil extracts and 10 cm³ strontium chloride are pipetted into 100 cm³ volumetric flasks. Distilled water is added to the mark, and the contents are thoroughly shaken.

Calibration solution preparation. 0, 1, 2, 3, 4, 5, 6, 8, 10, 15 and 20 cm³ of aliquots diluted standard magnesium solution are pipetted into 1000 cm³ volumetric flasks, and 100 cm³ strontium chloride is added to each flask.

If the soil extract is diluted 10-fold, 10 cm³ 1 mol/dm³ potassium chloride must also be added. For 100 and 200-fold dilutions, potassium chloride supplementation can be omitted. Distilled water is added up to the mark, and the contents are well shaken. The magnesium concentrations of the members of the series are 0, 0.1, 0.2, ..., 2.0 µg/dm³, while their strontium contents are the same as the concentrations of the soil extracts (Table 9.2).

The total exchangeable magnesium content of the soil can be determined only by repeated extraction. The total magnesium content can be measured only after destroy-

Table 9.2. Supply limit values (ppm) of various soils (1 mol/dm³ KCl extracts)

Soil mechanical composition	Supply			
	K _A	poor	fair	good
Sand	≤ 30	≤ 40	40–60	> 60
Sandy loam, loam	31–42	< 60	60–100	> 100
Clayey loam, clay	≥ 43	< 100	100–200	> 200

ing alkaline. The above magnesium forms are determined only for specific purposes, and primary to establish the extent of reserve supplies. Procedure descriptions are available in the Hungarian books *Soil and Nutrient Investigation Methods* (Ballenger and di Gleria, 1962), and *The Methodology of Soil and Agrochemical Investigations* (Buzás, 1988).

9.2. Determination of magnesium content in plants

To determine the magnesium contents of plants, complexometric titration, atomic absorption and ICP spectrometry can be used.

Complexometric determination is reliable only when phosphate and other interfering ions are precipitated (Loch, 1965). For this purpose, zirconium oxychloride at pH 4.8 is used. The precipitation of interfering ions slows down the otherwise rapid complexometric determination procedure. The advantages of instrumental methods are that they permit the measurement of relatively small concentrations, disturbing effects can easily be excluded, and the measurement procedure is quick. The ICP technique is expensive. Accordingly, atomic absorption spectrometry is preferred for the determination of plant magnesium contents.

Plant material can be prepared for the determination procedure in two ways:

1. dry digestion (ashing),
2. wet digestion (nitric acid + hydrogen peroxide).

The wet digestion of plant material (nitric acid + hydrogen peroxide) and nutrient element determination with ICP were described by Chao-Young Luh Huang and Schulte (1985).

The two techniques were compared by Ali et al. (1988).

The principle of the ashing procedure

The plant material is ashed, and the ash is dissolved in hydrochloric acid. After the dehydration of silicic acid, magnesium is measured in hydrochloric acid solution in the presence of strontium chloride.

Reagents: 1 mol/dm³ hydrochloric acid: 80 cm³ concentrated hydrochloric acid is diluted to 1000 cm³ by the addition of distilled water.

Concentrated nitric acid (HNO₃).

Strontium chloride solution. 40.32 g SrCl₂ · 6H₂O is dissolved in 500 cm³ distilled water, and the volume is made up to 1000 cm³ with distilled water in a volumetric flask. The solution contains 10 mg strontium per cm³; when used, it is diluted 10-fold.

Procedure

Ashing, stock solution preparation. 1 g dried, ground plant material is weighed on an analytical balance and transferred to a crucible.

The sample is slowly pre-ashed over a gas flame or on an electric plate and is then heated in a furnace for 6–8 hours at 500 °C. Halfway through the heating the crucibles are allowed to cool, 1–2 drops of concentrated nitric acid are added to the ash and heating is continued to complete oxidation of the material.

The crucibles are again cooled, one drop of concentrated nitric acid and 5 cm³ 1 mol/dm³ hydrochloric acid are added, and the ash is transferred into an evaporating dish. The contents of the dish are evaporated to dryness on a water-bath. This is necessary for the dehydration of silicic acid gel. In this way, metal adsorption by silicic acid gel is prevented and subsequent losses can be avoided. The dry residue is again treated with 5 cm³ 1 mol/dm³ hydrochloric acid and the solution is filtered into a 50 cm³ volumetric flask. After several washings with distilled water, the volume is adjusted to the mark.

Stock solution dilution. The plant extract should be diluted to the optimum measurement range (0.2–2.0 µg Mg/cm³). Simultaneously, strontium chloride is added to prevent the formation of thermally stable magnesium compounds (magnesium phosphates), which would otherwise result in a reduced absorption. Determination of the magnesium content of plants is generally performed at a 100-fold dilution. For this, 1 cm³ stock solution, 10 cm³ 1 mol/dm³ hydrochloric acid and 10 cm³ strontium chloride solution are pipetted into a 100 cm³ volumetric flask and distilled water is added to bring the volume up to the mark. The strontium concentration is 1 mg Sr/cm³.

Magnesium measurement. Measurement is carried out at 282.5 nm. The optimum air/acetylene ratio, slit width, and burner height vary with the type of the apparatus. Accordingly, test experiments must be run to check application instructions.

Calibration solutions

Reagents: Magnesium carbonate; concentrated hydrochloric acid.

Standard magnesium solution (A): 3.4683 g anhydrous magnesium carbonate is suspended in a small amount of distilled water, and 80 cm³ concentrated hydrochloric acid is gradually added. After complete dissolution of the magnesium carbonate, distilled water is added to make the volume up to 1000 cm³.

Concentration: 1000 mg Mg/dm³; 1 cm³ of solution contains 1 mg magnesium.

Diluted standard magnesium solution (B): 100 cm³ solution A is diluted to 1000

cm³ by the addition of distilled water. The solution contains 0.1 mg magnesium per cm³.

Preparation of calibration solution series: 0, 1, 2, 3, 4, 5, 6, 8, 10, 15 and 20 cm³ aliquots of diluted standard magnesium solution are pipetted into 1000 cm³ volumetric flasks. 10 cm³ strontium chloride solution and 100 cm³ 1 mol/dm³ hydrochloric acid solution are added to each flask. The content of each volumetric flask is adjusted to the mark by the addition of distilled water, and then thoroughly shaken. The magnesium concentrations of the series are 0, 0.1, 0.2, ..., 2.0 µg/cm³; their strontium content is 1 mg Sr/cm³.

The principle of the nitric acid + hydrogen peroxide

The principle of the nitric acid + hydrogen peroxide wet digestion is that the plant matter is destroyed by nitric acid with the addition of hydrogen peroxide. After the removal of silicic acid by filtration, the magnesium content is measured in the nitric acid-containing solution in the presence of strontium chloride.

Reagents:

Concentrated nitric acid,

Concentrated hydrogen peroxide,

Strontium chloride solution (prepared as described in connection with ashing).

Procedure

Digestion, preparation of stock solution. 1 g dried, ground plant matter is weighed on an analytical balance, and transferred to the test-tube of the block digester. 10 cm³ concentrated nitric acid is added and the mixture is allowed to stand overnight. The next day it is heated for 30 minutes at 60 °C. Then, after the addition of 3 cm³ 30% hydrogen peroxide, it is gradually heated to 120 °C. It is kept at this temperature for 90 minutes. When digestion is completed, the mixture is cooled and filtered into a 50 cm³ volumetric flask. After several washings, distilled water is added to adjust the volume to the mark.

Dilution of stock solutions. For magnesium determination, the solubilized plant matter is diluted 100-fold. For this, 1 cm³ stock solution and 10 cm³ strontium chloride solution are measured into a 100 cm³ volumetric flask, and distilled water is added to the mark.

The procedures of magnesium measurement and of standard magnesium solution preparation are the same as described in connection with ashing.

Preparation of calibration solution series: 0, 1, 2, 3, 4, 5, 6, 8, 10, 15 and 20 cm³ aliquots of diluted magnesium standard solution are pipetted into 1000 cm³ volumetric flasks. 10 cm³ strontium chloride solution and 0.2 cm³ concentrated nitric acid are added to each flask. The contents of the volumetric flasks are made up to the mark by the addition of distilled water, and they are well shaken. The magnesium concentrations of the series are 0, 0.1, 0.2, ..., 2.0 µg/cm³, their strontium content is 1 mg Sr/cm³.

9.3. Determination of magnesium in animal feeding stuffs

This group of materials is not uniform from analytical point of view. It covers the classical vegetable feedstuffs (grain, hay, silage, etc.) and industrial mixed feeds. There are considerable differences in the concentrations of the component to be measured, and in the compositions of materials to be determined. This means that there are differences in matrix effect too, and hence in the analytical methods applied.

Vegetable feedstuffs (grain, green forage, hay, silage, etc.)

For the determination of magnesium, the first step is to convert the solid material into the liquid phase. Similarly as described in the preceding section (on the determination of magnesium in plants), there are two practicable procedures.

Dry combustion. In this method, the organic substances are ashed at 550 °C. The ash contains the inorganic components (including the magnesium content) in oxide form. Treatment of the ash with dilute hydrochloric or nitric acid is applied to obtain the stock solution.

Wet digestion. In this method, the oxidation of organic substances in the sample is carried out in the liquid phase, with oxidizing inorganic acids. There is no uniform procedure for wet digestion. A mixture of nitric acid and sulphuric acid, followed by a mixture of perchloric acid and hydrogen peroxide in order to complete the oxidation process, is frequently used. The wet digestion is more complicated and more dangerous (because of the harmful effects of the nitrous gases) than the dry combustion, and hence is not so wide spread.

Lyons et al. (1985) applied Kjeldahl digestion for the inductively coupled plasma (ICP) determination of magnesium. The result was acceptable. (Kjeldahl digestion is suitable for the determination of nitrogen, and thus the crude protein content of materials.)

Wet digestion has long been performed in hermetically sealed equipment, because of the benefits (no loss of material, less acid is required for the digestion, there is therefore a lower risk of impurities from the chemicals, etc.). As a pressure of 40–50 bar develops during the process, special materials and technical constructions are required.

The first wet digestion procedures were carried out in teflon-coated, "steel bombs", which were heated in a drying oven. The procedure was suitable for serial measurements. White and Thomas (1989) applied microprocessor-controlled equipment for the digestion of samples prior to the determination of magnesium by ICP.

Nowadays, microwave digestion systems are spreading quickly. The equipment is already serially produced. In these instruments, the closed digestion is carried out in special plastic vessels, in a computer-controlled process, with microwave heating.

This digestion technique is of great promise, though is not so wide spread for feedstuffs, in part because of the high price of the instruments, and in part because of

the small sample size, which is approximately 0.5 g. In feedstuff analysis, this sample size is not large enough, because of homogeneity problems. With the development of high-pressure equipment (ca. 100 bar), this latter problem will probably be eliminated.

The magnesium in the prepared solutions is now determined mainly by atomic absorption spectrophotometry (AAS). The great advantages of this method are its high sensitivity and selectivity. Accordingly, the AAS method has practically supplemented classical titrimetric magnesium determinations, since there is no need for the separations required in the classical measurements in order to eliminate the disturbing effects of other ions.

However, disturbing effects do occur in the AAS measurement of magnesium. Phosphorus, aluminium and silica cause negative errors. Similarly as with plants, in the analysis of feedstuffs the disturbing effects of these elements can be eliminated by means of the addition of lanthanum or strontium compounds.

The presence of a high calcium level may cause a positive error in the AAS determination of magnesium. (This disturbing effect is much less than that of phosphates.) Laurylpyridinium chloride at 0.1 mol/dm³ has been recommended for the elimination of both effects (Tokahashi et al., 1988). A brief description of the AAS determination of magnesium is given later in this chapter. There is a Hungarian standard for the determination of magnesium in feedstuffs by this method (6830/21), whereas there is no international standard for the determination of magnesium in feedstuffs. The ISO (International Organization for Standardization) has only a draft proposal concerning such a method for the time being.

In the determination of magnesium by AAS, the flame procedure is adopted almost exclusively. Chinese authors applied in graphite furnace, i.e. the electrothermic atomization method, for the determination of magnesium in forage (Yuan Junhna, 1990). The procedure is mainly important theoretically, since the magnesium concentration of feedstuffs is generally large enough for its determination to be adequate in every respect, despite the lower sensitivity of the flame method.

Among the *other instrumental methods*, the ICP method, i.e. plasma emission spectrometry, is spreading. It is to be expected that this method will not be so widely successful as the AAS procedure. There are two essential reasons for this: the price of the instrument (which is approximately three times more than the price of an AAS spectrophotometer), and the troublesome elimination of the sample matrix effect (a considerable problem in the case of feed supplements, because of their complicated composition; see below).

However, there are numerous publications on the determination of magnesium in feedstuffs by ICP. Hoenig and Scohart (1983) compared the results obtained in the measurement of vegetable feedstuffs by ICP and AAS. There was no essential difference between the results. Debersaques et al. (1988) measured the magnesium contents of feedstuffs, together with eleven other elements, by ICP. The procedure was rated as quick.

The *near infrared reflectance (NIR) spectroscopy technique* is a further possibility for instrumental measurement. This recent procedure is essentially a molecular spectroscopy method, based on the interaction of near-infrared radiation (of well-defined wavelength and energy) and the components of the material to be measured. As a consequence of the interaction, energy is adsorbed, in proportion to the concen-

tration of the component. Thus, through measurement of the difference in intensity between the incident and reflected rays on the surface of the material, the concentration of the component can be measured.

Clark et al. (1987) performed the mineral analysis of wheatgrass and alfalfa samples by NIR spectroscopy, and determined a further eight elements in addition to magnesium. In the theoretically interesting procedure, it is presumed that the inorganic salts are linked with organic compounds (e.g. magnesium in chlorophyll) and this permits their determination.

Jones et al. (1987) and Stoltz (1990) reported similar results, though their main aim was the determination of fibre components and vegetable protein, in addition to the determination of magnesium and other inorganic elements. In spite of successful publications, the NIR technique is not recommended for the determination of magnesium, since it is a correlative method, i.e. it is based on a correlation of the optical properties of the material and the results measured in classical laboratory analyses. The regression constants given by the calibration procedure are related to the optical properties of the samples used in that procedure, and the accuracy of the procedure for other samples may therefore be doubtful. Further, the calibration process requires the analysis of at least 50–60 samples, which is very expensive, and there is a regular need for calibration.

Another procedure suitable for the *determination of magnesium in feedstuffs* is neutron activation analysis. Stable isotopes in the material are converted to radioisotopes in response to irradiation that induces nuclear reactions. These radioisotopes may be determined both qualitatively and quantitatively by measurement of their characteristic radiation. From the content of the radioisotope, the content of the primary isotope, and hence the quantity of the component to be determined, can be deduced.

Suschny et al. (1982) determined magnesium and other inorganic components in milk powder. Samndralwar et al. (1987) applied the neutron activation technique for multielemental analysis of hay millings. Magnesium and six other elements were analysed by neutron activation analysis and AAS in grass. The magnesium results were very similar for the two methods. (Danbara et al., 1989).

Despite these results, the process is not expected to become widespread, mainly because of the special requirements from a technical point of view and as concerns the need for highly qualified laboratory staff in a simple isotope laboratory. Additionally, the sensitivity of the process is proportional to the power of the radiation source. The neutron flux of present neutron generators should be developed in this respect. Nevertheless, the method is not only important theoretically, since it may be used to advantage in serial analysis, where the compositions of the samples are very similar.

Industrial feedstuffs

The complex field of industrial feedstuffs includes all materials, which used directly or indirectly for purposes of animal feeding and previously made by an industrial process.

Feedstuffs derived from the milling, sugar, brewing, vegetable oil, starch and distilling industries or of animal origin

The methods described above for vegetable feedstuffs are theoretically applicable for determination of the magnesium in feedstuffs in this group. Nevertheless, in practice, dry ashing and the AAS method are applied almost exclusively.

Feedstuff additives (premixes, complete premixes, supplements, concentrates, etc.)

The materials belonging in this group of feedstuffs are intermediates of mixed feed processing. They differ in composition and the range of concentration of the components, but they all contain, in concentrated form, the biologically active materials necessary for animal feeding. They usually comprise 0.5, 5, 10 or 20% of the finished feedstuffs.

Morphologically, they are solid, granulous mixtures, analytically, they have a complex sample matrix, and their analysis is rather difficult. The purpose of the analysis is usually the quality control of the manufactured products. From the aspect of magnesium determination, this reduces the possibilities considerably. Most manufacturers nowadays apply magnesium addition only in the case of cattle or more rarely, sheep.

The AAS method is applied almost exclusively for the determination of magnesium in feedstuff additives, mainly because of its selectivity. The sensitivity, the other great advantage of the AAS method is rather disadvantageous in this case, since it is necessary to dilute the stock solution of the sample 100- or 1000-fold, for the magnesium concentration to be in the optimal range ($1 \mu\text{g}/\text{cm}^3$). For sample preparation, it is practical to apply dry ashing combined with previous dissolution of a large proportion of the inorganic substances with hydrochloric or nitric acid, the remaining organic substances then being ashed and the residue dissolved.

The other methods (classical methods, ICP, etc.) for the determination of magnesium in feedstuff additives are not so general, since they are more complicated because of the sample matrix effect.

Industrial mixed feedstuffs

The ready feeds similarly to the feedstuff additives, contain many components. As the concentrations of the components are lower, the sample matrix effect can be handled more easily.

The AAS method is the most widespread for the determination of magnesium in ready feedstuffs too.

Willem G. de Ruig (1986) reported on an interlaboratory test, in the course of which magnesium and seven other mineral components were measured in ready feedstuffs and other feedstuffs (fishmeal, corn, blood powder, etc.) by AAS. The reproducibility was considered acceptable.

Koupparis et al. (1983) reported an interesting method. They measured spectrophotometrically magnesium contents of mixed feedstuffs by means of a microprocessor-controlled, automatic and continuous instrument. The colour was developed with calmagite (calmagite is not specific for magnesium, since calcium and iron disturb the measurement). The instrument also measured the crude protein and phosphorus contents of the feedstuffs.

Determination of magnesium in feedstuffs by AAS

1. *Field of application.* Animal feeding stuffs and feedstuffs additives

2. *Reagents.* All reagents must be of analytical quality and the water used must be double distilled water.

Metallic magnesium or magnesium carbonate

Hydrochloric acid, concentrated ($d = 1.19 \text{ g/cm}^3$)

Lanthanum chloride or strontium chloride

3. *Apparatus.* Usual laboratory equipment, and in particular:

Atomic absorption spectrometer, fitted for the determination of magnesium, using an air/acetylene flame.

Analytical balance.

Electrically heated muffle furnace, capable of being controlled at $550 \pm 10^\circ \text{C}$.

Quartz or platinum crucibles.

Sand bath or hot plate, capable of being controlled at approximately 150°C .

Ashless filter paper.

Beakers, volumetric flasks, etc.

4. *Preparation of reagents*

10% (v/v) hydrochloric acid

Dilute 285 ml concentrated hydrochloric acid to the mark with water in a 1000 cm^3 volumetric flask and mix.

0.1 mol/dm^3 hydrochloric acid solution

Dilute 8.25 ml concentrated hydrochloric acid to the mark with water in a 1000 cm^3 volumetric flask and mix.

1 g/dm^3 magnesium stock solution

Weigh 1.000 g metallic magnesium, transfer it to a 1000 cm^3 volumetric flask, dissolve it in approx. 100 cm^3 10% (v/v) hydrochloric acid, dilute to the mark with water and mix.

Weigh 3.4683 g magnesium carbonate, transfer it quantitatively to a 1000 cm^3 volumetric flask, suspend it in about 100 cm^3 water, add 80 cm^3 concentrated hydrochloric acid to dissolve the carbonate, dilute to the mark with water and mix.

100 mg/dm^3 standard magnesium solution

By means of a pipette, transfer 10 cm^3 stock solution to a 100 cm^3 volumetric flask, dilute to the mark with 0.1 mol/dm^3 hydrochloric acid and mix.

Lanthanum chloride or strontium chloride solution (as a spectral buffer)

Weigh 17.660 g lanthanum chloride or 18.090 g strontium chloride, transfer it into a 1000 cm^3 volumetric flask, dissolve it in about 100 cm^3 water, dilute to the mark with water and mix. 1.0 cm^3 of the solution is taken in the final dilution (10 cm^3).

Lanthanum chloride or strontium chloride blank solution

Transfer 10 cm³ lanthanum or strontium chloride solution into a 100 cm³ volumetric flask, dilute to the mark with 0.1 mol/dm³ hydrochloric acid, and mix.

5. Procedure

Preparation of test solution.

Samples containing organic matter. To the nearest 1 mg weigh, 5 to 10 g test sample (the mass depending on the expected magnesium content) into an incineration dish. Place the incineration dish into a cold muffle furnace, close the furnace and gradually heat to 550±10 °C in approximately 90 minutes. Maintain this temperature until the ash is free of carbon particles (if necessary, for 16 hours, i.e. overnight), then remove the incineration dish and leave it to cool. Transfer the ash to a 250 cm³ beaker, moisten the ash with water, then rinse the incineration dish with a total of approximately 5 cm³ concentrated hydrochloric acid, collecting the rinsings in the beaker. Take care during the addition, as a violent reaction may occur. Evaporate the contents of the beaker to dryness on a sand bath or hot plate controlled at approximately 150 °C. To the beaker containing the sample, add 30 cm³ 10% (v/v) hydrochloric acid, and bring to the boil. Filter, collect the filtrate in a 250 cm³ volumetric flask, dilute to the mark and mix.

Samples not containing organic matter. To the nearest 1 mg weigh, 1 to 5 g test sample (the mass depending on the expected magnesium content) into a 250 cm³ beaker. Add to the beaker 50 cm³ 10% (v/v) hydrochloric acid, and bring to the boil. Filter, collect the filtrate in a 250 cm³ volumetric flask, dilute to the mark with water and mix.

Samples containing considerable inorganic matter. To the nearest 1 mg weigh, 1 to 5 g of the test sample, (the mass depending on the expected magnesium content) into a 250 cm³ beaker, add 50 cm³ 10% (v/v) hydrochloric acid, and bring to the boil. Filter and collect the filtrate in a beaker. Incinerate the organic matter remaining on the filter paper, transfer the ash into the beaker containing the filtrate, bring to the boil and filter if it is not clear.

Blank test. Prepare a solution in the same way as for the test solution, carrying out all the specified operations, using all the reagents, but omitting the test sample.

Calibration. Prepare calibration solutions from the standard magnesium solution as follows:

Dilute the standard solution with 0.1 mol/dm³ hydrochloric acid and add 1 cm³ lanthanum or strontium chloride solution per 10 cm³ diluted standard solution. The dilutions are chosen so that appropriate calibration solutions are obtained (0.1–1.3 µg/cm³). The series of calibration solutions is given as a guide, with the understanding that it may be displaced slightly, depending on the sensitivity of the instrument. If this is the case, the operator should determine the final dilution of the test portion to obtain the optimum conditions.

The absorbances of the calibration solutions are measured against the lanthanum or strontium chloride blank solution, with the atomic absorption spectrometer, at 285.2 nm, with an air/acetylene flame.

A graph may be plotted of, for example, the magnesium content in µg/cm³ versus the absorbance of the calibration solutions.

Determination. Test solution and blank are diluted with 0.1 mol/dm³ hydrochloric acid, and 1 cm³ lanthanum or strontium chloride solution is added per 10 cm³ final

diluted test solution. The absorbances of the test solution are measured against the reagent blank in parallel with and under circumstances identical to the measurement of the calibration solutions. Two determinations are made on test portions taken from the same test sample.

Calculation of results. The results are calculated via the calibration graph, and the magnesium content is expressed as a mass percentage.

Repeatability. The difference between the results of determinations carried out simultaneously or in rapid succession by the same analyst must not exceed 10% of the mean value of these two determinations.

9.4. Determination of magnesium in biological fluids

The early methods were adaptations of the traditional analytical chemical methods. The calcium content of the sample was first precipitated with oxalate. The phosphate content of the magnesium ammonium phosphate precipitated from the filtrate after the removal of calcium oxalate was determined by the well-known molybdenum blue method according to Denis (1922), or by the molybdovanadate method of Simonsen et al. (1947).

These methods involve many steps and require a large sample volume, and they are therefore not used routinely. New reagents and new methods have made the determination of magnesium possible in clinical-chemical laboratories. Most of them are photometric, and some of them complexometric methods.

A rather simple colour reaction was described by Orange and Rhein (1951), in which the coloured complex formed between magnesium and thiazole yellow G (titan yellow) was measured by photometry. Protein is first removed from the sample with 10% trichloroacetic acid. The dissolved magnesium content is then complexed with a solution of thiazole yellow G in the presence of the protective colloid gum ghatti. In alkaline medium, a reddish complex is formed, which is measured photometrically. The modification of the colour reagent thiazole yellow G by Szélenyi (1971) permitted magnesium determinations in the serum without deproteinization; in this method, polyvinyl alcohol is used as protective colloid. The determination may also be carried out in the protein-free supernatant of the sample.

In spite of the protective colloid, the stability of the magnesium complex of thiazole yellow G is not satisfactory. At present, two reagents are used which form coloured complexes with magnesium in biological fluids, eliminate the disturbing effect of calcium if the optimal conditions are selected, and ensure a satisfactory accuracy of the photometric measurement. These are calmagite [3-hydroxy-4-(2-hydroxy-5-methylphenylazo)-1-naphthalenesulphonate] and magon or xylidyl blue.

The method based on the colour reaction between calmagite and magnesium was described by Gindler (1971). Its essence is as follows: the colour reaction is brought about in a strongly alkaline ($\text{pH} = 11$) medium, the disturbing effect of calcium is eliminated by EGTA [ethyleneglycol-bis-(β -aminoethyl ether)-N,N,N',N'-tetraacetic acid].

The method most widely used in Hungarian clinical laboratories is based on the xylidyl blue colour reaction according to Mann and Yoe (1956), and Mann (1957), as modified by Bohuon (1962). Its essence is as follows: in a weakly alkaline medium ($\text{pH} = 10$), xylidyl blue reacts selectively with the magnesium content of biological fluids to give a red colour. The reaction is suitable for photometry, provides satisfactory stability, and is well reproducible. The colour reagent is dissolved in alcohol, in which it may be stored for a long time.

In view of its widespread use, the prescription of the method is given below.

Xylidyl blue may be obtained as the non-sulphonated compound (xylidyl blue II, magon) or as its sulphonated derivative (xylidyl blue I, magon sulphonate). Both forms are suitable for the colour reaction. Chemically, xylidyl blue I is 1-azo-2-hydroxy-3-(2,4-dimethylcarboxanilido)naphthalene-1'-(2-hydroxybenzene-5-sodium sulphonate), M_r 513. The non-sulphonated compound has M_r 411.

Reagents:

1. *Colour reagent*: 12 mg xylidyl blue II (or 15 mg xylidyl blue I) is dissolved in about 80 cm^3 absolute ethanol by gentle refluxing on a water-bath. After cooling, the volume is made up to 100 cm^3 with absolute ethanol; if necessary, the solution is filtered through analytical filter paper. The solution may be permanently stored in well-closed, chemically clean plastic or glass containers protected from light, at room temperature.

2. *Borate buffer solution*: 2.0 g disodium tetraborate decahydrate ($\text{Na}_2\text{B}_4\text{O}_7 \cdot 10\text{H}_2\text{O}$) is dissolved in about 80 cm^3 deionized water by warming. After cooling, the solution is made up to 100 cm^3 with deionized water. The solution may be stored indefinitely at room temperature in well closed containers. Its concentration is 52 mmol/dm^3 .

3. *Standard magnesium solution*: 246 mg magnesium sulphate heptahydrate ($\text{MgSO}_4 \cdot 7\text{H}_2\text{O}$) is dissolved in deionized water and made up to 100 cm^3 . The solution is preserved with chloroform. This is the stock solution of the magnesium standard, with a concentration of 10 mmol/dm^3 . Before use, an aliquot of this stock solution is diluted 10-fold with deionized water. The magnesium concentration of the diluted standard is therefore 1.0 mmol/dm^3 . Further standards with magnesium concentrations of 0.5, 1.5 and 2.0 mmol/dm^3 , may also be prepared from the stock solution for control of the linearity.

4. *Perchloric acid solution for deproteinization*: 2.8 cm^3 , 70% perchloric acid is diluted with deionized water to 100 cm^3 . The concentration of this solution is 0.33 mol/dm^3 . Instead of perchloric acid, 5% trichloroacetic acid may be used (0.3 mol/dm^3). Both may be stored for a long period in a cool place.

Determination procedure:

A) With deproteinization

	Sample (cm^3)	Standard (cm^3)	Blank (cm^3)
Cold perchloric acid solution	0.400	0.400	0.400
Serum or diluted urine	0.100	—	—
Standard	—	0.100	—
Deionized water	—	—	0.100

After thorough mixing and standing for 10 minutes the mixtures are centrifuged.

	Sample (cm ³)	Standard (cm ³)	Blank (cm ³)
Borate buffer solution	1.000	1.000	1.000
Clear supernatant	0.100	0.100	0.100
Colour reagent	1.000	1.000	1.000

After thorough mixing in magnesium-free glass test-tubes, the mixtures are allowed to stand for 10 minutes. Photometry is performed within 30 minutes at 505 nm, or with a colour filter at 490–520 nm, or at the Hg 492 line.

Instead of perchloric acid, 5% trichloroacetic acid may be used for deproteinization, in the same proportions and in the same way. The photometric measurement is carried out against a blank. The absorbance of the reagent blank may be determined against distilled water.

Calculation:

$$[\text{sample}] = \frac{A_{\text{sample}} - A_{\text{blank}}}{A_{\text{standard}} - A_{\text{blank}}} \cdot [\text{standard}]$$

A_{sample} = absorbance of the sample (if necessary, corrected by the blank value).

A_{blank} = absorbance of the reagent blank (if the measurement is carried out against distilled water).

A_{standard} = absorbance of the standard.

Remarks. The procedure may be simplified: the colour reagent and the borate buffer may be mixed in equal proportions immediately before the determination. In this case, 0.1 cm³ of the supernatant is mixed with 2.0 cm³ of reagent mixture. The further course of the determination is unchanged.

The chemical purity of the test-tubes centrifuge tubes and vessels, and also the ion-free condition of the water used for the solutions and for the determination of the reagent blank should be carefully observed. Attention should also be paid to the elimination of environmental contamination (magnesium-containing substances, talc, etc.).

The linearity of the method is good up to a concentration limit of about 1.6 mmol/dm³. It is also advisable to control the instrument with a standard series.

B) Without deproteinization

Immediately before the determination, the same volumes of colour reagent and borate buffer are mixed together (reagent mixture).

	Sample (cm ³)	Standard (cm ³)	Blank (cm ³)
Reagent mixture	2.000	2.000	2.000
Sample	0.020	—	—
Standard	—	0.020	—
Deionized water	—	—	0.020

After thorough mixing and standing for 10 minutes, photometry within 30 minutes as in variation A. The calculation and remarks are also the same as in A.

Further remarks. If the bilirubin concentration of the samples is high, a sample blank should be employed: 1 volume of absolute ethanol is added to 1 volume of borate buffer solution. 0.02 cm³ of sample added to 2 cm³ of this mixture is measured photometrically against the mixture at the appropriate wavelengths. The measured absorbance difference, i.e. the blank of the sample, is subtracted from the absorbance measured for the colour reaction of the sample.

The same procedure is to be followed in the event of a slight turbidity. For some serum samples, an increasing turbidity may be observed in the ethanolic borate buffer medium. This is encountered mainly in pathological hyperglobulinaemias.

For urinary magnesium determination, the urine is diluted 2-fold or 4-fold with deionized water. On collection, the pH of the urine is adjusted to 3–4 with a few drops of hydrochloric acid. The result is multiplied by the degree of dilution.

Haemolytic serum samples are not suitable for determination, because of the considerably higher concentration of magnesium in the erythrocytes than in the plasma.

The magnesium supply of the organism cannot be deduced from the magnesium concentration of the erythrocytes, since the latter depends greatly on the magnesium supply during erythropoiesis.

“Normal” ranges:

serum: 0.7–1.0 mmol/dm³

cerebrospinal fluid: 1.0–1.5 mmol/dm³

urine: 0.4–4.1 mmol/dm³; 2.0–6.2 mmol/day

With the aim of eliminating the above problems, a number of authors dissolved the colour reagent in a concentrated solution of an organic base, e.g. tris(hydroxymethyl) aminomethane buffer or triethanolamine buffer.

By using the latter buffer, Velösy and Szabó (1976) developed the following method.

Stock solution of magnesium reagent: 8.2 mg xylidyl blue II (or 10.3 mg xylidyl blue I) is dissolved in 110 g triethanolamine (analytically pure) by moderate warming. The solution may be stored for several months in a plastic container, protected from light.

Working reagent: immediately before use, the necessary amount of reagent is prepared by carefully diluting and mixing (without bubble formation) reagent stock solution with the same amount of deionized water.

Determination procedure:

	Sample (cm ³)	Standard (cm ³)	Blank (cm ³)
Working reagent	2.00	2.00	2.00
Sample	0.02	—	—
Standard	—	0.02	—
Deionized water	—	—	0.02

After thorough mixing and standing for 5 minutes, photometry is carried out within 30 minutes, between 490 nm and 520 nm, or at the Hg 492 nm line, against the blank, in a 1-cm cell.

Calculation: the same as in the ethanolic borate buffer method.

Remarks: the working reagent itself is very viscous. If the cells are not dry, it is advisable to rinse them with a 1 : 1 mixture of analytically pure triethanolamine and deionized water before the measurements. In this way, the concentration differences and the changes in refraction index within the cells may be eliminated.

Another way to reduce the viscosity: the amount of colour reagent in the triethanolamine base is doubled. The stock solution thus obtained is diluted immediately before use with deionized water. Proportions: 1 volume of stock solution is mixed with 2 volumes of deionized water (it is also possible to dilute with 3 volumes of deionized water).

The procedure and calculation are the same as above.

Deproteinization of the sample may be necessary with this method too, for example in cases of turbid sera from strongly jaundiced patients. Deproteinization is performed as described for the borate buffer method. Here again 0.1 cm³ of supernatant is taken with 2 cm³ of triethanolamine working reagent. The subsequent procedure is the same as above.

The chemical purity of the vessels and cells is essential. They should therefore be washed and soaked in dilute (0.1 mol/dm³) hydrochloric acid or nitric acid, then washed with distilled water until they are acid-free, rinsed several times with deionized water, and finally dried in a dustproof, clean place.

Ethanol containing hydrochloric acid (e.g. Ebner's solution II) is also very suitable for the cleansing of cells before use. Thorough rinsing with deionized water is necessary in this case too, of course.

The complexometric methods mentioned in the introduction have not become widespread in medical chemistry because they require large samples and detection of the end-point is not precise enough. For the sake of completeness, the principles of another method will be outlined: complexometric determination of the serum calcium and magnesium on the same sample. The measuring solution is EDTA (ethylenediaminetetraacetic acid), while the indicator is Eriochrome blue SE (Szabó, 1971).

Calcium is titrated in a strongly alkaline medium. After the transition, the alkaline pH is reduced with ammoniacal ammonium chloride buffer. The released indicator now reacts with the magnesium ion makes possible the titration of magnesium with EDTA.

The method of reference for the determination of magnesium in biological fluids is atomic absorption spectrometry.

For routine clinical purposes, the total magnesium concentration may be determined most reliably by the borate buffer-alcoholic xylidyl blue method with deproteinization.

An excellent review of the magnesium metabolism may be found in the monography Durlach (1988). Some of its fundamental findings are as follows.

In evaluations of the magnesium concentration of the serum (plasma), certain points should be taken into consideration:

1. In this fluid, about one-third of the total magnesium content is bound to proteins (mainly albumin).
2. One-tenth of the remaining two-thirds is found in complexes. Complexes are formed with citrate, bicarbonate, phosphate, etc. The remaining nine-tenths is present as free magnesium ion.

Accordingly, 90% of the ultrafilterable two-thirds of the serum magnesium concentration is made up of free magnesium ion, which have a mean concentration of about 0.5 mmol/dm^3 .

The total magnesium concentration of the serum is influenced by the albumin (total protein) concentration of the sample, due to the differences in concentration of protein-bound magnesium, 99% of the magnesium in the organism is intracellular. Thus, only 1% is to be found in the extracellular space.

The magnesium content of the organism may be examined by means of magnesium loading. The amounts of magnesium excreted with the urine before and after a magnesium load are correlated with the amount of magnesium administered. In establishing the diagnosis of hypomagnesaemia or hypermagnesaemia, further data may be obtained by determination of the magnesium concentration of the erythrocytes through atomic absorption spectrometry. Normal value: $1.8\text{--}2.8 \text{ mmol/dm}^3$ erythrocytes.

Samples for the determination of cellular magnesium concentration are obtained by surgical intervention, by muscle, or needle biopsy.

The magnesium concentrations of the saliva, gastric and pancreatic juice and bile are usually lower than that of the plasma ($0.5\text{--}1.0 \text{ mmol/dm}^3$).

The physiological range of urinary magnesium excretion is $2.0\text{--}6.0 \text{ mmol/day}$ or $50\text{--}150 \text{ mg/day}$. If the kidney is intact, the magnesium excretion correlates positively with the protein uptake. The ratio of magnesium and urea in the urine may therefore be considered almost constant. Under normal circumstances, the amount of magnesium excreted in 24 hours, expressed in mg, divided by the amount of urea excreted in 24 hours, expressed in g, i.e. the quotient Mg/U , has a value of 4.7 ± 1.8 . If the amount of excreted magnesium is expressed in mmol/dm^3 , and that of the urea in mol/dm^3 , this quotient should be multiplied by 2.47, i.e. it is 11.6 ± 4.4 . Hypomagnesiuria associated with a Mg/U quotient smaller than 3 (in mg/g) is indicative of hypomagnesaemia compensated by the kidney. On the other hand, hypermagnesiuria accompanied by a Mg/U quotient higher than 6 (in mg/g) points to a considerable loss of magnesium relative to the protein intake.

The intestinal excretion and pathological hypersecretion of magnesium (e.g. in the neuromuscular form of magnesium deficiency or alcoholic cirrhosis) may be studied by means of ^{28}Mg which has a half-life of 21.3 hours.

References to Chapter 9

9.1. Magnesium determination in soil samples

- Ballenger, R., di Gléria, J. (1962): *Methods for Examination of the Soil and Manure*. Mezőgazdasági Kiadó, Budapest. (In Hung.)
- Buzás, I. (1988): *Textbook of the Methods of Soil and Agrochemical Examinations 2*. Mezőgazdasági Kiadó, Budapest. (In Hung.)

9.2. Determination of magnesium content in plants

- Ali, M. V., Zoltai, S. C., Radford, F. G. (1988): A comparison of dry and wet ashing methods for the elemental analysis of peat. *Canadian J. Soil Sci.* **68**, 443.
- Ballenger, R., di Gléria, J. (1962): *Methods for Examination of the Soil and Manure*. Mezőgazdasági Kiadó, Budapest. (In Hung.)
- Buzás, I. (1988): *Textbook of the Methods of Soil and Agrochemical Examinations 2*. Mezőgazdasági Kiadó, Budapest. (In Hung.)
- Chao-Youang Luh Huang, Schulte, E. E. (1985): Digestion of plant tissue for analysis by ICP Emission Spectroscopy. *Commun. in Soil Sci. Plant Anal.* **16**, 943.
- Loch, J. (1965): Determination of the Ca and Mg contents of plant tissues with complexone III. *Debreceni Agrártud. Főisk. Tud. Köz.* **11**, 259. (In Hung.)
- Mann, C. K., Yoe, J. H. (1956): Spectrophotometric determination of magnesium with sodium 1-azo-2-hydroxy-3(2,4-dimethylcarboxanilido) naphthalene-1'-(2-hydroxybenzene-5-sulfonate). *Anal. Chem.* **28**, 202.
- Pataki, L., Zapp, E. (1972): *Analytical Chemistry*. Tankönyvkiadó, Budapest. (In Hung.)
- Price, J. (1977): *Atomic Absorption Spectrophotometry*. Műszaki Könyvkiadó, Budapest. (In Hung.)
- Schachtschabel, P. (1954): Das Pflanzenverfügbare Magnesium des Bodens und seine Bestimmung. *Z. Pfl.-ernähr. Düng. Bodenk.* **67**, 9.
- Schachtschabel, P., Isermeyer, H. (1954): Die Magnesiumbestimmung mittels Titangelb. *Z. Pfl.-ernähr. Düng. Bodenk.* **67**, 1.

9.3. Determination of magnesium in fodders

- Clark, D. H., Mayland, H. F., Lamb, R. C. (1987): Mineral analysis of forages with near infrared reflectance spectroscopy. *Agron. J.* **79** (3), 485.
- Danbara, H., Koyama, M., Takada, J., Nakano, Y. (1989): Concentration of elements in grass. Intercomparison of analytical values between neutron activation analysis and atomic absorption spectrophotometry. Kyoto Daigaku Gensiro Jikkensho Gakujutsu Koenkai Koen Yoshishu **23**, 173-174. *Chem. Abstr.* **110**, 169794.
- Debersaques, F., Velghe, G., Aerts, J. (1988): Determination of mineral and trace elements in feed by plasma emission spectrophotometry. *Rev. Agric. (Brussels)* **41** (6), 1431.
- Hoening, M., Scohart, P. (1983): Application of inductively coupled plasma (ICP) emission spectrometry in inorganic analysis in agricultural chemistry. *Rev. Agric. (Brussels)* **36** (6), 1727.
- Jones, G. M., Wade, N. S., Baker, J. P., Rauch, E. M. (1987): Use of near infrared reflectance spectroscopy in forage testing. *J. Dairy. Sci.* **70** (5), 1086.
- Koupparis, M. A., Diamands, E. P., Malmstadt Howard, V. (1983): Automated determination of crude protein, phosphorus, calcium, iron and magnesium in feeds by using a stopped flow analyzer. *J. Assoc. Off. Anal. Chem.* **66** (1), 188.
- Lyons, D. J., Spann, K. P., Roofayel, R. L. (1985): Determination of total calcium, zinc, manganese, iron, magnesium and phosphorus in animal feeds and plant material using ICP spectrometry. *Analyst* **110** (8), 955.
- MSZ 6830/21: Determination of magnesium content in feedstuffs. Atomic absorption spectrometric method. (In Hung.)
- Samndralwar, D. L., Wankchade, H. K., Garg, A. N. (1987): Multielemental analysis of IAEA intercomparison standard hay powder, V-10 and some edible plant leaves by neutron activation. *J. Radioanal. Nucl. Chem.* **116** (2), 303.

- Stoltz, M. A. (1990): Provisional assessment of quality components in lucerne (*Medicago sativa*) and white clover (*Trifolium repens*) using near infrared reflectance spectrophotometer. *S. Afr. J. Plant Soil*. **7** (2), 105.
- Suschny, O., Dubczynsky, R., Veglie, A. (1982): Comparison of neutron activation analysis with other analytical techniques for the determination of inorganic constituents of milk powder. *J. Radioanal. Chem.* **69** (1-2), 147.
- Tokahashi, Mari, Takiyama, Kazuyoski (1988): Effect of laurylpyridinium chloride on determination of magnesium by flame AAS. *Bunseki Kagaku* **37** (12), 674-676. *Chem. Abstr.* **110**, 3784g.
- White, R., Thomas, K. (1989): Closed vessel sample decomposition by microprocessor controlled high temperature and pressure asher for elemental analysis by ICP. *J. Assoc. Off. Anal. Chem.* **72** (2), 387.
- Willem, G. De Ruig (1986): Atomic Absorption Spectrometric Determination of Calcium, Copper, Iron, Magnesium, Manganese, Potassium, Sodium, and Zinc in Animal Feeding Stuffs: Interlaboratory Collaborative Studies. *J. Assoc. Off. Anal. Chem.* **69** (6), 1009.
- Yuan, Junhna (1990): Determination of light common elements in forage by furnace AAS method. *Guangpuxue Yu Guangpu Fenxi* **10** (2), 74-75. *Chem. Abstr.* **113**, 229775f.

9.4. Determination of magnesium in biological fluids.

- Bohuon, C. (1962): *Clin. Chim. Acta* **7**, 811.
- Denis, W. (1922): *J. Biol. Chem.* **52**, 411.
- Durlach, J. (1988): *Magnesium in Clinical Practice*. John Libbey, London - Paris, 40, 42, 45, 47, 49, 53.
- Gindler, E. (1971): *Clin. Chem.* **17**, 662.
- Mann, C. K. (1957): *Anal. Chim. Acta* **16**, 155.
- Mann, C. K., Yoe, J. H. (1956): *Anal. Chem.* **28**, 202.
- Orange, M., Rhein, H. C. (1951): *J. Biol. Chem.* **189**, 379.
- Simonsen, D. G., Westover, L. M., Wertman, M. (1947): *J. Biol. Chem.* **169**, 39.
- Szabó, E. (1971): Communication by letter in the collection of methods of MOM, A-8.03/04. Budapest. (In Hung.)
- Szelényi, I. (1971): Communication by letter in the collection of methods of MOM, A-1.04.2. Budapest. (In Hung.)
- Velösy, Gy., Szabó, A. (1976): *Laboratory Diagnostics*. III, 55. (In Hung.)

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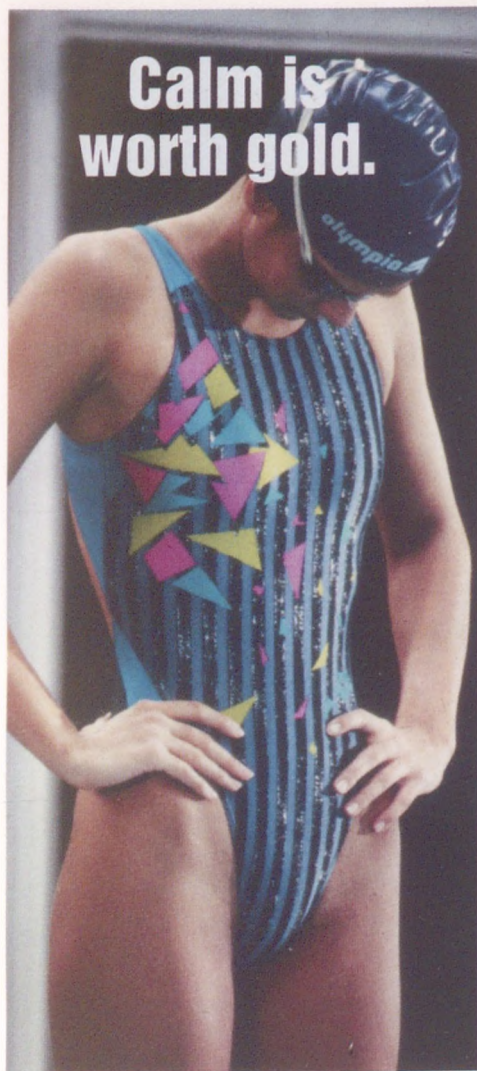
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**Calm is
worth gold.**



**The needed Magnesium
Plussz**

Plussz®

**Magnesium
effervescent tablet.**

Those who control their own nerves, controls everything. Magnesium helps to protect and maintain our calmness even in the worst rush or stress, and gives power to overcome our problems. Magnesium is a vital mineral. It eases the circulation process within the cells, its presence is indispensable for the normal functioning of the muscles and nerves and is necessary for recovery. It strengthens the heart and arterial system and raises the body's immunity against stress. 1-2 tablets daily is the recommended dose for a balanced level of magnesium.



Pharmavit®

ÉLETRE VALÓ.

**Pharmavit Rt.
Veresegyház**



Magnesium 250

For the treatment of magnesium deficiency as a result of reduced intake, absorption disorder or increased passage.

The recommended daily amount of magnesium is 300-350 mg for adults, 400 mg for adolescents and 450 mg for pregnant and nursing women. It would appear that out of factors that result in increased need, reduced intake and increased loss of magnesium the most important ones, from a practical point of view, are hypomagnesaemia due to chronic diuretic treatment, refractory hypopotas-saemia, cardiac insufficiency, treatment with digitalis and magnesium deficiency that cannot be verified by serum assay.

Due to its cardio-protective effect, it can be used as complementary treatment in cases of ischemic cardiopathy and hypertension.

The effervescent, water soluble Magnesium 250 mg Pharmavit tablets, administered orally, can be helpful in the treatment and prevention of chronic conditions of magnesium deficiency. ATC: A12 CC 06

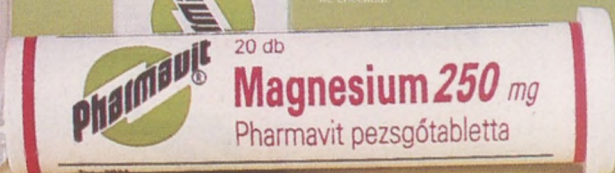
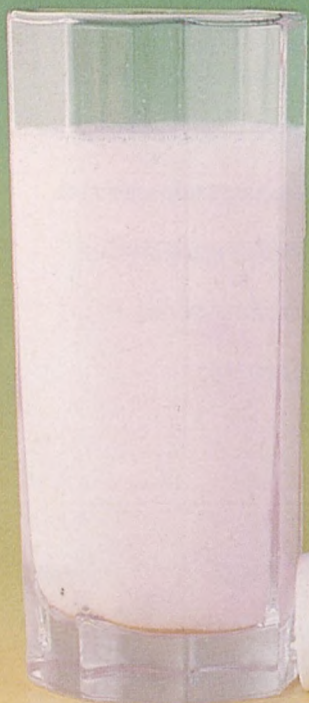
Magnesium 250 mg Pharmavit effervescent tablets.

Active ingredients: 420 mg magnesium oxydatum (250 mg magnesium), 150 mg ascorbic acid in every effervescent tablet.

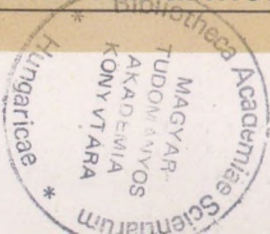
Dosage: Adults: 1 effervescent tablet 3 times a day, children up to 5 years of age: 1 effervescent tablet a day, children between 5-10 years of age: 1 effervescent tablet once or twice a day, children older than 10: 1 effervescent tablet 2 or 3 times a day dissolved in a glass of water.

Interactions with other drugs: It interferes with the absorption of oral tetracyclines, iron salts and sodium fluoride. After having taken these drugs allow a 3 hour period before taking magnesium.

Warning: Prolonged use of the preparation in large amounts can lead to hypermagnesaemia. Its symptoms are not specific: lethargy, vomiting, hypotension, bradycardia, hyporeflexia, changes in ECG and depression of the central nervous system. If these symptoms occur, the serum magnesium level has to be checked.



THE ACTIVE INGREDIENT IN THE PREPARATION IS MAGNESIUM.



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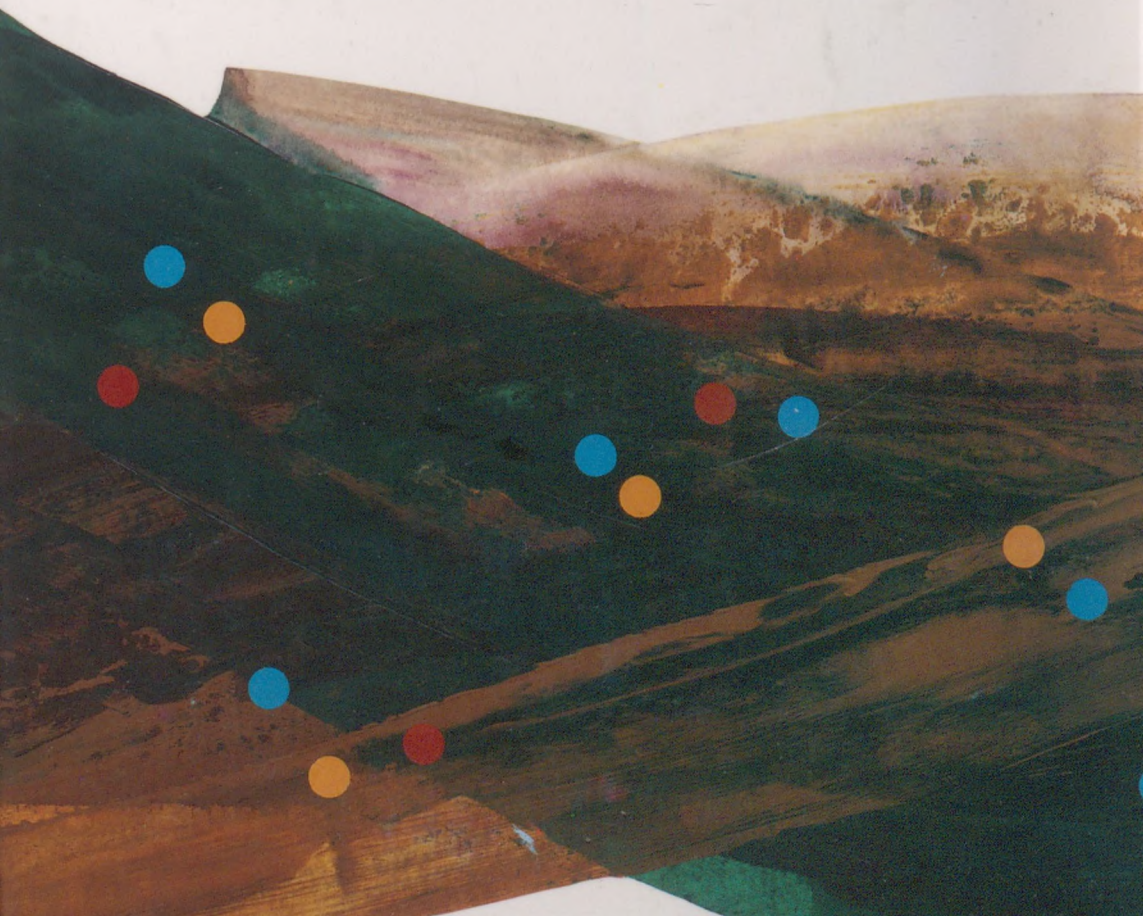


This multidisciplinary book surveys recent knowledge and advances regarding magnesium. Chlorophyll, the green pigment of plants, is not synthesizable without magnesium, which is also the fourth most important element found in the human body. The environmental and biological roles and functions of magnesium, from soil and water, from plants and animals to the human organism are summarized.

A *geological* description is followed by the biomedical portion of the book which deals with *absorption/malabsorption* and *dietetics* of elemental magnesium. Etiology and cardiovascular consequences of *magnesium deficiency syndrome* are discussed in detail. An up-to-date review of the *cardiac electrophysiology* and clinical use of magnesium is included. Various chapters deal with (patho-)physiology and clinics of magnesium regarding nephrology (*elimination*), its relationship to the regulation of arterial blood pressure, *neurology/psychiatrics*, *obstetrics*, *gastrointestinal motility* and *urinary stone formation*. The *biopharmaceutical/analytical* chapter provides a summary of the chemistry and pharmacy of magnesium compounds with particular emphasis on therapeutical uses.



Akadémiai Kiadó, Budapest



As has been described earlier, a magnesium deficiency is to be seen first on older, i.e. basal leaves. The strongest symptoms are usually localized chlorotic spottiness, with or without necrosis.

Although visual diagnostics provides fast information on the symptoms, this method is still not sufficient itself for a clear-cut answer, since a hidden nutrient deficiency cannot be revealed in this way. However, analytical diagnosis based on plant or leaf analysis yields reliable information on the nutrient supply or deficiency. The principle underlying plant analysis to monitor the nourishment status is that, in the developmental periods of importance for optimal growth and yield, different plant parts (leaf, leaf stalk, apical meristem, etc.) are characterized by well-defined nutrient contents and nutrient ratios. The determination of nutrient concentrations necessary for a harmonious nutrient supply is possible only via analytical measurements. The characteristic magnesium contents of some important crop plants are listed in *Table 3.32*. Of these data, the results of the analysis of winter wheat are emphasized. The magnesium supply of winter wheat (plant analysis on ca. 56,000 hectares) at the time of stooling reveals that on more than 40% of the area the magnesium supply of winter wheat was inadequate. For 21% of the plants, the magnesium deficiency could be explained by the inadequate magnesium supply of the soil. Winter wheat deficient in magnesium could be found even on soil very well supplied with magnesium. In order to ensure the optimal magnesium supply, it is essential that, in addition to soil analyses, plant analyses also be carried out in the course of the vegetative period and that, when necessary, magnesium be supplemented by foliage spraying.

3.3. The effects of magnesium on biomass formation and special metabolism in plant tissue culture

It is evident from the preceding section that magnesium is indispensable for plant development. In connection with the utilization of natural magnesium sources in crop plants, it was pointed out there that a deeper knowledge of the effect of the magnesium supply provides an opportunity for enhancement of the effectivity of agricultural production. In order to achieve this goal, it is first absolutely necessary to know how plants absorb magnesium from the soil and what role this element plays in their life processes (Kiss, 1983).

In this section, the results of experiments with plant tissue cultures will be utilized to demonstrate, that in addition to influence primary metabolic processes, magnesium also has effects on the secondary or special metabolism.

The effects of magnesium on the growth and essential oil content of organized camomile cultures

Since camomile is at present one of the best-known and most sought-for herbs in Hungary and is nowadays cultivated rather than collected in Nature, it appears of interest to demonstrate how magnesium affects the growth of organized camomile