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Review Article

Magnesium (and Trace Substance) Deficiencies in the Pathogenesis of Cancer

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ABSTRACT

Except for a few experimental models of magnesium (Mg)-deficiency-induced neoplasms, less attention has been paid in the past quarter century in the Western world to this macromineral than to the trace elements; e.g., selenium (Se) and zinc (Zn), and to vitamins, deficiencies of which are each considered probable factors in oncogenesis. Although early epidemiologic studies showed an inverse correlation between the amount of Mg in soil and water and the incidence of (gastric) cancer, and several animal studies supported the premise that Mg has a prophylactic effect against induction of cancer, other studies showed that Mg supplementation increased the growth of established experimental tumors. Thus, enthusiasm for this approach subsided. The early epidemiologic findings have since been confirmed, and there have been studies demonstrating the importance of Mg in maintaining immunocompetence, and others indicating that immunodeficiencies increase susceptibility to the development of cancer. Evidence has now accrued that indicates that Mg deficiency increases susceptibility to chemical oncogens. The abnormal metabolism of tryptophan (yielding a carcinogenic metabolite) that indicates functional or absolute pyridoxine deficiency is an indirect clue to Mg deficiency. Vitamin B_6-activated enzymes require Mg as a cofactor. However, the early warnings against the use of Mg as part of an antineoplastic program against established cancer were justified, since rapidly metabolizing cells (such as cancers) are dependent on Mg.

There are similarities between experiences with Mg and with Se and Zn. All three are required for normal metabolism; Se also protects against free radicals in the environment. Mg and Zn have increased established tumor growth, and their depletion has been applied to antineoplastic programs, with risks comparable to those of using antimetabolic agents.

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MAGNESIUM DEFICIENCY IN THE PATHOGENESIS OF CANCER

Conflicting Early Laboratory Findings: Epidemiologic Evidence

That the status of Mg—in the body or environment—might be important in the development of cancer excited interest during the first third of this century. Early findings of low Mg levels in human and animal cancers (*1–5*), and in whole blood (*6, 7*) and serum (*8*) of cancer victims, and the inverse correlation of (low) Mg content of soil or water and (high) incidence of cancer (*9–17*), led to studies of the influence of Mg on animal cancers. Some reported that Mg administration inhibited the development of tar-induced tumors (*18–21*). Delbet (*9*), who first noted the low incidence of stomach cancer in areas with high Mg soil content, considered Mg to have a prophylactic rather than a curative effect in established cancers. Others soon reported that Mg administration had little or no effect on experimental cancers (*11, 22, 23*) or actually enhanced the growth of transplanted tumors (*24–26*). Thus Shear (*27*) in 1933 and Haury (*28*) in 1942 cautioned against the use of Mg in antineoplastic regimens. Publications on the epidemiologic correlation of high cancer rates with low soil Mg levels began to appear again in the 1950s. Heineman (*29*) and Nieper (*30*) provided statistical verification of the earlier epidemiologic findings, as did studies confirming the early reported low cancer rates in Egypt (*11–13*) and other desert lands rich in Mg (*31*). Extremely high stomach cancer rates (40.7 and 29.2/100,000 in men and women, respectively) were reported by Bazikinian (*33*) in the Ukraine, where the percent of Mg in the soil is low (1.16), in contrast to the much lower mean stomach cancer rate (10/100,000) in Armenia, where the average Mg content of the soil is 2.5 times as high. A comparable difference in incidence of cattle leukemia has been reported by Aleksandrowicz and Stachura (*34*), depending upon the availability of Mg in the soil used for pastorage.

Magnesium in Experimental Oncogenesis

Magnesium deficient animals have developed several forms of neoplasms without known exposure to other oncogenic agents, and in some instances have exhibited increased susceptibility to development of transplanted or otherwise induced tumors. The mechanisms by which Mg deficiency exerts

these effects are not resolved. Among the possibilities are: (a) damage to cell membranes, with resultant easier cell penetrability by oncogenic agents: chemical, viral, or other; and (b) interference with immunocompetence, with resultant impaired surveillance against aberrant cells that give rise to cancer.

Magnesium deficiency-induced lymphomata. The first neoplasm that was associated with experimental Mg deficiency was lymphosarcoma, with predominant involvement of the thymus (*35*), considered by Jasmin (*36*). Thymic and splenic hypertrophy had already been reported by Hungerford and Karson (*37*) in acutely Mg-deprived rats. That lymphosarcomas could be produced later in survivors of acute depletion, as shown by Jasmin (*35*) and Bois (*38*), was confirmed by Johnson (*39*), Battifora et al. (*40, 41*), and McCreary et al. (*42*). Hass et al. (*43*) have pointed out that the malignant lymphoma, produced during the subacute phase of Mg deficiency, has occurred only in Sprague-Dawley, Holzman, and Wistar rats that were kept on synthetic diets containing less than 8 mg% of Mg from the time of weaning for at least ten weeks. The incidence of malignant lymphomas has been 15–50% (*41, 43, 44*). When the Mg-deficient diet was started at 120–150 days of age, no lymphomata developed, nor did they develop after 155 days of Mg deficiency, at which time the thymus was often atrophic (*43*). The lymphoma has been transmissable by use of live cells, but not by devitalized cells, cell particulates, or cell-free filtrates (*43–46*). Neonatal rats are most vulnerable, particularly when Mg deficient (*41–43*).

Possible influence of calcium excess in magnesium-deficiency-lymphomata. The diets used in these studies contained an extremely high Ca/Mg ratio: as high as 140/1 (*47*), which Bois (*48*) and Alcock et al. (*47*) speculated might stimulate proliferation of thymocytes, because calcium injection into rats has increased thymocyte mitosis (*49*) and high Ca concentrations stimulate thymocytes in vitro (*infra vide*). However, optimal Mg concentrations in vitro seem to be even more critical than calcium for normal lymphocyte function, although both are needed (below). Thus perhaps the extreme Mg depletion of the rats on the Ca/Mg intake of 140/1 might have obtunded the Ca-stimulatory effect that resulted in thymic hyperplasia in rats given tenfold less Ca (*47*). Why it did not do so in the rats that developed lymphosarcomas (above) rather than just hyperplasia (*47*) is not clear. Further confusing the issue is the development of thymoma in one of four Mg-depleted rats that were also hypocalcemic as a result of parathyroidectomy (*48*), and the thymic hypoplasia in some of the rats on dietary Ca/Mg of 14/1 (*47*). Note should be taken here of the virus-like particles seen in some of the lymphosarcomas reported (*43, 44*). It is conceivable that the rats that developed lymphomata might have been carriers of oncogenic viruses, to which their resistance was reduced by their Mg depletion.

Effects of calcium and magnesium on lymphocytes in vitro. Normal lymphocyte transformation, in vitro, in response to phytohemagglutinin (PHA) is inhibited by ethylenediaminetetracetic acid (EDTA), which chelates

both Mg and Ca (50). Whitney and Sutherland (*51*) showed that mixed human lymphocytes, cultured in media free of Ca^{2+} and Mg^{2+}, responded to excess calcium by progressively increased deoxyribonucleic acid (DNA) synthesis to 3.5 times control values. In contrast, addition of a physiologic amount of Mg^{2+} to the medium increased DNA synthesis, but further increasing it produced no additional enhancement. Rat thymocytes are also stimulated by Ca^{2+} in vitro (*52*) and by Mg^{2+} (*53*, *54*). Brennan and Lichtman (*55*) found that Mg is more potent than is Ca in stimulating murine lymphoblast proliferation. C. Seelig (*56*) has shown that culture of lymphocyte–monocyte fractions of human blood in Mg-deficient media results in morphologically and functionally abnormal cells.

Whether this in vitro manifestation of Mg-deficiency-induced morphologic abnormality in human lymphocytes (and neutrophiles) (*57*), which is augmented by Ca deficiency, is relevant to experimental Mg-deficiency-induced impairment of immunologic surveillance (i.e., against cancer, *infra vide*) or to development of leukemia (below) requires study. In vitro studies with transplantable mouse lymphoma cells have shown that, when they are cultured in media low in Mg and Ca, variant cells emerge with increased oncogenicity (*58*).

Magnesium deficiency-induced leukemia. Leukocytosis has been observed during acute hypomagnesemia in rats (*37*, *41*, *42*, *59–64*) and calves (*65*). Kashiwa and Hungerford (*59*) reported increases in circulating leukocytes of 2-fold (monocytes), 6-fold (neutrophils), and 13-fold (eosinophils). The leukocytosis declined with the duration of the Mg deficiency, but the neutrophilia persisted at lower levels during the chronic phase (*43*, *61–64*) and tissue eosinophilia increased (*37*). The bone marrow often became hypercellular early (*62*, *64*).

Myeloid leukemia developed in some of the chronically Mg-deficient rats (*41*, *43*, *61–63*). Battifora (*41*) reported that the incidence of myelogenous leukemia, developing within four months to a year among several hundred Sprague-Dawley chronically magnesium deficient rats was about 10%. They exhibited chloroleukemia, massive splenomegaly, and usually retroperitoneal and thoracic lymph node enlargement. Histologically immature neutrophils were found in blood and as infiltrates of parenchymatous organs. Injection of spleen-derived living leukemic cells (but not of dead cells, cell fragments, or cell-free filtrates) into newborn rats produced a 90% incidence of leukemia. Serial transplantation for 20 generations resulted in increased oncogenicity with successive transplantations. Electron microscopic examination showed no virus-like particles. The leukocytosis of Mg deficiency was reversible by Mg supplementation, but McCreary et al. (*62*) found that once leukemia developed, Mg supplements influenced neither the leukocytosis nor the granulocyte percentage.

Magnesium deficiency and bone tumors. Hyperplasia and even early neoplasia of bone has been reported in Mg-deficient rats. Osteomyelosclerosis (such as is frequently seen in leukemia) and subperiosteal desmoid tumors have been reported by Bélanger and Hunt (*66–68*) and by Lai et al. (*69*) in

chronically Mg-deficient rats. The bony overgrowth that seems "midway between a true tumor and connective tissue hyperplasia" was considered related to decreased bone Mg, particularly in the organic phase of bone (*66, 67*). The tumor, which consisted mainly of fibroblasts, with numerous mitotic figures, was reversed by Mg supplementation, suggesting that there had been accumulation of cells incompetent to differentiate properly. Parathyroidectomized Mg-deficient rats had a large tumoral mass consisting of external layers of fibrous tissue, then cartilage, and then an internal layer of bone (*68*). Parathyroid hormone administration reduced the amount of cartilage and increased the growth of abundant bone throughout the central cavity of femur and tibia. Failure of osteogenic precursor cells to attain full differentiation was also shown by Bélanger et al. (*70*) in Mg-deficient rats with bone matrix implanted intramuscularly.

Magnesium deficiency and chemical oncogenesis. The influence of Mg on the growth of implanted, irradiation, or chemically-induced cancers is not consistent. Addition of the weakly leukemogenic agent, 2-acetylaminofluorine, or of dimethylbenzanthracene (DMBA) to the Mg-deficient regimen that caused myelogenous leukemia in significant numbers of rats, favored an increased incidence (*61, 62*). However, the leukemia caused by lead subacetate or allylisopropylacetylurea was not significantly influenced by Mg deficiency (*43*).

Marullaz (*18, 19*) and Delbet and Palios (*20, 21*) observed that Mg supplementation had a prophylactic effect against development of skin cancer caused by application of tar. However, Serbescu (*26*) showed that rabbits fed

TABLE 1

Effect of $McCl_2$ in Drinking Water of Mice Exposed to Dermatologic Carcinogens (adapted from Bazikinian, 1971)

A. GIVEN DURING APPLICATION OF DMBA

DMBA PAINTED ON SKIN DAILY	NO.	DURATION OF Mg R_x	MICE WITH TUMORS (%)	AVERAGE NO. OF TUMORS/MOUSE	DEATHS (%)
-WITHOUT $MgCl_2$	30	0	82	1.10	27
-$MgCl_2$ (15mgMg/kg/d)	30	30 DAYS	66	0.80	20

B. GIVEN IMMEDIATELY FOLLOWING DBA INJECTION

DBA (3mg SUBCUT., SINGLE INJECTION)	NO.	DURATION OF Mg R_x	MICE WITH TUMORS (%) 7 MOS. AFTER DBA		DEATHS (% AT 200 DAYS)
-WITHOUT $MgCl_2$	30	0	83		40
-$MgCl_2$ (15mgMg/kg/d)	30	30 DAYS	66		21
-$MgCl_2$ (")	30	200 DAYS	37		10

C. STARTED AFTER OR BEFORE AND DURING DMBA APPLICATION

DMBA PAINTED ON SKIN DAILY	NO.	TIME OF Mg ADMINISTRATION		MICE WITH TUMORS (%)	AVERAGE NO. OF TUMORS/MOUSE	DEATHS (%)
		PRE-DMBA	AFTER DMBA STARTED			
-WITHOUT $MgCl_2$	20	0	0	74	0.90	35
-$MgCl_2$ (15mgMg/kg/d)	30	0	8-56 DAYS	65	0.82	42
-$MgCl_2$ (")	31	7	30	50	0.63	20
-$MgCl_2$ (")	29	7	53	41	0.55	16

$MgSO_4$ were much more susceptible to coal tar cancer than were those not so supplemented. Sugiera and Benedict (*25*) found that Mg-deficient rats survived transplants of Flexner-Jobling carcinoma more frequently and longer than did those on a high Mg diet, and Jinguu (*24*) reported that Mg administration accelerates the rate of growth of transplanted Kyoto sarcoma. Bazikian (*33*) has reviewed the USSR literature on the influence of Mg on tumor induction. Transplantable Ehrlich ascites tumor, rat sarcoma 45, and rabbit Brown-Pearce carcinoma developed more slowly in rodent recipients fed Mg salts than in those not so supplemented (*71*). Intraperitoneal injection of $MgSO_4$ 40 min before exposure of mice to thiophosphamide reduced its blastomogenic effects and allowed for survival of half the mice; those that developed neoplasms despite pretreatment with Mg survived longer than did controls (*72*). Bazikian's (*33*) studies with mice painted daily with DMBA, or given a single injection of dibenzanthracene (DBA) (30 mice/group), showed that daily Mg administration had some protective effects when started the day application of the oncogenic agent was begun (Table 1A) and that the longer the supplementation after a single DBA injection, the better the protecting effect (Table 1B). When there was a delay of 8 days after daily DMBA applications had begun, the mice that developed tumors had a shorter (than control) survival rate. In contrast, prophylactic Mg administration that was continued throughout the period of DMBA application was significantly protective (Table 1C). In a study of cyclophosphamide's effect on tumor growth in mice that had been injected with Ehrlich ascites tumor cells, with

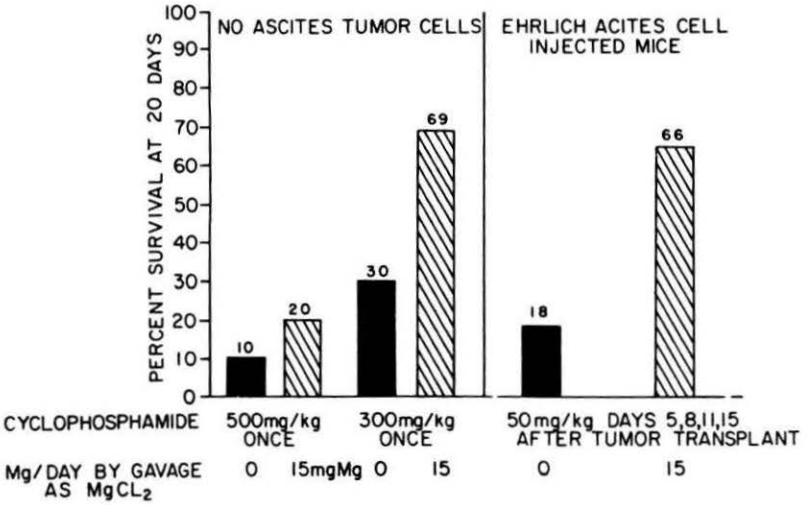


FIG. 1. Reduction of toxicity of cyclophosphamide by magnesium in mice (adapted from Bazikian, 1971).

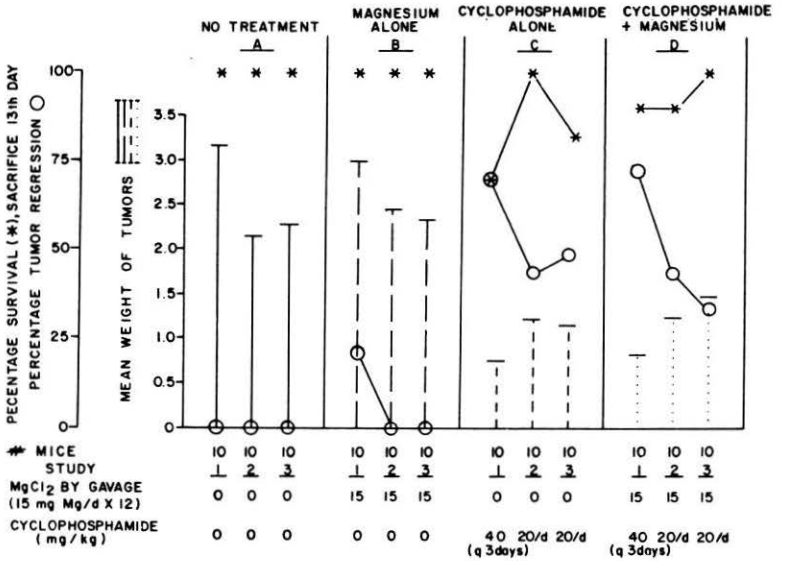


FIG. 2. Effect of magnesium on tumor growth in mice injected with Ehrlich ascites cells with and without cyclophosphamide therapy (adapted from Bazikian, 1971).

and without $MgCl_2$, Bazikian (*33*) first showed that Mg significantly decreased the toxicity of the antineoplastic agent, both in control and Ehrlich ascites cell-injected mice (Fig. 1.) Although $MgCl_2$ alone did not significantly alter the tumor growth after subcutaneous injection of Ehrlich ascites cells in mice, all the mice survived to time of sacrifice at 13 days (Fig. 2A,B). Mice given sublethal doses of cyclophosphamide alone showed substantial tumor regression, whether or not $MgCl_2$ was given daily, but the Mg administration increased percentage survival from 70 to 90% (Fig. 2C,D). The tumors reached the same (less than control) weights whether (the lower) therapeutic dose of cyclophosphamide was given with or without $MgCl_2$, but the percentage survival (at time of sacrifice: 13th day) was better in Mg-supplemented mice (Fig. 2C,D).

Oncogenic agents that cause membrane damage and abnormal magnesium levels. Oncogenic agents can disturb cell membrane functions with loss of intracellular (ic) Mg. Anghileri and his co-workers, having observed that a Mg-dependent enzyme (pyrophosphatase), which has some antimitotic and antineoplastic activity, is diminished in tumor tissue (*73*) despite increase in total tumor-content of Mg and even greater increases in tumor content of Ca (*74*), suggested that tumors might have a suboptimal Mg concentration or that its efficacy is inhibited by the excess Ca (*73*). They then demonstrated that animals fed 4-dimethylanimobenzene (DAB) did, in fact, exhibit changes in

hepatic cell ionic permeability, with mitochondrial damage, Ca influx, and Mg efflux, which triggers the development of cholangiocarcinoma (*75–77*). Immediately after starting the DAB feeding, the blood Mg levels rose, a reflection of release of ic Mg (*77*). In the hepatic cancer caused by thioacetamide, the rise in hepatic Ca preceded that of Mg, and the investigators postulated that it was the increase in ic Ca that was etiologically related to the impending neoplasm (*78*). Rubin (*80*) has suggested that stimulation of cell growth by excess Ca could be caused by displacing Mg from membrane binding sites. This is an accord with the DAB-induced acute increase in blood Mg (*77*) and the lower Mg than Ca levels in hepatic tumors when compared to normal liver. The most notable change was in the phospholipid–Mg complex, which Anghileri (*79*) suggested might be a definitive alteration responsible for the abnormal ionic permeability of precancerous and cancerous cells.

It might be oncogen-perturbed membrane function that is responsible, first for the loss of essential ic cations, such as Mg and K, and later for the accumulation of excessive Ca, Na, and even Mg, as it is in hypoxia-damaged myocardial cells (*81*). Polimeni and Page (*82*) have proposed that the accumulation of Mg, in this case, might be mediated by degradation of adenine nucleotides with ic release of inorganic phosphate, with which the Mg reacts, becoming nonfunctional (*81*). Wallach (*83*) has shown that (hepatic) cell membranes exert a major, direct control over ic Mg levels that is dependent on its binding to cellular ligands and influenced by alterations in extracellular pH and Ca concentrations (*84*). Sanui (*85*) has shown that ic acidosis decreases binding of Mg to subcellular membranes. Oncogenic agents can directly lower tissue levels of Mg, and of such essential trace minerals as Zn or Se, that have anti-

TABLE 2

Oncogens Cause Membrane Damage and Abnormal Levels of Magnesium and Calcium

MITOCHONDRIAL DAMAGE
- DISRUPTION OF Mg - PHOSPHOLIPID COMPLEX ___
→ - ABNORMAL IONIC PERMEABILITY ↓, THEN ↑ Mg*, (Zn) ↑ Ca**

ACIDOSIS, HYPOXIA, ↑ ec Ca → ↓ Mg - BINDING TO CELL MEMBRANE LIGANDS; LOSS OF i.c. Mg; TRANSITORY ↑ BLOOD Mg

BERYLLIUM → DISPLACES Mg IN BONE

IRRADIATION → MALABSORPTION → ↓ Mg (Zn); MOBILIZATION CELL Mg
+ FREE RADICALS (↑ Zn, Se, E-REQUIREMENTS)

* ↑ Mg IN TUMOR AS: (1) REQUIRED NUTRIENT FOR ACTIVE GROWTH
(2) PO_4 - PRECIPITATE (Pi FROM DEGRADED ADENINE NUCLEOTIDES)

** ↑ Ca IN TUMOR: (1) DISPLACES Mg FROM BINDING SITES → Mg LOSS
(2) INCREASES MITOSIS
(3) PO_4-PRECIPITATE

neoplastic activity (*infra vide*), and it has been postulated that this effect can contribute to their carcinogenicity (*86–88*). Beryllium, which is a potent Mg antagonist (*89*), has produced osteogenic intramedullary sarcoma with markedly subnormal Mg (and Ca) tumor levels in rabbits (*90*) (Table 2).

There is a much higher incidence of lymphomatous neoplasms (and of uterine adenocarcinoma) in mice that are exposed to multiple sublethal doses of X-irradiation when they are maintained on a purified diet, as compared to a natural diet (*91*). Whether this might be a result of magnesium deficiency seems plausible in view of the experimental and clinical evidence of magnesium malabsorption caused by irradiation (*92*).

Magnesium Levels in Experimental and Human Cancers

Although most of the experimental evidence indicates that loss of cellular Mg plays a role in carcinogenesis, once the neoplasm has developed it is difficult to predict whether Mg levels will be depressed or elevated. They have persisted at low values in human osteogenic sarcomas (*93*), and low serum Mg levels have also been reported in patients with malignant neoplasms (*94–96*), and even in patients with breast carcinoma, who have been reported to have high blood (*97, 98*) or tumor (*99–102*) Mg levels. The blood levels of Mg in patients with leukemia are inconsistent. They seem to depend on the nutritional status, drug therapy, and type of leukemia (*103*), and perhaps the stage of the disease. Rosner and Gorfien (*104, 105*) reported elevated plasma and blood cell Mg levels in patients with chronic lymphatic leukemia and chronic myeloid leukemia. Mg-responsive hypocalcemia and hypomagnesemia was found in acute leukemia of childhood by Jaffe et al. (*95*), whereas patients with acute leukemia have developed significantly increased serum Mg during therapy (*103*)—suggesting its release from damaged malignant cells. Anghileri (*74, 106*) has shown that the Mg concentration in tumors is highest at the time of fastest growth, a not surprising observation in view of the high Mg requirements for metabolism and growth (*80*). Collery et al. (*107*) have reported cyclic variations in plasma and erythrocyte Mg levels of cancer patients, the more malignant the growth, the shorter the intervals between peaks of levels.

Magnesium and Immunosurveillance against Cancer

Magnesium deficiency impairs host defenses. The thymic abnormalities produced by magnesium deficiency, and the in vitro thymocyte abnormalities produced by magnesium inadequacy in the culture medium, *supra vide*, suggest that magnesium deficiency might impair cell-mediated host surveillance against neoplasms caused by a variety of oncogenic agents or contributed to by other deficiencies. Thymic atrophy has been mentioned in young rabbits (*108*) and in calves (*65*) on magnesium-deficient diets, as well as in rats (*43, 47*). Other immunologic defects have been associated with low Mg levels. These include impaired granulocyte activity: clumping, adhesiveness,

and phagocytosis (*43, 57, 109–115*) and depressed antibody production (*43, 114, 116–118*).

Possible relationship of abnormal pyridoxine metabolism of cancer patients to Mg-deficiency and impaired host defenses. Abnormal tryptophan metabolites (indicative of disturbed pyridoxine metabolism) have been reported in patients with bladder cancer (*119–126*), and in many with breast cancer (*126–130*). Two of the abnormal metabolites found in the urine: 3-hydroxyanthranilic acid (OHA) and 3-hydroxykynurenine have induced bladder cancer (*131*) and leukemia (*132*) in animals. Since OHA is a strong inhibitor of oxidative phosphorylation, and in particular of α-oxoglutarate oxidation—steps that require Mg as a cofactor (*89, 133, 134*)—the possibility that Mg deficiency might be participatory should be explored. Aikawa (*135*) has shown that a pyridoxine antagonist causes mobilization of tissue Mg, and that pyridoxine administration increases Mg uptake. Rigo et al. (*136*) showed that prolonged vitamin B_6 deficiency produces hypomagnesemia. The transitory hypermagnesemia, produced by Aurousseau et al. and Durlach (*137, 138*) during pyridoxine depletion might be analogous to that seen in rats with B_6-antagonist-caused loss of tissue Mg (*135*). It was reversed by pyridoxine supplementation (*135, 137, 138*) to the extent of producing hypomagnesemia—perhaps as the Mg moved into the cells (*137, 138*).

Abnormal tryptophan metabolism has also been seen in patients with Hodgkin's disease (*139–141*), which DeVita et al. (*141*) have correlated with the anergy of that disease, and that is caused by pyridoxine deficiency (*142–144*). Perhaps deficiencies of both Mg and pyridoxine intensify susceptibility to carcinogens.

Abnormal host defenses and cancer. It is not surprising that Hodgkin's disease and other lymphomatous or leukemic neoplasms are associated with impaired host defenses (*139–141, 145–150*), since these are diseases of cells involved in immunologic processes. Fairley (*151*) evaluated the work done on immunity in malignant disease to 1969, and noted that the optimism occasioned by the early observation that normal dogs rejected transplanted sarcoma by flooding it with lymphocytes and plasma cells (*152*) was followed by prolonged pessimism when hundreds of studies failed to prove relevant to the human disease. He reviewed the evidence that victims of cancer have altered immune mechanisms. Klein (*153*) and Allison (*154*) have pointed out that neonatal thymectomy, treatment with antilymphocyte serum, or whole-body irradiation can eliminate or decrease resistance to tumor growth or spread. Since Mg deficiency in young animals causes thymic abnormalities, and irradiation causes Mg loss, *supra vide*, and since immunoimpairments resembling those seen in cancer patients have been produced by Mg deficiency in vivo and in vitro, *supra vide*, it is possible that deficiency of this macromineral, which is not uncommon early in life (*155, 156*), might be contributory to susceptibility to cancer.

TRACE MINERAL DEFICIENCIES IN CANCER

The possibility that trace metal (e.g., Se and Zn) deficiencies might contribute to susceptibility to cancer is actively being investigated. Brief note is taken here of aspects of these deficiencies that indicate interrelationships and imbalances among those nutrients that might contribute to susceptibility to oncogenic factors. For example, antineoplastic chemicals are often also carcinogenic, and the paradoxical effects have been attributed (in the case of agents that bind or remove minerals) to elimination of essential metal–enzyme components or cofactors, anti-oxidants, or free-radical scavengers (*87, 88*).

Selenium Deficiency in Cancer (*Fig. 3*)

Interest developed in Se as an essential element, the major effects of which (like vitamin E) were: (a) in protecting cellular and subcellular membranes from damage caused by lipid-peroxidation and free-radical reactions (*157–159*); and (b) in maintaining normal oxidative metabolism (*160*), an enhancing effect on the α-ketoglutarate system having been demonstrated (*161*). The epidemiologic data, showing that residents of areas high in Se are at lower risk of cancer than are residents of areas low in Se (*162–166*) are in concordance with Szent-Györgi's (*167*) suggestion that electron transfer reactions are important in control of cell division and that abnormalities (such as are produced by excess free-radicals) can lead to cancer. Shamberger et al. (*162*) have found that blood-bank specimens from low Se areas were low in Se, and also showed lower blood Se in cancer victims than in normal subjects (*166*). They have also presented evidence that peroxidation of food fats gives rise to mutagens (*168*). Aleksandrowicz et al. (*169–171*) have shown still another way in which Se might protect environmental oncogens. They have prevented aflatoxin's mutagenic effects on cultured lymphocytes by addition of Se to the medium, and suggest that Se might protect against the oncogenicity of toxins produced by common (Zn-requiring) fungi by inhibiting their immunosuppressant effects. Schrauzer et al., having correlated low blood Se levels of cancer patients with subnormal sulfhydryl, anti-oxidant activity (*172*), demonstrated Se's antineoplastic activity in experimental models (*173–176*).

Possible interrelations among selenium, vitamin E, and magnesium (*Fig. 4*). It would be interesting to ascertain whether susceptibility to Se-deficiency-related cancer might be influenced by the status of Mg. For example, might the protective effective of Se or vitamin E against lipid–peroxide- and free-radical-induced membrane damage (*157, 159*) be intensified by Mg, the deficiency of which alone causes cellular and subcellular membrane damage (*80, 81*)? The impaired erythrocyte membrane stability that is produced by vitamin E deficiency in rats (*177, 178*) is not reversed or protected against by Se (*178*). It resembles, however, that seen in infants (*179*), particularly when

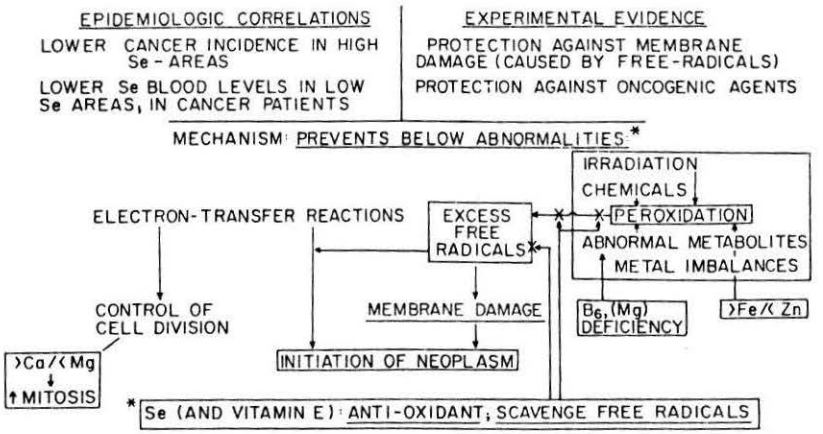


FIG. 3. Selenium deficiency and cancer interrelations with other imbalances contributing to excess free radicals and peroxidation.

bottle-fed rather than breast-fed (*180*), or premature (*181*), and those infants are not only prone to vitamin E deficiency (*179–181*), but also to Mg deficiency (*155*, *156*). There is direct evidence that the red blood cell membranes of Mg deficient rats are abnormal (*182*) and that experimental Mg deficiency causes hemolysis (*40*, *64*). Schwarz (*158*) mentioned that Mg supplementation prevented signs of vitamin E deficiency. Also, muscle damaged by vitamin E deficiency is low in Mg (*183–185*), and Mg deficiency intensifies the muscle degeneration of vitamin E deficiency (*186*).

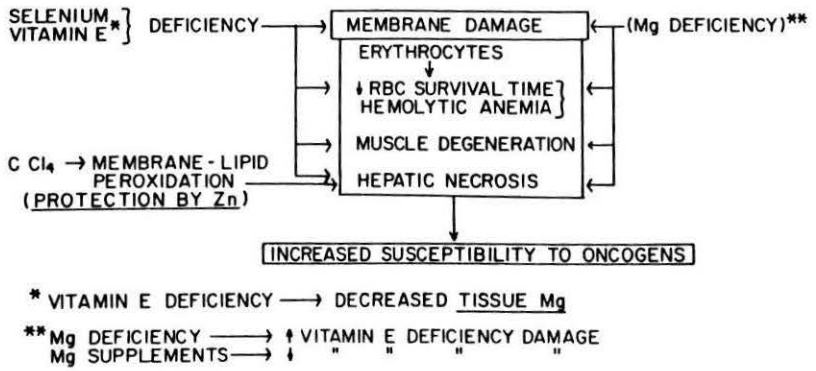


FIG. 4. Selenium, vitamin E, and magnesium deficiencies: role in membrane damage and oncogenesis.

ZINC DEFICIENCY IN CANCER

Most of the evidence that Zn deficiency might play a role in the pathogenesis of cancer is indirect. It has not been implicated in epidemiologic correlation of geological factors and cancer. However, there is a high incidence of cancer, usually at a late phase, in several diseases characterized by Zn depletion. For example, alcohol causes zincuresis (*187*, *188*) as does liver disease, whether it is caused by alcoholism or viral hepatitis (*189–191*). Protein-calorie-malnutrition (PCM) is associated also with diarrhea and mineral—including Zn—depletion in infancy (*192*, *193*), as are other forms of intestinal malabsorption such as steatorrhea (*194*), regional ileitis (*195*), and other inflammatory bowel diseases and conditions with massive loss of intestinal secretions (*196*). Hepatic cirrhosis and carcinoma are high in frequency in areas in which PCM is common (*197*, *198*), and hepatic injury including cancer has been reported in adult coeliac disease (*199*). Regional ileitis (*200*) and adult sprue (*201*, *202*) are also associated with a high incidence of intestinal cancer and of small bowel lymphoma (*202*, *203*). Alcoholics, who often also have malabsorption, are unduly prone to head and neck cancer (*204–206*). To attribute these disorders to Zn deficiency alone is not possible, since all are associated with multiple nutritional deficiencies, including that of Mg. In the case of acrodermatitis enteropathica (AE) a genetic disease that causes subnormal intestinal absorption of Zn (*207–209*), and that responds to Zn supplementation of AE infants (*207–212*) and of certain strains of calves that develop AE (*213*), Zn deficiency seems the predominant factor. Thus the T-cell dysfunction (*211*, *212*, *214*) and subnormal chemotaxis of monocytes and granulocytes of AE infants (*209*, *215*), and the thymic hypoplasia of AE calves (*212*, *213*), and the immunologic improvement produced by Zn supplements (*209*, *211–213*, *215*) indicate an important role of Zn in immunocompetence. Zn-deficient rats have exhibited marked inhibition of T-cell immunity (*216*) and lesser suppression of humoral responses (*216*, *217*). Although these findings have been considered explicatory of the increased susceptibility to infection caused by Zn deficiency, they may also indicate suppressed immunosurveillance against cancer. In fact, Zn-deficient rats have been shown by Mathur (*218*) to develop malignant changes after palatal application of 4-nitroquinoline N-oxide, and by Fong et al. (*219*) to increase the incidence and shorten the lag time for induction of esophageal tumors by methylbenzylnitrosamine. Pories et al. (*220*) propose that Zn deficiency can predispose to cancer by: (1) decreasing immunosurveillance, (2) interfering with normal healing with resultant prolonged inflammation and epithelial overgrowth, and (3) increasing tissue-susceptibility to mitogens and other toxins (*221*).

Zn protects against cell damage that can allow for initiation of the neoplastic process. Zn administration has prevented carbon tetrachloride (CCl_4)-induced hepatic cirrhosis (*222*), an effect that Chvapil et al. (*223*, *224*) attribute to Zn protection against CCl_4 peroxidation of the lipids of intracellular membranes. They also showed that Zn inhibits membrane

lipid-peroxidation in normal rats, with resultant increased membrane stability (*225*). This anti-oxidant activity might be protective against oncogenic agents, supra vide. Zn has, in fact, shown protective activity in several experimental oncogenic models. Gunn et al. (*226*, *227*) halved the incidence of cadmium (Cd)-induced sarcomas in rats, and prevented Cd-induced interstitial cell testicular tumors of rats and mice by Zn injection. Poswillo and Cohen (*228*) inhibited DMBA-induced cheek tumors of hamsters, an effect confirmed by Edwards (*229*). Zinc has inhibited initiation of transplanted tumor growth in recipient mice: sarcoma 180 (*230*) and Lizio leukemia (*231*), and prolonged survival of mice injected with BES 147 lymphatic leukemia cells (*231*).

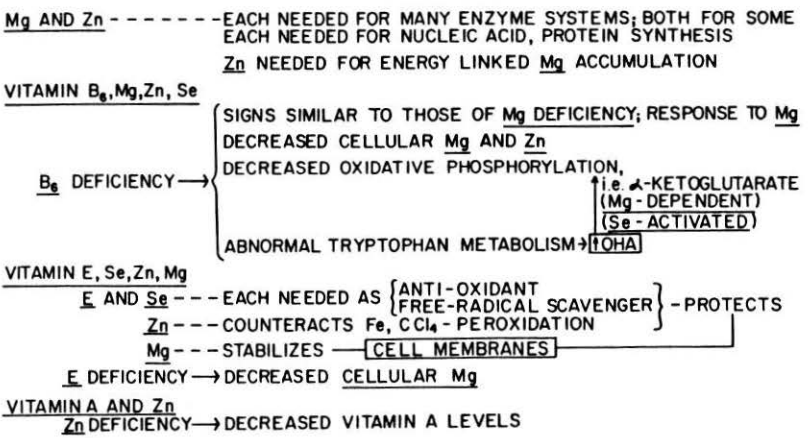
INTERRELATIONS AMONG ZINC, MAGNESIUM, AND VITAMINS

Declining Intakes, Particularly Early in Life

As with Mg, the intake of which has been declining during this century [the greatest impact being on those with the greatest rate of growth, with infants likely to be at greatest risk (*155*, *156*)], the falling Zn intake may impact most on infants. Schroeder (*232*) has shown that food processing causes substantial Zn loss, and Sandstead (*233*) reports that pregnant American women ingest diets that are marginal or deficient in Zn. Hambidge and Droegemueler (*234*) found that even healthy women from middle and upper socioeconomic groups show significant declines in plasma and hair Zn levels from the 16th to the 38th week of gestation. Study of hair Zn levels in different age groups from that same socioeconomic category (to exclude manifest undernutrition) showed that American infants from three months to four years of age had a disproportionate representation among those with evidence of Zn depletion (*235*), a finding not true for Thai infants (*236*) or British bottle-fed infants (*237*). Thus Walravens and Hambidge (*238*) consider this finding in American young children not a physiological variant, but an indication that the neonate does not acquire sufficient Zn reserves *in utero* to meet growth needs during infancy, particularly when fed formulas, the protein content of which is reduced to that comparable to breast milk. Such formulas deliver less than half the Zn provided by mother's milk. Similarly, cow's milk-fed infants are more vulnerable to magnesium deficiency than are breast-fed infants (*155*, *156*). During the neonatal period, hypocalcemic seizures are commonly treated with calcemic agents, to which they do not respond as well as they do to Mg therapy (*239*). Hypercalcemia is a risk among older infants who are hyperreactive to vitamin D (*240*, *241*). Simultaneously low Mg and high Ca levels are damaging to arteries (*242*), heart, kidneys, and bone (*242*, *243*). In view of the thymic abnormalities caused by high Ca/low Mg dietary intakes in rats (*47*, *48*), and the lymphocytic dysfunctions produced by abnormal concentrations of Ca^{2+} and Mg^{2+} in culture media (*51–57*, *supra vide*), it is

TABLE 3

Metabolic Interrelationships among Nutrients whose Deficiencies Predispose to Cancer



conceivable that unphysiologic levels in vivo might interfere with immunocompetence.

METABOLISM AND VITAMINS (TABLE 3)

Both Zn and Mg are required for nucleic acid synthesis and activity of many enzymes, and each participates in maintaining membrane stability. Of particular interest, in considering Zn/Mg interrelationships is the requirement for Zn (*133, 244–247*) by enzymes and for processes that are Mg dependent (*245, 246*). Brierley et al. (*248*) have shown that Zn is necessary for energy-linked Mg accumulation by (heart) mitochondria. It may be that the linked Zn/Mg metabolic roles are responsible for the comparable inconsistencies in their levels in patients with neoplasms. The unreliability of Mg levels have been considered here (*supra vide*); the contradictory data as to Zn levels have been considered by Pories et al. (*220*). Another provocative metabolic interrelationship between Zn and Mg is that with pyridoxine. Many of the metabolic steps are Mg dependent (*supra vide*); pyridoxal phosphokinase is also Zn dependent (*247*). Tissues of pyridoxine-deficient rats lose not only Mg (*135, 137, 138*), but also Zn (*249*).

The role of Zn in counteracting membrane lipid peroxidation is reminiscent of the effects of Se and vitamin E. And finally, Vallee et al. (*250*) noted that there was a metabolic interrelationship between Zn and vitamin A, deficiency of which has been implicated (by epidemiologic studies) in cancers of the upper alimentary tract (*251, 252*) and of the respiratory tract (*252–254*).

Cassidy et al. (*255*) have reviewed the evidence that animals fed a Zn-deficient diet develop markedly reduced plasma vitamin A levels, and are considering the possibility that some of the manifestations of alcoholic cirrhosis might be mediated by the observed vitamin A deficiency. Shamberger and Willis (*256*) have reviewed the evidence that vitamin A has inhibited several experimental cancers.

Magnesium and Zinc Depletion in Treating Cancer

Because of the importance of both Mg and Zn in metabolic cancer cells, means of depleting the body of these minerals have been employed in antineoplastic programs. De Wys and Pories (*257*) have reviewed the rationale for nutritionally depleting Zn, and the experimental tumors, which tend to concentrate Zn, that have responded to this approach. Mg depletion by hemodialysis has also been employed to inhibit growth of experimental and clinical advanced malignancies (*258–260*). Since these elements are needed for normal rapidly metabolizing cells, and their deficiencies are associated with many adverse effects, this approach is at least as hazardous as is the use of antimetabolites.

CONCLUDING COMMENTS: COMPLEXITIES IN ISOLATING DEFICIENCIES THAT CONTRIBUTE TO ONCOGENESIS

The most important roles of the essential macro- and microminerals, absolute or relative deficiencies of which are implicated in the development of neoplasms, are: (a) maintenance of membrane stability (directly or by protecting against damage by free radical or other damaging agents), and (b) maintenance of immunosurveillance against aberrant cells. Emphasis has been placed, in this paper, on Mg, which plays intrinsic roles in both functions, and has been shown to protect against several types of experimental tumors, and for which there is epidemiologic supporting evidence. The negative attitude towards Mg in cancer studies originally derived from early studies showing enhancement of the growth of some experimental tumors, an attitude that has been reinforced by recent use of Mg depletion to treat cancer. These experiences parallel those encountered with Zn. Careful scrutiny of how best to use both prophylactically, as well as the other essential trace elements and vitamins, is warranted. Interrelationships of deficiencies, imbalances, metabolic errors, and poisons and oncogenic agents in the environment make isolation of a single deficiency as *the* causative factor in carcinogenesis unlikely.

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