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EFFECTS OF ESTROGEN ON TISSUE MAGNESIUM CONTENT POSSIBLE INFLUENCE ON CARDIOVASCULAR AND BONE DISEASE

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INTRODUCTION.

The greater resistance of female laboratory animals than males, and of young women than men to cardiomyopathic drugs or disease, respectively, calls attention to the possibility that female sex hormones may be cardioprotective. However, the lowering of plasma magnesium in women and animals on oral contraceptives would appear, at first glance, to increase the risk of cardiovascular disease, both because decreased plasma magnesium has been correlated with increased risk of intravascular coagulability, and because magnesium has been established as a cardioprotective agent. Further analysis of the finding with the oral contraceptives, of the effects of estrogens, and of the sex difference in magnesium retention and tissue levels, points to the likelihood that the cardioprotective effect of estrogens may be mediated by their enhancement of tissue retention of magnesium.

TABLE I
SEX AND AGE DIFFERENCES IN MORTALITY RATES FROM ARTERIOSCLEROTIC HEART DISEASE (PER 100,000 WHITE POPULATION)

	MEN	WOMEN	SEX DIFFERENCE MEN/WOMEN
25-29	4.3	1.0	4.3:1
30-34	15.8	2.7	5.9:1
35-39	50.1	6.5	7.7:1
40-44	124.2	19.4	6.4:1
45-49	254.9	40.8	6.2:1
50-54	462.6	85.6	5.4:1
55-59	719.0	183.6	3.9:1
60-64	1,119.1	384.4	2.9:1
65-69	1,622.0	687.5	2.4:1
70-74	2,291.1	1,211.0	1.9:1
75-79	3,243.2	2,053.9	1.5:1
80-84	4,802.5	3,508.1	1.3:1
85- >	7,248.7	6,233.7	1.2:1

(Adapted from J.S. Stamler in Atherosclerosis and its Origins, Academic Press, 1963)

CARDIOPROTECTIVE EFFECT OF ESTROGENS.

It is well known that pre-menopausal women are at much less risk of cardiac disease than are men, but that in the years following the menopause their susceptibility to cardiac disease increases steadily until, during old age, there is little or no sex difference in incidence of cardiovascular disease (1, 7, 84) (Table I). This presumptive evidence of the cardioprotective effects of female sex hormones is supported by several laboratory findings. Female dogs and rabbits have been shown to be more resistant than males to digitalis-induced arrhythmias (27, 71). GRINNELL and SMITH (27) have shown that castrated females are as susceptible to digitalis toxicity as males, and that estrogen replacement (2 mg/day) markedly improves their resistance to arrhythmias, but not to the extent seen in estrus (Table II). Pregnant dogs are more resistant than non-pregnant

TABLE II
SEX DIFFERENCE
ESTROGEN EFFECT ON DIGOXIN TOXICITY IN DOGS

	ARRHYTHMIA (AV. MINUTES TO ONSET	FATE
7 MALES	13.6	FIBRILLATION (7) — 1 SURVIVED ON TREATMENT, 1 TERMINATED, 5 DIED
14 FEMALES (CASTRATE)	14.3	FIBRILLATION AND DEATH IN ALL
13 FEMALES (CASTRATE + ESTROGEN)	31.7	ALL SURVIVED
4 FEMALES (ANESTRUS)	26.0	ALL SURVIVED
3 FEMALES (ESTRUS)	71.6	ALL SURVIVED

(Adapted from E.H. Grinnel and P.W. Smith, Proc. Soc. Exp. Biol. Med., 94: 524-527, 1957

females to necrotizing arteritis produced by a high fat diet and renal insufficiency (HOLMAN and JONES) (32). Female rats are more resistant than males to isoproterenol-myocardial necrosis, an effect that RONA *et al.* (72, 73), attributed to the slower rate of growth of the females. Advanced pregnancy in rats has been shown to protect against: (1) dihydrotachysterol-induced arteriosclerosis (SELYE) (80); (2) the cardiovascular necrosis and calcification of vitamin D excess (POTVLIEGE) (67); (3) phosphate + corticosteroid-induced cardiomyopathy (SELYE) (81); and (4) hyperparathyroid myocardial necrosis (LEHR *et al.*) (40, 43, 47-52). The cardioprotective effect of late pregnancy against high doses of parathyroid hormone was shown by LEHR and KRUKOWSKI (44, 47) to be effected by an ovarian factor, which was more likely to be estrogen than progesterone. Additional evidence of estrogen's cardioprotective influence has been provided by SELYE *et al.* (82, 83) who have shown that 10 mg/kg/day of estrogen (ethylestrenol) was almost fully protective against steroid + PO_4, and digitalis-induced cardiomyopathies (82). In the dihydrotachysterol model (83) 2 mg/kg/day was almost fully protective. RONA *et al.* (73) however, were unable to protect against isoproterenol-cardiotoxicity with estrogen (Tables III, IV).

TABLE III

PROTECTION AGAINST CARDIOVASCULAR LESIONS BY ADVANCED PREGNANCY

	LESION	PRODUCED BY	INVESTIGATOR
DOGS	NECROTIZING ARTERITIS	HIGH FAT INTAKE + RENAL INSUFFICIENCY	HOLMAN & JONES (1953)
RATS	ARTERIOSCLEROSIS	DIHYDROTACHYSTEROL	SELYE (1958)
RATS	CARDIOVASCULAR NECROSIS AND CALCIFICATION	VITAMIN D EXCESS	POTVLIEGE (1962)
RATS	MYOCARDIAL NECROSIS	PO_4 + CORTICOSTEROID	SELYE (1957)
RATS	MYOCARDIAL NECROSIS	PARATHYROID EXCESS	LEHR & KRUKOWSKI (1961, 1962)

How estrogen exerts its effect on the heart is uncertain. That there is a marked increase of cardiac output during pregnancy, that returns to previous non-pregnant levels, was demonstrated in 1915 by LINDHARD (56) and verified by other investigators since then (2, 5, 10, 28, 66), an effect which has also been demonstrated in women on estrogen + progesterone oral contraceptives (87). UELAND and PARER (85) have demonstrated that infusion of estrogens into sheep mimics the cardiovascular effects of pregnancy, and commented that estrogen seem to have a direct cardiac glycosidic effect, increasing the force of contraction of cardiac muscle. WALTERS and LIM (87) have considered the direct effect of estrogen on the actomyosin-ATP and contractile mechanism of the myocardium (CSAPO (11); KING *et al.* (54)) as possibly explanatory.

ESTROGEN EFFECT ON MAGNESIUM LEVELS.

The possibility that the cardioprotective effect of estrogen may be mediated through an increased tissue retention of magnesium should also be considered (Table V). Metabolic balance studies have shown that young women on a marginal magnesium intake tend to be less susceptible than men to loss of magnesium (SEELIG (79); DURLACH *et al.* (4, 17, 20). Since plasma Mg tends to be lower in young women, particularly when they are on oral contraceptives (15, 19, 23-25), than it is in men (13, 24, 74), one must examine other tissues for differences in Mg content.

Estrogen has been shown to increase the myometrial content of castrated animals (BEST and PICKLES (8); CSAPO (11); WALAAS (86). Higher non-target tissue levels have been seen after estrogen administration, and better retention of magnesium has been found in females than in males. WHITFIELD and TIDBALL (89) have found that estrogen (1 mg estradiol/day), given to ovariectomized rats on a Mg-deficient diet, protected against development of the deficiency syndrome and against loss of skeletal muscle Mg and as compared with castrated Mg-deficient rats not on hormonal replacement therapy. WATCHORN and MCCANCE (88) found that serum Mg levels of male Mg-deficient rats fell to lower levels than did those of females, and that their general condition was generally poorer. ALCOCK and MACINTYRE (3) found

TABLE IV

PROTECTION AGAINST CARDIOVASCULAR LESIONS BY ESTROGEN

	ABNORMALITY	PRODUCED BY	ESTROGEN* PROTECTION	INVESTIGATOR
DOGS	ARRHYTHMIA	DIGOXIN	2 mg/day	GRINNELL & SMITH (1957)
RATS	CARDIOMYOPATHY	PO_4 + CORTICOSTEROID	10 mg/day	SELYE (1970)
		DIGITALIS		
RATS	CARDIOMYOPATHY	DIHYDROTACHYSTEROL	2 mg/day	SELYE (1970)
RATS	CARDIOMYOPATHY	ISOPROTERENOL (80 mg/kg)	No Protection	RONA et al (1963)

*Magnesium administration also protects

TABLE V

ESTROGEN EFFECTS ON MAGNESIUM LEVELS

METABOLIC BALANCE: YOUNG WOMEN RETAIN MORE MAGNESIUM ON MARGINAL INTAKE (THAN MEN)	SEELIG (1964) DURLACH et al (1969,1970)
PLASMA MAGNESIUM: LOWER IN WOMEN ON ORAL CONTRACEPTIVES; RELATIONSHIP TO MENSTRUAL CYCLE	GOLDSMITH et al (1963,1966,1970) DURLACH (1970) DeJORGE et al (1967)
MYOMETRIAL MAGNESIUM: HIGHER FOLLOWING ESTROGEN TREATMENT OF CASTRATED ANIMALS	BEST, PICKLES (1965) CSAPO (1956)
SKELETAL MUSCLE MAGNESIUM: HIGHER FOLLOWING ESTROGEN TREATMENT OF CASTRATED ANIMALS ON MAGNESIUM DEFICIENT DIET	WHITFIELD & TIDBALL (1968)
BONE MAGNESIUM: HIGHER ON ORAL CONTRACEPTIVES (IN RATS)	GOLDSMITH & BAUMBERGER (1967)

that young male rats on an ample dietary intake of magnesium retained more magnesium than did young females; on a deficient diet, they lost more magnesium daily (Table VI). The somewhat greater susceptibility of male than female Mg-deficient rats to develop elevated plasma cholesterol (36), and the significantly higher liver Mg levels of healthy young female than male rats (35) show a trend in the same direction, as do the elevated bone Mg levels of rats on estrogen/progesterone (24).

The decrease in plasma magnesium levels of women on estrogen/progesterone contraceptives, reported in detail by GOLDSMITH *et al.* (23-26), and confirmed by others (de JORGE (15); DURLACH (19), has been correlated with the cyclic increase in endogenous estrogen secretion (13, 23, 26, 64). This drop in blood Mg has created concern lest this contribute to increased risk of thrombo-embolic phenomena (19, 23, 25, 57). DURLACH (18, 19), who verified the increased platelet aggregation caused by estrogen-induced depression of plasma Mg, emphasized the importance of administering magnesium to patients on estrogen therapy, whether as contraceptives, or for treatment of prostatic carcinoma or osteoporosis.

TABLE VI

SEX DIFFERENCE IN MAGNESIUM BALANCE OF RATS ON ADEQUATE AND DEFICIENT MAGNESIUM INTAKES

	MAGNESIUM INTAKE (m Eq/Day)	MAGNESIUM EXCRETED (m Eq/Day)		DAILY MAGNESIUM BALANCE (m Eq/Day)
		FECAL	URINARY	
MALES	4	31.6 ± 8.1	5.2 ± 1.2	-32
FEMALES	4	23.0 ± 2.3	2.0 ± 0.2	-20
MALE	272	127.0 ± 10.2	71.9 ± 4.0	+73
FEMALE	272	139.0 ± 7.6	94.3 ± 5.3	+39

Adapted from Alcock and Macintyre, Clin. Sci. 22: 185-193, 1962

ESTROGEN/PARATHORMONE: INFLUENCE ON BONE, HEART, AND MAGNESIUM RETENTION.

The use of estrogen in the treatment or prevention of osteoporosis (14, 61, 65, 90), which increases in frequency after the menopause (14, 33, 60, 61, 63, 65), as does the incidence of the bone-wasting form of hyperparathyroidism (59, 63), suggests an interrelationship of parathyroid hormone and estrogen. NORDIN *et al.* (33, 65,90) having observed that the bone loss of aging begins between 46 and 55 years of age in women, and is far more frequent thereafter than in men, have suggested that estrogens inhibit the bone-resorbing action of parathormone (33). Direct evidence of estrogen/parathormone antagonism on bone accretion and resorption of calcium has been provided by RANNEY (69). Magnesium bone levels are also affected in opposite directions. MARTINDALE and HEATON (58) have shown that parathyroid hormone increases the rate of magnesium loss from bone *in vitro*; GOLDSMITH and BAUMBERGER (24) have shown that female sex hormones raise bone levels of Mg in rats. The fact that estrogen lowers plasma Mg may shed some light on the higher incidence of bone wasting disease when the endogenous secretion of estrogen decreases. Hypomagnesemia has been clearly demonstrated, by BUCKLE *et al.* (9), to stimulate parathyroid secretion, even when calcium levels are kept constant. The effect of parathyroid secretion is to mobilize, not only calcium, but magnesium from bone (16, 22, 29). It is plausible that the estrogen-lowered plasma Mg may stimulate parathyroid secretion. If that stimulation causes parathyroid hyperplasia, as LARVOR *et al.* (41) have shown hypomagnesemia to do in calves, when the ovaries cease functioning the hyperplastic parathyroids may continue to mobilize the bone minerals excessively, without counteraction by estrogen.

The role of parathyroid hormone in soft tissue transport and homeostasis of Mg has not as yet been elucidated. It should be noted, however, that para-

thyroid hormone participates importantly in the normal transport of magnesium and inorganic phosphorus into the mitochondria (39, 70, 75, 76). LEHR *et al.* (44, 45, 53, 54) have, in fact, demonstrated an early drop in myocardial Mg and PO_4 that preceded cardiac necrosis in parathyroidectomized phosphate-loaded rats. Such decreases in myocardial magnesium have also been reported in other experimental cardiomyopathies (6, 12, 21, 30, 31, 38, 45, 54, 62, 77, 78) and in hearts of patients who died of myocardial infarcts (30, 37, 68, 78).

LEHR *et al.* (42, 46, 55) have demonstrated that reniprival cardiac necrosis does not develop in parathyroidectomized rats, whereas the « corticosteroid phosphate » myocardial necrosis is dramatically aggravated in the absence of the parathyroid glands. The contrasting influence of parathyroidectomy under these two experimental conditions is explained by LEHR and KRUKOWSKI (46) as due to the effect of parathyroid hormone upon the availability of myocardial Mg. In the first instance, the overproduction of parathyroid hormone following bilateral nephrectomy causes continuous mobilization and thus enormous accumulation of phosphate in blood and soft tissues. In the second instance, the increase of parathyroid hormone secretion elicited by oral NaH_2PO_4 loading of intact rats is beneficial, since the phosphaturic effect of the hormone protects against phosphate accumulation in blood and soft tissues and the consequent danger of hypocalcemia and hypomagnesemia. Hence, in both models of experimental myocardial necrosis, hyperphosphatemia is the common denominator and Mg depletion by binding to phosphate may occur. The decreased availability of Mg for vital, intracellular metabolic processes may, in turn, constitute an important factor in the pathogenesis of the myocardial injury.

CONCLUDING REMARKS.

In view of the considerable evidence of the cardioprotective effect of magnesium, and of the loss of myocardial Mg early in the course of many cardiomyopathies, the loss of the Mg-retaining effect of estrogen may well contribute to the increased incidence of cardiac disease in aging women. Whether the increased bone pathology that is seen in women over the age of fifty is contributed to by a loss of skeletal Mg, is an unresolved question.

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SUMMARY.

Effects of estrogen on tissue magnesium content possible influence on cardiovascular and bone diseases

The sex and age differences in incidence of cardiovascular and bone-wasting diseases suggest that estrogen has a protective effect in these systems. Estrogen administration has, in fact, been shown to protect against cardiotoxic drugs in animals. The high incidence of osteoporosis in post-menopausal women may be related to the absence of estrogen's inhibition of parathyroid hormone-mobilization of bone minerals. The decrease of plasma levels of magnesium, induced by oral contraceptives, which may contribute to the enhancement of blood coagulability, is associated with increased bone deposition of magnesium rather than impaired intestinal absorption or increased urinary excretion of this element. The higher tissue levels of magnesium, and the greater resistance to dietary Mg-deficit of female versus male animals, and the better retention of Mg by young women than men on marginal Mg-intakes, supports the premise that estrogen may exert its cardioprotective effects by favorising tissue retention of magnesium.

RESUME.

Effet des œtrogènes sur le taux du Mg tissulaire : possible influence sur les maladies cardiovasculaires et osseuses

Les différences selon l'âge et le sexe dans la survenue des maladies cardiovasculaires et les décalcifications suggèrent que les œtrogènes ont un effet protecteur dans ces systèmes.

L'administration d'œstrogène protège effectivement contre les drogues cardiotoxiques.

La haute incidence des ostéoporoses chez la femme en phase post-ménopausique peut être due à l'absence d'inhibition par les œstrogènes de la mobilisation par la parathormone des minéraux osseux. La baisse de la magnésémie plasmatique provoquée par les contraceptifs « per os » qui peut contribuer à accroître la coagulabilité sanguine est associée à une augmentation de dépôt magnésique dans l'os plutôt qu'à une absorption intestinale diminuée ou une hyperexcrétion urinaire de cet élément. Les taux plus élevés de Mg tissulaire et la plus grande résistance à la carence magnésique expérimentale de la femelle par rapport au mâle ainsi que la rétention magnésique meilleure chez les jeunes femmes que chez l'homme d'apports

magnésiques marginaux supporte l'hypothèse selon laquelle les œstrogènes peuvent devoir leurs effets cardioprotecteurs à une rétention tissulaire magnésique accrue.

ZUSAMMENFASSUNG.

Wirkung des Estrogens auf den Magnesium Gewebsgehalt; Möglicher Einfluss auf Kreislauf und Knochen erkrankungen

Die Geschlechts-und-Alters unterschiede im Prozentsatz der kardiovaskulären Erkrankungen und Knochenatrophien, machen es wahrscheinlich, dass Estrogen eine Schutzwirkung auf diese Systeme ausübt. Der hohe Prozentsatz der Osteoporose in post-klimakterischen Frauen ist möglicherweise verbunden mit der Abwesenheit der durch Estrogen verursachten Hemmung der Knochen mineralmobilisierung durch das Hormon der Parathyroidea. Die Senkung der Magnesiumspiegels im Blutplasma, die durch orale Contraceptive (Empfangsverhütungsmittel) verursacht wird und die zur Steigerung der Blutgerinnung beitragen mag, geht Hand in Hand mit einer erhöhten Deposition des Magnesiums im Knochen und nicht mit einer Störung der Darmabsorption oder mit erhöhter Ausscheidung dieses Elementes im Harn. Der höhere Gewebsspiegel des Magnesiums, und der grössere Wiederstand gegen Magnesiummangel, in der Nahrung weiblicher Tiere im Vergleich zu männlichen Tieren, wie auch die bessere Retention des Magnesiums bei jungen Frauen im vergleich zu Männern im Fall marginaler Magnesiumeinnahme, unterstützen die Annahme dass die herzchützende Wirkung des Estrogens möglicherweise darauf beruht, dass Estrogen die Retention des Magnesiums im Gewebe begünstigt.

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