does not contain a Kpn I site (Fig. 4), three or more section of human DNA very closely related to pPE-4000 must be present on a chromosome other than 2, 5, 9, or 12. An unambiguous assignment of the various λB4-specific human DNA fragments has not yet been achieved.

Our data demonstrate that IFN-β–related DNA is dispersed in the human genome. The murine IFN-β system also appears to be complex. Skup *et al.* (*6*) reported the isolation of two distinct partial cDNA clones (20/11 and 3/10) that appear to correspond to murine IFN-β mRNA's. They based this conclusion on experiments in which the cDNA clones were immobilized on nitrocellulose filters and hybridized with IFN mRNA preparations, after which the hybridized mRNA was eluted and analyzed for IFN-β activity with a translation assay. Clones 20/11 and 3/10 are different from each other and are different from well-known murine IFN-β_1 cDNA (*7*). Finally, because the human 0.8-kb IFN-β_1 gene hybridized with DNA sections of length greater than 5 kb in each of the λB3 and λB4 clones, and because the IFN-β_1 gene lacks introns (*1*), the possibility arises that the IFN-β_1 gene may have arisen from the IFN-β–related DNA located on the other chromosomes through a process of gene conversion, as has been found in several other gene families (*8*). The observation that λB3 DNA not only hybridizes with an IFN-β_1 cDNA probe but also hybridizes with an IFN-α_1 cDNA probe reveals an unexpected facet of the human interferon gene family—the origins of the α and β interferon systems must be more closely intertwined than has been recognized thus far.

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Magnesium Deficiency and Hypertension: Correlation Between Magnesium-Deficient Diets and Microcirculatory Changes in situ

Abstract. *Rats maintained for 12 weeks on diets moderately or more severely deficient in magnesium showed significant elevations in arterial blood pressure compared to control animals. Examination of the mesenteric microcirculation in situ revealed that dietary magnesium deficiency resulted in reduced capillary, postcapillary, and venular blood flow concomitant with reduced terminal arteriolar, precapillary sphincter, and venular lumen sizes. The greater the degree of dietary magnesium deficiency the greater the reductions in microvascular lumen sizes. These findings may provide a rationale for the etiology, as well as treatment, of some forms of hypertensive vascular disease.*

Numerous hypotheses have been suggested to account for the development of primary hypertension in man (*1*), including salt (NaCl) intake, overall nutrition, and genetic make-up (*1, 2*). It has also been proposed that increased blood pressure is due to a supersensitivity of blood vessels to the constrictor actions of endogenous neurohumoral substances (for example, adrenergic amines, angiotensin, or vasopressin) or to a decreased sensitivity of blood vessels to endogenous vasodilator substances (for example, prostaglandins) (*1*). All of these hypotheses have generated some controversy, and exactly how a sustained increase in arteriolar and venular vascular tone is brought about in a variety of clinical and experimental forms of hypertensive disease remains a mystery (*1*).

Several recent studies point to a causal relation between decreased concentrations of magnesium ion (Mg^{2+}) in blood or tissues and hypertension; the incidence of hypertension is high in geographic areas with soft drinking water or magnesium-poor soil (*3–6*). Since 1925, it has been known that pharmacologic doses of magnesium salts can somehow produce hypotension and attenuate high blood pressure in hypertensive patients; more recently, long-term administration of lower doses of magnesium salts has decreased requirements for antihypertensive drugs (*7*). Hypomagnesemia has been reported in a number of hyperten-

Table 1. Influence of moderate and more severe dietary magnesium deficiency on arterial blood pressure, serum magnesium, and body weight of rats. Values are means ± standard errors. The number of animals in each group is given in parentheses. The corresponding values at the initiation of the experiments were as follows. Controls: 108.5 ± 8.8 mmHg; 0.95 ± 0.08 mmole/liter; 122 ± 8.2 g. Moderately Mg-deficient: 106.0 ± 9.6 mmHg; 0.96 ± 0.06 mmole/liter; 120 ± 8.4 g. Severely Mg-deficient: 108.00 ± 8.0 mmHg; 0.94 ± 0.08 mmole/liter; 124 ± 8.0 g. (N = 4 in each group.)

Parameter	Group			F-ratio
	Controls	Moderately Mg-deficient	More severely Mg-deficient	
Arterial blood pressure (mmHg)	110.6 ± 2.2 (11)	131.1 ± 2.0*† (12)	142.8 ± 3.4*† (8)	42.27
Serum Mg^{2+} (mmole/liter)	0.98 ± 0.02 (14)	0.66 ± 0.03*† (6)	0.27 ± 0.01*† (6)	242.8
Body weight (g)	303.2 ± 19.6 (14)	323.6 ± 18.8 (12)	322.8 ± 12.8 (8)	0.41

*Significantly different from controls by analysis of variance ($P < 0.001$). †By Scheffe's test any paired comparison among the groups for arterial blood pressure and serum Mg is statistically significant ($P < 0.05$).

sive patients in different geographic areas (*8*).

Artificial lowering of the Mg^{2+} content of isolated coronary, cerebral, and peripheral blood vessels from rats, rabbits, piglets, and dogs, as well as man, induces rapid, contractile responses and potentiates the actions of a variety of neurohumoral constrictor agents, including adrenergic amines and angiotensin (*9*). Acute hypermagnesemia inhibits the spontaneous tone of arteries and veins both in vitro and in intact animals, and decreases arterial resistance to blood flow (*9, 10*). Thus, evidence is accumulating to suggest that extracellular Mg^{2+} plays a critical role in the regulation of vasomotor tone.

It has been suggested that some forms of hypertension could be due to the direct effects of a hypomagnesemic state on arteriolar and venular tone (*6, 11*). The hypomagnesemia could produce progressive vasoconstriction of arterioles, precapillary sphincters, and venules in the microcirculation, and this would eventually increase overall systemic vascular resistance, curtail capillary blood flow, and result in hypertensive disease. To investigate the possibility that arteriolar, precapillary sphincter, and venular constriction can be produced in intact hypomagnesemic animals, we determined the influence of decreased dietary intake of Mg^{2+} on microvascular tone, blood pressure, and serum Mg^{2+} concentrations.

Young male Wistar rats (100 to 130 g) were given free access to a magnesium-deficient diet (Altromin C1035; Mg^{2+}, 5 mmole/kg; Ca^{2+}, 180 mmole/kg) for 12 weeks. Some rats on this diet had access to distilled water with 4 mmole of $MgCl_2$ per liter (moderately Mg-deficient); others had access to distilled water without $MgCl_2$ (more severely Mg-deficient). A third group of rats (controls) received a magnesium-enriched diet (Mg^{2+}, 80 mmole/kg; Ca^{2+}, 180 mmole/kg) for the 12-week period. Control rats were pair-fed to prevent differences in weight. After the 12-week period, rats from each group were lightly anesthetized with either pentobarbital sodium (30 mg/kg) or ketamine hydrochloride (50 to 65 mg/kg). Mean arterial blood pressure was measured by a cannulated femoral artery connected to a Statham pressure transducer. For determination of Mg^{2+} concentration in serum, blood was taken from the tail. After the addition of 5 percent trichloroacetic acid and 0.1 percent $LaCl_3$, the blood was centrifuged and the Mg^{2+} assayed by atomic absorption spectrophotometry on a Perkin-Elmer model 303. For the studies on the mesenteric microcirculation in vivo, lumen sizes of terminal arterioles (just before origin of metarterioles), precapillary sphincters, and venules (*12*) were measured quantitatively with an image-splitting television microscope recording system (*13*).

Measurement of arterial blood pressure revealed that the moderately and more severely magnesium-deficient rats had mean values approximately 20 and 32 mmHg, respectively, higher than the normotensive control animals (Table 1), despite the fact that the body weights of all three groups were comparable. The serum Mg^{2+} concentrations in the moderately and more severely magnesium-deficient rats were 67 and 28 percent, respectively, of the normotensive controls (Table 1).

Examination of the mesenteric microcirculation revealed fewer true capillary vessels and reduced blood flow in the capillaries, postcapillary venules, and collecting venules compared to control mesenteric microvasculatures. Measurement of the lumen sizes revealed that all three types of microvessels in the moderately as well as more severely magnesium deficient animals exhibited vasoconstriction or enhanced vascular tone. The vessel measurements also revealed that there is a progressive, quantitative reduction in lumen sizes (Fig. 1) as the degree of Mg^{2+} deficiency (assessed by serum concentrations) increases (Table 1). For example, the lumen sizes of precapillary sphincters were reduced by 13 percent in the moderately deficient rats and by 33 percent in the more severely deficient rats (Fig. 1). Similar, though less extreme, changes in lumen sizes were also seen in terminal arterioles and venules (Fig. 1). The intact microvessels of the magnesium-deficient animals also showed greater constrictor responses to neurohumoral agents, for example, adrenergic amines and vasopressin (*14*).

The effects of extracellular Mg^{2+} on

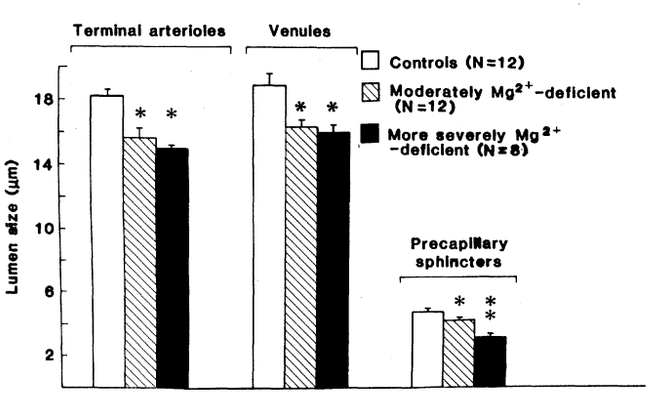

Fig. 1. Effects of 12 weeks of magnesium deficiency on lumen sizes of terminal arterioles, venules, and precapillary sphincters in rats. All values are means ± standard errors of the mean. Single asterisks signify mean values significantly different from controls ($P < 0.01$, analysis of variance). For comparison of terminal arterioles, venules, and precapillary sphincters, the F-ratios are 17.76, 8.89, and 15.93, respectively. Double asterisks signify values significantly different from controls and moderately Mg^{2+}-deficient rats ($P < 0.01$, Scheffe's test).

vascular tone are reflections of this metal's influence on membrane permeability to Ca^{2+} as well as on binding, translocation, and on membrane stability (*6, 9–11*). Studies show that Mg^{2+} sites in the blood vessel membrane can act physiologically to regulate entry and exit of Ca^{2+} (*6, 9, 11, 15, 16*). Lowering the concentration of extracellular Mg^{2+} increases total exchangeable and intracellular Ca^{2+} fractions in blood vessels (*6, 16*). Such findings indicate that when extracellular Mg^{2+} is lowered, Ca^{2+} influx is enhanced, causing contraction (*6, 9, 11, 16*). The potentiated constrictor responses to vasoactive agents in the presence of reduced extracellular Mg^{2+} are possibly also due to enhanced influx and translocation of Ca^{2+} into the microvascular smooth muscle cells. Since Mg^{2+} can affect Na^+-K^+ transport across cell membranes by way of Na^+,K^+-dependent adenosinetriphosphatase activity and can affect contractile activity in vascular smooth muscle by influencing a Na^+-Ca^{2+} exchange mechanism (*20*), the present data are consistent with (i) reports indicating that experimental magnesium deficiency results in enhanced tissue uptake of sodium (*17*), (ii) altered levels of sodium in blood vessels (*1, 2*) and red and white blood cells (*18*), and (iii) the hypothesized defects in Na^+-Ca^{2+} exchange in hypertension (*19*). Our hypothesis is also consistent with reports of supersensitivity of blood vessels in hypertensive animals to endogenous neurohumoral constrictor substances, and with reports of subsensitivity of such blood vessels to some vasodilators (for example, prostaglandins), since magnesium deficiency potentiates neurohumoral constrictors while attenuating neurohumoral vasodilators (*6, 9, 11, 20*). The hypothesis is also consonant with suggested roles for dietary factors and geographic epidemiologic factors in the etiology of hypertensive disease, since there has been a steady decline in dietary intake of Mg^{2+} since around 1900 (*4, 5*); there are now several reports of hypomagnesemia in hypertensive patients (*8*); and there are numerous reports of a higher than normal incidence of hypertensive disease in certain geographic regions around the globe (*3–5*).

A progressive hypomagnesemia early, or later, in life could produce progressive peripheral vasoconstriction of arterioles, precapillary sphincters, and venules. The familial tendency to develop primary hypertension is consonant with our findings, since the level of Mg^{2+} in certain tissues is under genetic control (*21*). Adequate Mg^{2+} intake or metabolism would prevent these vascular events. Such a rationale would explain why the administration of magnesium salts lowers arterial blood pressure (*7*).

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