NUTRITION and HEART DISEASE

Edited by

Herbert K. Naito, Ph.D.
The Cleveland Clinic Foundation
and
Department of Chemistry
Cleveland State University
Cleveland, Ohio

SP MEDICAL & SCIENTIFIC BOOKS
a division of Spectrum Publications, Inc.
New York • London 1982

Proc. 19th Ann Mtg Am Coll Nutr. 1977

3

Early Nutritional Roots of Cardiovascular Disease

MILDRED S. SEELIG

INTRODUCTION

The cardiovascular diseases of infancy and childhood that are common enough to require specialty medical care and surgical correction are a development of the past 30 to 40 years, as is the epidemic of sudden death of men under 50 from ischemic heart disease (IHD). Less widely recognized is the evidence that sudden death from IHD has also occurred in infancy and childhood, with increasing frequency during the same period of time, as has generalized arteriosclerosis in very young infants, and atherosclerosis, hyperlipemia, and hypertension in older infants and children (Seelig, 1980). The initiating cardiovascular lesion can begin very early in life (in some individuals during gestation; in many during early infancy). The years during which cardiovascular diseases of all ages have increased in incidence correlate with the years during which major dietary changes were made in the industrialized countries. The amount of magnesium consumed has slowly declined; the consumption of vitamin D and phosphates (both substances that decrease magnesium retention) have risen sharply in the period from the 1920s to the present. It is thus important to note that experimental magnesium deficiency causes arterial and cardiac lesions much like those reported in thousands of infants under 2½ years of age (Seelig, 1980), and that excesses of vitamin D or phosphate, or both, intensify the abnormalities (reviews: see Seelig, 1980; and Haddy, 1980).

Table 1. Arterial Abnormalities in Infants Dead at Birth or in the First Month of Life (From Published Data, Tabulated by Seelig, 1980)

	Individual Cases (154)	*Pathology Surveys (>500)*
Arterial Pathology		
Affected Arteries:		
Coronaries (Small; Medium* Major)	16 25	>170
Aorta	27	?
Pulmonary	11	?
Cerebral	1	?
Visceral (Renal, Pancreatic, etc.)	12	?
Generalized	13	?
Pathologic Changes:		
Intimomedial Thickening	15	124 (18 of 54 Autopsied**)
Intimomedial, Elastica Degeneration	13	51
Intimomedial, Elastica Calcification	14	?
Lipid Infiltration	0	15
Thrombi	13	2
Atresia, Coarctation (Aorta, Pulmonary)	25	(in 140 with EFE: 36% of 1580 Autopsied)**

*Rarely examined.
**In 1 series.

Table 2. Cardiac Abnormalities Suggestive of Myocardial Hypoxia in Infants Dead at Birth or Dying Within First Month (From Published Data, Tabulated by Seelig, 1980)

	Individual Cases (154)	*Pathology Surveys (>500)*
Myocardial Damage:		
Mural	36	?
Subendocardial, Papillary Muscle	34	?
Multifocal, Disseminated	26	?
Massive Infarct	14	5
Pathologic Changes:		
Myocardial Necrosis, Cell Infiltration	41	?
Myocardial Calcification	28	?
Myocardial Fibrosis	37	?
Myocardial Lipid Infiltration	2	?
Endocardial Fibroelastosis	80	206
Conduction System Abnormality*	7	33
Outflow Obstruction:		
Supra-, Sub-, and Valvular Stenosis (Coarctation; Atresia on Artery Table)	25	>3

*Rarely examined.

Table 3. Arterial and Associated Abnormalities in Infants >1 Month to 2½ Years with Ischemic Heart Disease (Mostly Autopsy) (From Published Data, Tabulated by Seelig, 1980)

	Individual Cases (251)	*Pathology Surveys (About 2500)*
Arterial Pathology		
Arteries Affected:		
Coronaries (Small, Medium*	41	70*
Large)	69	>600
Aorta	17	>350
Pulmonary	22	
Visceral (Renal, Pancreatic, etc.)	30	
Generalized	34	>150*
Pathologic Changes:		
Intimomedial Thickening	67	>300*
Intimomedial, Elastica Degeneration	35	> 50*
Intimomedial, Elastica Calcification	45	> 50*
Lipid Infiltration, Atheroma	2	50 (Late)
Thrombi	24	
Atresia, Coarctation	20	>350

*Rarely reported.

Table 4. Cardiac Abnormalities Suggestive of Myocardial Hypoxia in Infants >1 Month to 2½ Years (Mostly Autopsy) (From Published Data, Tabulated by Seelig, 1980)

	Individual Cases (251)	*Pathology Surveys (About 2500)*
Myocardial Damage:		
Mural	35	?
Subendocardial; Papillary Muscle	48	?
Multifocal, Disseminated	39	> 50*
Massive Infarct	20	28
Pathologic Changes:		
Myocardial Necrosis; Cell Infiltration	63	?
Myocardial Calcification	26	?
Myocardial Fibrosis	40	?
Myocardial Lipid Infiltration	5	?
Myocardial Cellular (Enlargement)	2**	
(Early Change)	1**	<100**
Endocardial Fibroelastosis	111	>600
Conduction System Abnormality*	18	
Outflow Obstruction	40	About 800
Supra-, Sub-, and Valvular–Stenosis		About 250

*Rarely examined.

**UM–Ultramicroscopy or special stain.

FETAL AND INFANTILE CARDIOVASCULAR DAMAGE IN WHICH HYPOXIA OR ISCHEMIA IS IMPLICATED

Analysis of the literature (Seelig, 1980) has disclosed over 150 individually described infants and more than 500 listed in surveys of autopsied infants who had been stillborn or died in the first month of life with arterial or cardiac lesions or both—such as have been associated with hypoxia (Tables 1 and 2). The literature analysis also revealed over 250 individually reported cases and about 2500 in pathology surveys of infants dying after one month to 2½ years of age (Tables 3 and 4). Among those who were stillborn, or who died within the first few days of life, the lesions must be assumed to have occurred during gestation or perinatally. As indicated in the top portions of Tables 5 and 6, data on the condition or history of the mother have been given infrequently. When cited, the conditions were generally those that predispose to fetal malnutrition and hypoxia and resultant intrauterine growth retardation (IUGR), reflected by infants that are small for gestational age (SGA). The early necrotic changes found in arteries of myocardium of infants born with severe perinatal hypoxia (Gruenwald, 1949), and the endocardial fibroelastosis (EFE) found in infants with neonatal hemolytic disease (Hogg, 1962), suggest that placental abnormalities that interfere with fetal oxygenation earlier in gestation might play a role in some of the grosser congenital cardiac anomalies (Johnson, 1952), as well as in the arteriosclerosis found at birth and early infancy. Scrutiny of individual case reports and pathology surveys shows that, although infrequently examined, involvement of the small- and medium-sized coronary arteries was reported almost as frequently as was disease of the major coronaries. Blanc et al. (1966), whose group had observed coronary disease in only 0.6 percent of 6000 consecutive autopsies of neonates to 12-year-old children, found that when the small (e.g., terminal) branches of the coronaries were examined, the incidence of coronary disease and associated myocardial infarction (MI) rose to 12 percent of 153 consecutive autopsies. They stated that the myocardial fibrosis and calcification found in some cases suggested that the myocardial necrosis might have been prenatal. Lesions of the subendocardium and of the papillary muscles (the most frequently involved sites in early infancy), and disseminated multifocal lesions (which probably reflect disease of the small intramyocardial arteries (for a review, see Seelig and Haddy, 1980) were more frequently reported than were massive infarctions. However, that as many as 19 infants under a month of age, and that 48 more from one month to 2½ years should have died of massive MIs is startling. It should be noted that infantile MI was reported to be occurring with increasing frequency (Sabiston et al., 1960), particularly in association with anomalous origin of coronary arteries—a group excluded from the tabulation referred to here.

Table 5. Abnormalities During Gestation and Antemortem in Infants Stillborn or Dead in <1 Month with Pathologic Evidence of Ischemic Heart Disease (From Published Data, Tabulated by Seelig, 1980)

	Individual Cases (Data on ½ of 154)	*Pathology Surveys (Rarely Reported: >500)*
Pre-Eclampsia, eclampsia, diabetes mellitus Mother >38 years old	11	D.M.: 1/20–1/43* >38:1/84
Maternal immaturity; multiple; frequent births	17	9% (multiple) of 97 with cardiomegaly
Abnormal gestation; RH incompatibility	28	43 with EFE**
Fetal distress (Cardiac; ECG)	35	34
Difficult; Caesarian deliveries	10	?
Placenta praevia; abnormality	8	12
Low birth weight	10	37% of 620 LBW had cardiomegaly
Infantile cyanosis, respiratory distress	56	21 noted
Tachycardia; arrhythmia; block; other ECG abnormalities	15	10 noted
Cardiomegaly; congestive heart failure	31	?
Sudden death	10	?

*With congenital heart disease.
**EFE = Endocardial fibroelastosis.

Marked intimomedial hypertrophy, sometimes with necrosis and calcification, has been described in coronary and other arteries of very young infants. The incidence of such arterial changes cannot be ascertained from a retrospective survey of the literature, since some studies include sites of intimal proliferation and fibrosis ("cushions") as precursors of atheromata (Dock, 1946; Fangman and Hellwig, 1947), whereas others specifically exclude them as normal variants (Schornagel, 1956; Robertson, 1960; Oppenheimer and Esterly, 1967). More generalized intimal and medial proliferation and fibrosis is being increasingly considered an early manifestation of infantile arterial disease, that in a severe form has been termed "occlusive infantile arteriopathy" (Witzleben, 1970). Such infantile arterial disease might be the early form of adult atherosclerosis (Danilevicus, 1974). The most definitive pathology studies in this area are those by Neufeld and Vlodaver (1968, 1971). Their findings indirectly implicate nutritional, more than genetic, factors in the different susceptibilities to atherosclerosis of different racial groups, by analyzing the thickness of the arterial walls of infants and children of three

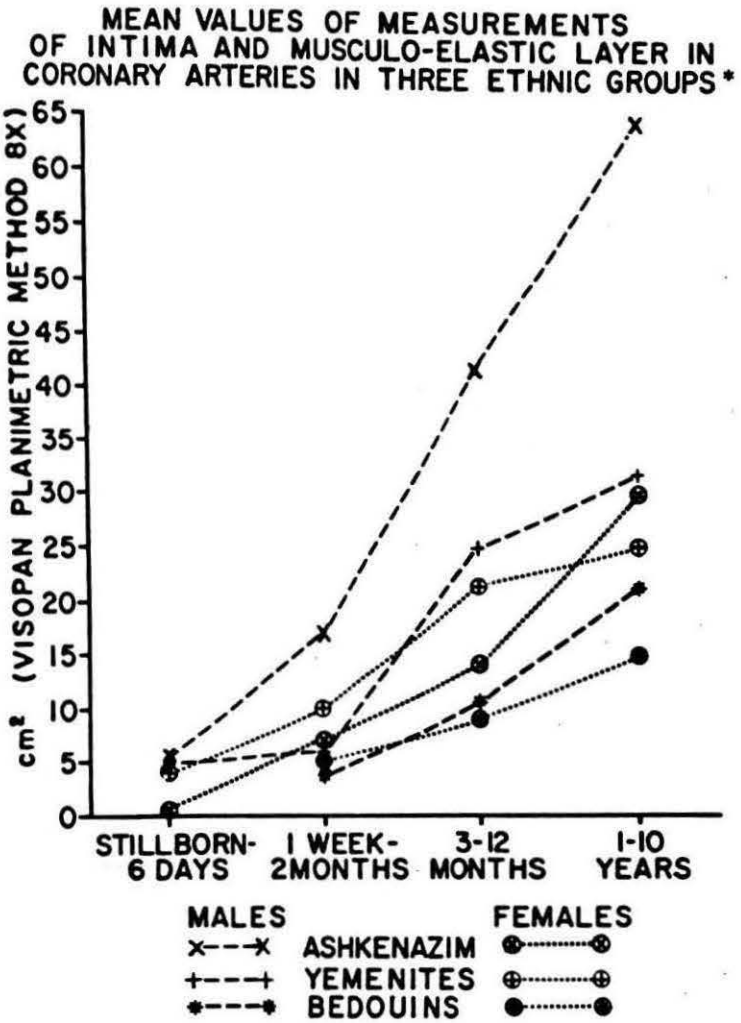
Table 6. Abnormalities During Gestation and Infancy in Infants >1 Month to 2½ Years with Evidence of Ischemic Heart Disease (Mostly Autopsy) (From Published Data, Tabulated by Seelig, 1980)

	Individual Cases (251)	*Pathology Surveys (About 2500)*
Pre-eclampsia, eclampsia*	9	?
Maternal immaturity; multiple; frequent births*	37	?
Fetal distress, placental abnormality*	6	?
Low birth weight*	19	?
Infantile cyanosis, respiratory distress (excluding pre-terminal)	93	?
Growth and mental retardation	35	>150**
Irritability, seizures, tremors	31	Occasional*
Apathy, atony, apnea	20	?
Syncope	16	> 70
Deafness	9	(Occasional labyrinth calcific*)
Cardioeachs	10	<700
Cardiomegaly, murmurs, failure	97	(Antemortem ?)
Tachycardia, bradycardia, block, other arrhythmia, ECG abnormality	76	>200
Hypertension	19	>750***
Hyperlipemia*	11	?
Hypercalcemia*	20	?
Sudden death (including sudden onset of short terminal illness)	87	(At Least 100)

*Rarely reported.
**In outflow obstructive disease; sometimes with ↑ Ca; vitamin D toxicity.
***All with coarctation.

Semitic groups in Israel: Ashkenazim (Jews of European derivation), Yemenite Jews, and Bedouins. It was among the male Ashkenazim, the group with the highest incidence of early IHD, that there was the most intimomedial thickening (Fig. 1). Although it was present in the earliest months, the difference became marked in the Ashkenazi males as age progressed, as graphed for 3- to 12-month-old infants and >1- to 10-year-old boys.

Endocardial fibroelastosis is the condition reported most often in the cases tabulated: the localized or patchy forms are more frequent in the younger group (Table 2) and the diffuse thick form is more frequent in the



*Adapted from Neufeld and Vlodaver, 1971; from Seelig, 1980.

Fig. 1

older infants (Table 4). These lesions are included because they have been attributed to hypoxia and to ischemia (Craig, 1949; Johnson, 1952; Horley, 1955; Elliott and Elliott, 1973). Gross (1941) noted the similarity of the myocardial lesions associated with early EFE to that of adult bland MI. Elliott and Elliott (1973) remarked that endomyocardial scars of young infants are generally in areas most remote from the coronary blood supply

and thus most vulnerable to hypoxia. Intimomedial thickening of the intramyocardial coronaries, that might well be responsible for inadequate blood supply to the terminal arterioles, has been reported in EFE (Craig, 1949).

It is provocative that many of the infants with luminal narrowing of the small coronaries, EFE or myocardial necrosis, whose antemortem histories had been reported, had had conduction or ECG abnormalities and not a few were reported to have died suddenly (Tables 5, 6). Tachycardia, atrial fibrillation, depressed or inverted T waves, prolonged P-R intervals, ST depression, and partial to complete heart block have all been reported, some even *in utero* (Blumberg and Lyon, 1952; Kelly and Andersen, 1956; Moller et al., 1964; Oppenheimer and Esterly, 1967). An infant born with A-V block died at two months of age with degeneration and calcification of the conducting tissue (Miller et al., 1972). Young infants with EFE were found to have involvement of the purkinjeal zone (Elliott and Elliott, 1973), a possible clue to the frequency of conduction abnormalities that have led to sudden infant death (SID) associated with EFE. Degenerative changes have also been found to be frequent in portions of the A-V node and bundle of His in infants–both in those who had died of the SID syndrome (unknown cause) and in those with identified causes of death (Anderson et al., 1970). Similar lesions were found in a baby who developed normally until a conduction defect suddenly appeared at 12½ months, leading to death a month later (Lev et al., 1967). SIDS is commonly thought to occur in infants who had been completely well; Naeye et al. (1976) have reported histories of symptoms in many resembling those listed on Tables 5 and 6. Kastor (1973) has proposed that the cause of many electrical disturbances of the heart is unknown, and that some–such as A-V block and the Wolff-Parkinson-White syndrome–might be forms of congenital heart disease. He consideres fibrosis of the peripheral bundle branches to be probably "acquired"; the foregoing data suggest that the acquisition can be very early in life.

It has been suggested that fibrosis and elastic tissue changes, seen both in coronary arteries and endocardial lesions of infants and children with EFE might be similarly caused (Esterly and Oppenheimer, 1967). Metabolic defects leading both to coronary lesions and to EFE have been considered plausible (Kelly and Andersen, 1956; Davies and Coles, 1960). Hypoxia and mechanical factors (Moller et al., 1964; Franciosi and Blanc, 1968), or predominantly outflow-obstruction (Bryan and Oppenheimer, 1969) have been implicated. Outflow-obstruction, commonly caused by great-vessel coarctation or valvular stenosis, has been considered part of the metabolic condition that increases susceptibility to hypervitaminosis D. It has been suggested that the specific malformation might depend on the magnitude, time, and extent of overdosage or degree of susceptibility (Taussig, 1965, 1966; Beuren et al., 1964, 1966), but that all of the outflow-obstructions and possibly other cardio-

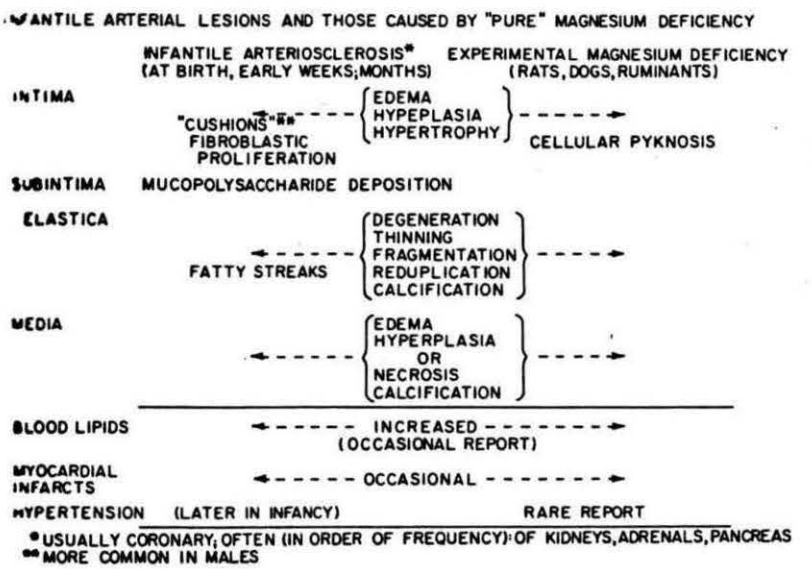


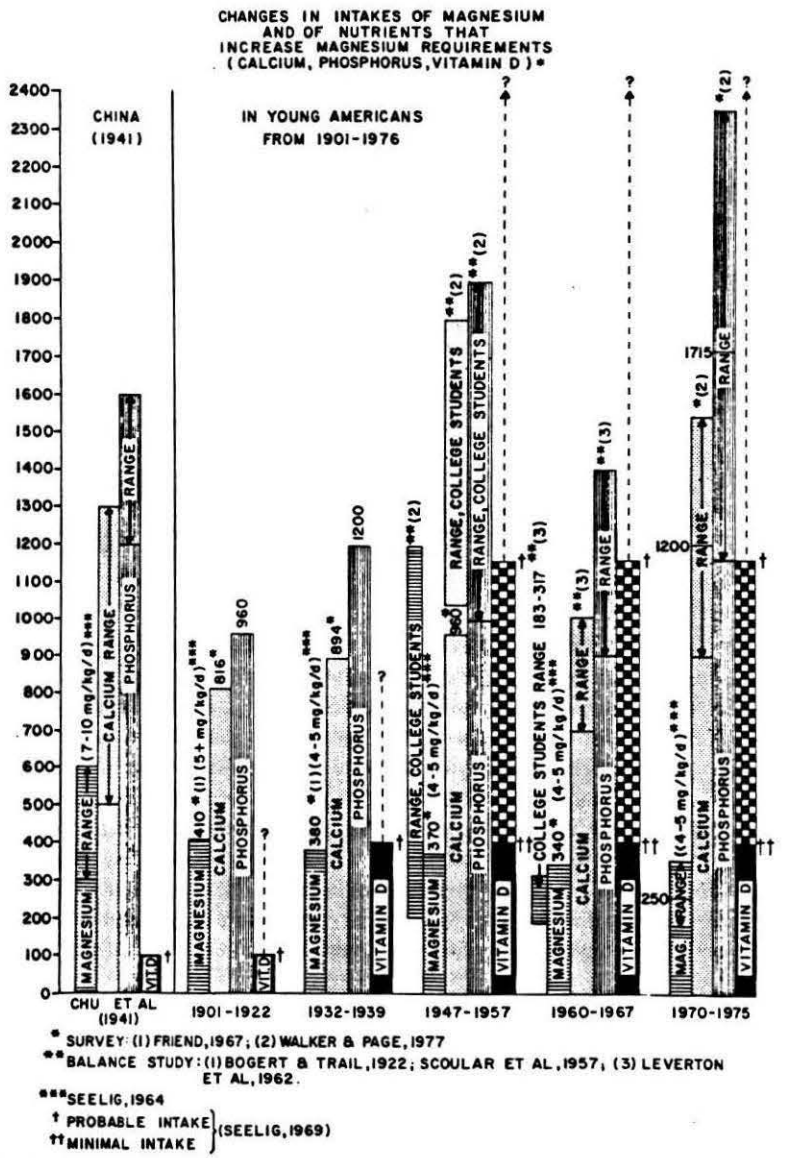
Fig. 2

vascular abnormalities might be part of the same disease process (Beuren, 1978 [personal communication]). This concept suggests that at least some of the major cardiac arterial anomalies that had been excluded from the tabulations (Seelig, 1980) from which the cited figures were derived might justifiably have been included–as possibly resulting from fetal malnutrition and hypoxia caused by maternal nutritional imbalances and placental damage.

It is important to note, in considering the damage caused by excess vitamin D to heart and arteries (Seelig, 1969b), that vitamin D excess causes magnesium loss (review: see Seelig, 1980; Seelig and Haddy, 1980), and that vitamin D excess and dietary magnesium deficiency have each been implicated in hyperlipemia and hypertension (reviews: see Linden, 1977; Seelig, 1980; Seelig and Haddy, 1980; Haddy and Seelig, 1980).

IS MAGNESIUM DEFICIENCY A FACTOR IN INFANTILE CARDIOVASCULAR DISEASE?

The coronary and cardiac lesions of stillborn and very young infants resemble those of experimental animals maintained on diets that are notable, predominantly, for magnesium deficiency (Seelig and Haddy, 1980); (Fig. 2). That this may be more than a fortuitous finding is suggested by the evidence that magnesium insufficiency is likely, both during gestation and infancy.



* SURVEY: (1) FRIEND, 1967; (2) WALKER & PAGE, 1977

** BALANCE STUDY: (1) BOGERT & TRAIL, 1922; SCOULAR ET AL, 1957; (3) LEVERTON ET AL, 1962.

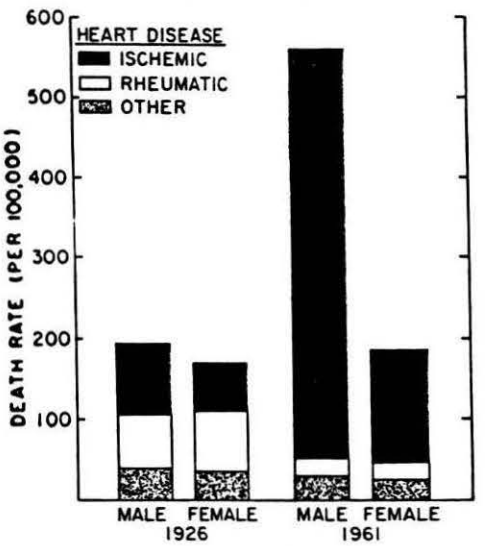
*** SEELIG, 1964

† PROBABLE INTAKE } (SEELIG, 1969)
†† MINIMAL INTAKE }

*From Seelig, 1980.

Fig. 3

MALE AND FEMALE DEATH RATES FROM HEART DISEASE IN CANADA IN 1926 AND 1961 IN THE AGE GROUP 45 TO 64



FROM T. ANDERSON, (1973)

Fig. 4

Decreased Magnesium Intake and Availability

Figure 3 depicts the contrast in dietary intakes by a prerevolution middle-class population in China (Chu et al., 1941) (as representative of the Orient, where the incidence of cardiovascular disease has long been accepted as lower than it is in the Occident) and those during this century in the United States (Bogert and Trail, 1922; Leverton et al., 1962; Friend, 1967; Scoular et al., 1957; Seelig, 1969b; Walker and Page, 1977). The graph depicts the decline in magnesium intakes and the steep rises in intakes of vitamin D and phosphate, each of which increases magnesium requirements either by increasing its urinary excretion (vitamin D) or by interfering with its absorption (phosphate): the vitamin D from the mid 1920s on, and the phosphate (largely in soft drinks) from the 1940s on. It is thus important to note that both vitamin D and sodium phosphates have been used to produce or intensify experimental cardiomyopathy, and that magnesium (often with potassium and chloride) has been protective (Selye, 1958; Lehr and Krukowski, 1963; Lehr, 1965; Sos, 1965; Seelig, 1972; Seelig and Heggtveit, 1974; Seelig and Haddy, 1980).

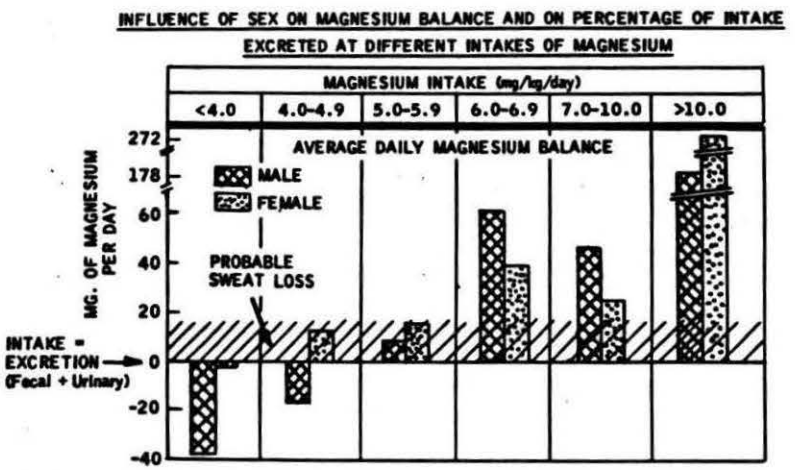


Fig. 5

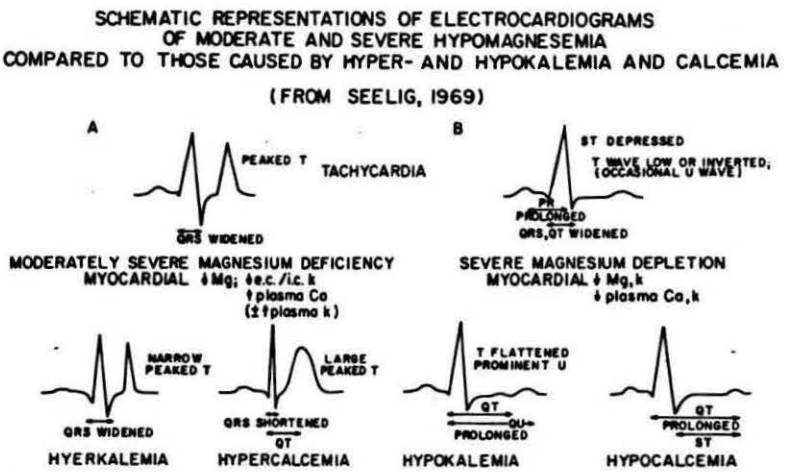


Fig. 6

Correlation of Decreased Magnesium and Increased Cardiovascular Disease

Sudden Death from IHD

It is possible that the combination of declining intakes of magnesium with sharp increases in vitamin D and phosphate intakes might have contributed to the sharp rise in incidence of IHD in men from 1926 to 1961 (Fig. 4; Anderson, 1973). The difference in retention of magnesium by young men

and women on marginal intakes of magnesium (Fig. 5) first suggested to the author that a common denominator between the lower incidence of IHD in young women than young men, and in the Orient than in industrialized countries, might be the magnesium retained or ingested (Seelig, 1964). The similarity of abnormal ECGs of infants to those of magnesium deficiency (Fig. 6; Seelig, 1969a; Burch and Giles, 1977) and the similarity of arterial damage caused by magnesium deficiency to that reported in arteries supplying the conduction system of infants, many of whom died suddenly (*supra vide*), is further inferential evidence that magnesium deficiency should be considered as sudden death.

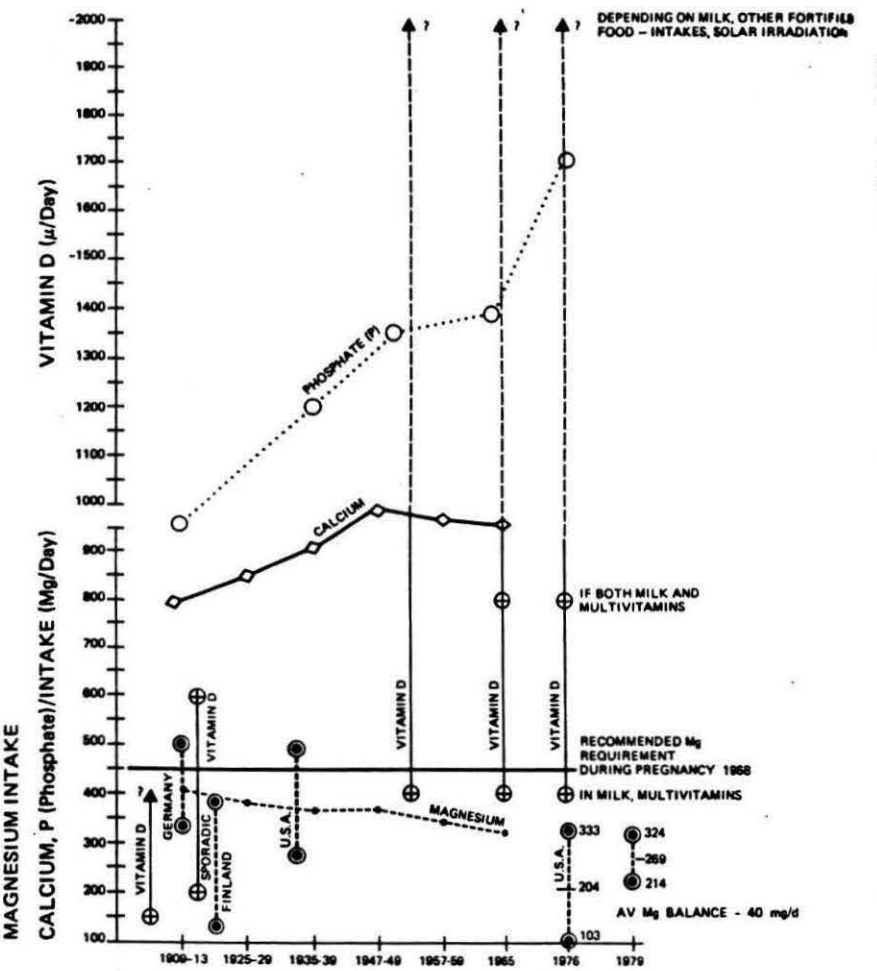
Inadequate Magnesium During Gestation

Superimposing ranges of magnesium intakes during pregnancy on a graph depicting the average calcium intake and the probable range of vitamin D intakes (Fig. 7; Seelig, 1978, 1980), shows that magnesium needs of pregnant women, and thus of their unborn babies, are unlikely to be met by the typical American diet. The Food and Nutrition Board (1980) has recommended that pregnant and lactating women ingest 450 mg of magnesium a day, an amount not even approached in the most recent surveys of the dietary intakes of midwestern American women (Ashe et al., 1979; Johnson and Philipps, 1980). Hummel et al. (1936, 1937) published long-term balance studies of two pregnant women that suggest that the optimum intake during pregnancy might be even higher than 450 mg/day. Although we cannot draw general conclusions from even long-term studies of only two subjects, it is noteworthy that the mother of three very healthy children consistently consumed a diet that provided about 600 mg of magnesium daily during her fourth pregnancy, whereas a teenaged primipara with a poor nutritional history, whose magnesium intake approached that recommended, retained only half as much magnesium as did the multipara (Table 7). The compilation of published data (Fig. 8; Coons et al., 1935) confirms the much greater retention of magnesium by pregnant women on higher than on lower intakes.

Effect of Gestational Magnesium Deficiency on Incidence of Eclampsia and on Placenta and Fetus

Two groups of investigators studied the increase in magnesium present in human fetuses as they grew and matured (Table 8; Coons et al., 1935; Widdowson and Dickerson, 1962). The amount of magnesium acquired by the fetus increases markedly towards the end of gestation. On the other hand, pregnant rats kept on a magnesium-poor diet retained their own tissue mag-

MAGNESIUM INTAKES DURING PREGNANCY AND CHANGING AVERAGE INTAKES OF MAGNESIUM, CALCIUM, VITAMIN D DURING THE 20th CENTURY
(Derived from Friend, 1967; Seelig, 1969, 1971; Johnson & Phillips, 1976; Ashe et al, 1979)



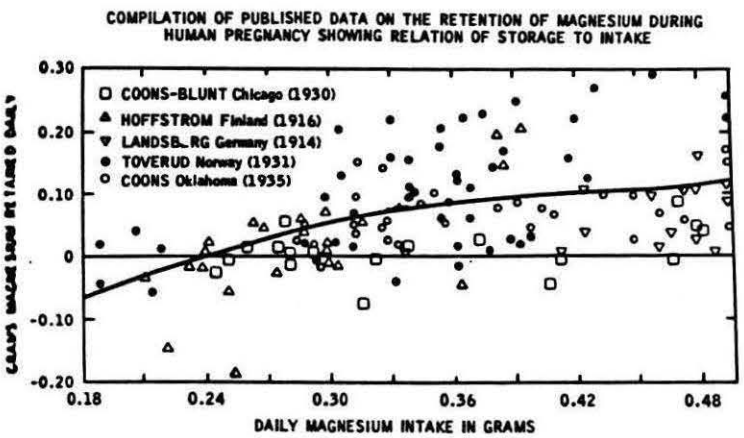
◇—◇ CALCULATED AVERAGE Ca INTAKE, ADULT
○···○ P INTAKE, ADULT
•------• AVERAGE Mg INTAKE
⊕—⊕ RANGE OF VITAMIN INTAKE
◉—◉ Mg INTAKES, PREGNANT WOMEN

Fig. 7

Table 7. Magnesium Retentions During Last Months of Pregnancy

	Average Daily Intake and Retention			
	*Healthy Quadripara** *(With Successful Pregnancies)*		*18 Year-Old Primipara*** *(Poor Nutritional History)*	
Month of Pregnancy	*Intake (mg Mg/day)*	*Retention*	*Intake (mg Mg/day)*	*Retention*
>6–7	614	+128	403	+ 58
>7–8	590	+ 85	392	+102
>8–9	615	+104	375	+ 25
>6–9 Total retention		9.6 grams		4.2 grams

*From Hummel et al., 1936.
**From Hummel et al., 1937.



From Coons, C.M., Oklahoma Agric. & Expt'l Station Bull., 223, 1935.

Fig. 8

nesium fairly well, whereas the amount of magnesium acquired by their fetuses was less than one-fifteenth that of controls (Table 9; Dancis et al., 1971). The magnesium-deficient pregnant rats and their fetuses were comparably hypomagnesemic.

Women with toxemic pregnancies retain high percentages of therapeutic parenteral doses of magnesium (Pritchard, 1955; Kontopoulos et al., 1980) and require large amounts to maintain pharmacologic levels of plasma magnesium (Fig. 9) (Pritchard, 1955; Hall, 1957; Flowers et al., 1962; Hutchinson et al., 1963; Harbert et al., 1968). These observations, and low pretreatment serum magnesium levels, have been interpreted as possibly pointing toward

Table 8. Increase in Total Body Magnesium with Fetal Growth

*Body Weight (Grams)	mg of Mg/kg (Dry Fat-Free Fetal; Infant)	Total mg of Mg in Fetus; Baby (Dry, Fat-Free)	**Age: Fetus, Baby (Lunar Months)		Average Mg (mg) Content in Fetus, Baby	Average Mg Uptake (mg/Day)
11.1	.09	0.9		(#)		
175	.14	24	3	(7)	15	0.5
400	.15	60	4	(3)	58	1.5
737	.21	165	7	(6)	173	2.6
1500	.21	320	8	(8)	306	4.7
2500	.23	580	9	(7)	512	7.4
3500	.22	760	10	(10)	703	9.0

*From Widdowson and Spray, 1951; Coons et al., 1935.
**From Widdowson and Dickerson, 1962.

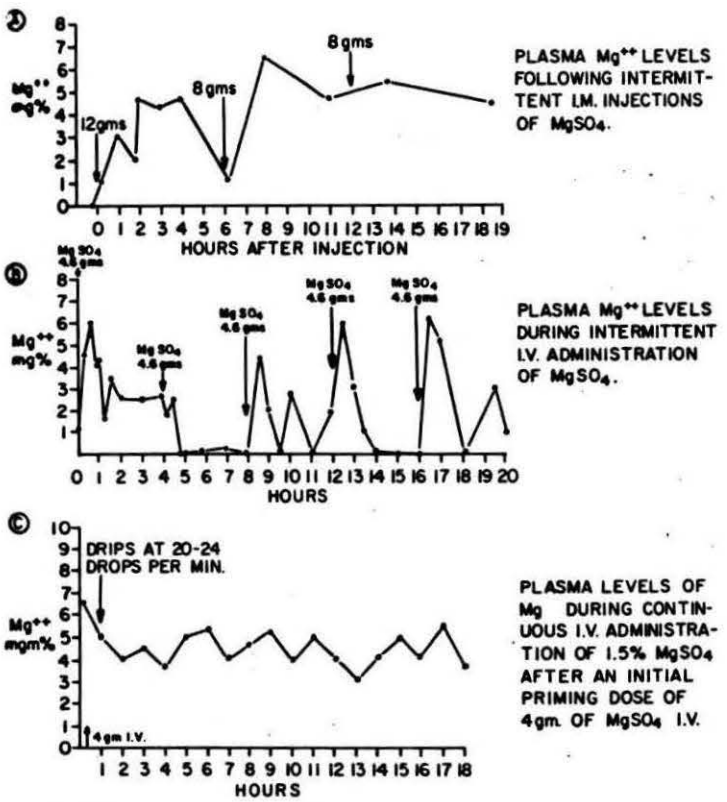
Table 9. Magnesium Levels in Maternal and Fetal Tissues (From Magnesium Deficient and Control Rats)*

	(mEq/L or kg ± SE)	
	Magnesium Deficient	Control
Maternal plasma	0.33 ± 0.03	1.6 ± 0.04
Maternal bone	176.0 ± 12.1	213 ± 0.8
Maternal muscle	24 ± 0.5	23 ± 0.8
Fetal plasma	0.31 ± 0.02	2.4 ± 0.07
Fetus	8.9 ± 0.22	142 ± 0.39

*From Dancis et al., 1971.

magnesium deficiency as a factor in preeclampsia and eclampsia (Flowers et al., 1965; McGanity, 1965; Lim et al., 1969; Muller, 1968; Muller et al., 1974; Hurley, 1971; Seelig and Bunce, 1972; Kontopoulos et al., 1980; Seelig, 1980; Weaver, 1980). The low levels of magnesium and high levels of calcium in placentas from women who had toxemic pregnancies or borne twins (Table 10; Charbon and Hoekstra, 1962) parallels that seen in placentas of magnesium-deficient rats (Dancis et al., 1971). Is the fact that both toxemic women and magnesium deficient rats have young that are SGA another indication of IUGR in magnesium-poor mothers? Johnson and Phillips (1980) reported a direct correlation between low magnesium intakes by the pregnant Wisconsin women surveyed, and low-birth-weight infants. Abnormalities during pregnancy were not reported.

It is possible that hypervitaminosis D during gestation might be contributory to abnormal placentas, as well as to the congenital heart disease cited earlier. Scarred, small, calcified placentas were produced in rats given excess vitamin D during pregnancy (Potvliege, 1962; Ornoy et al., 1968).



(FROM FLOWERS ET AL., 1962)

Fig. 9

Table 10. Calcium and Magnesium Content of Placentas (Tabulated by Charbon and Hoekstra, 1962)*

	Normal	*Twins*	*Pre-eclampsia*	*Eclampsia*
Magnesium (mg %)	8.87	6.94	6.49	4.30
Calcium (mg %)	86.4	124.6	942	134.6

*From Mischel, 1957.

Supravalvular aortic stenosis and EFE were produced in rabbits born to dams overdosed with vitamin D during gestation (Coleman, 1965; Friedman and Roberts, 1966). IUGR is a product of scarred placentas (Warkany et al., 1961; Scott and Usher, 1966; Wigglesworth, 1966), and there is a greater likelihood of its occurring in immature primiparas, mothers who have had previous SGA-infants or who have had six or more pregnancies. It is associated with a 16-fold increase of incidence of congenital heart disease (Scott and Usher, 1966). Required is investigation of the magnesium and vitamin D status of mothers suffering from toxemic pregnancy, who have had histories of abnormalities during pregnancy, or have had stillbirths, SGA-infants, or children with congenital heart disease.

Better insight into the magnesium status of pregnant and postpartum mothers and infants is likely to be obtained by determination of percentage-retention of a parenteral load of magnesium than by determining serum magnesium levels (Harris and Wilkinson, 1971; Caddell, 1975; Byrne and Caddell, 1975; Caddell et al., 1975a, b), assuming essentially normal renal handling of magnesium (Freeman and Pearson, 1966). It may now be difficult to ascertain whether relative or absolute vitamin D excess during human gestation affects the health of the mother, the placenta, or the infant, because vitamin D supplementation is normally unavoidable. This is particularly true in the United States and Canada, where milk, breakfast foods, and prenatal vitamins each usually provide all or some of the 400 I.U. of vitamin D recommended as both the recommended daily allowance and the maximal permitted amount (Committee on Nutrition, 1963; Seelig, 1970), an interesting situation for a substance to which there is an enormous variation in response (Fanconi, 1956; Seelig, 1969b, 1970). During the 1930s, when vitamin D-supplementation gained in popularity, and when it was starting to be given (usually with calcium salts) to pregnant women, two studies were undertaken that indicated that such supplementation might not be uniformly safe. Brehm (1937) found extensive placental calcification in two groups of 90 women each, who were given vitamin D_2 (one with and one without calcium lactate) during pregnancy. Such placental calcification was not seen in the four other groups of 90 women each, who were given (1) only calcium lactate, (2) cod liver oil, (3) both, or (4) neither. This study was undertaken when the incidence of calcified placentas, fused sutures and decreased size of fontanels, and difficult labors, was found to have increased in incidence after the practice of vitamin D supplementation had been instituted in an obstetrical clinic. Another group of investigators, also concerned about the possible effect of vitamin D supplementation during pregnancy on increased bone density, and on cranial suture closure of infants that might contribute to difficult labors, found that in several instances, in which women received vitamin D_2 and calcium phosphate, maternal and cord blood levels of calcium

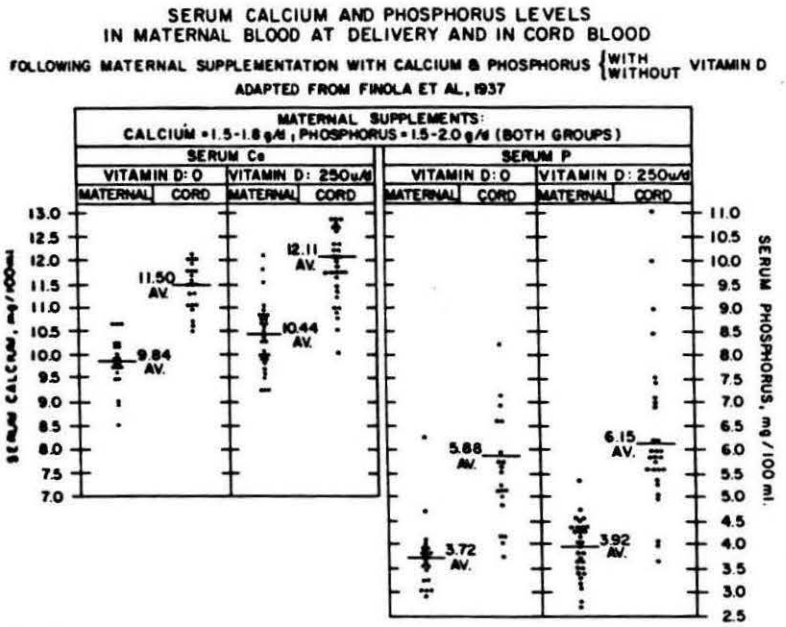


Fig. 10

were at pathologically high levels (Fig. 10; Finola et al., 1937). Although the average cord phosphorus levels were almost the same in the supplemented and nonsupplemented groups, a few infants born to supplemented mothers were hyperphosphatemic. Magnesium levels were not measured.

Vitamin D During Infancy; Human Versus Cows' Milk

Another common change during most of this century was the shift from breast- to bottle-feeding. Cows' milk has a much higher P/Mg ratio that does human milk: 7.5/1 versus 1.9/1 (Cockburn et al., 1973). Thus, it is not surprising that hyperphosphatemia is more prevalent in formula-fed than in breast-fed infants, with and without vitamin D supplements (Figs. 11, 12; Pincus et al., 1954). The same investigators also measured the serum calcium levels of the same groups of infants, and reported an unexpected finding: among the formula-fed infants, despite the higher concentrations of calcium in cows' than in human milk, the serum calcium levels of several infants were lower than in any of the breast-fed infants (Fig. 12). The lowest calcium levels were in several infants given the larger amount of vitamin D. Adapting

SERUM PHOSPHORUS LEVELS IN INFANTS FED BREAST MILK OR COWS' MILK WITHOUT AND WITH VITAMIN D SUPPLEMENTS

(ADAPTED FROM PINCUS ET AL., 1954)

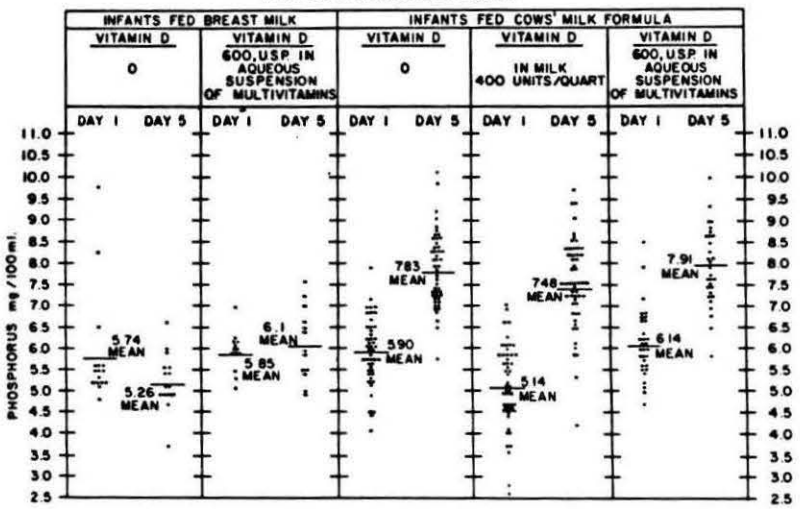


Fig. 11

SERUM CALCIUM LEVELS IN INFANTS FED BREAST MILK AND COWS' MILK WITHOUT AND WITH VITAMIN D SUPPLEMENTS

(ADAPTED FROM PINCUS ET AL., 1954)

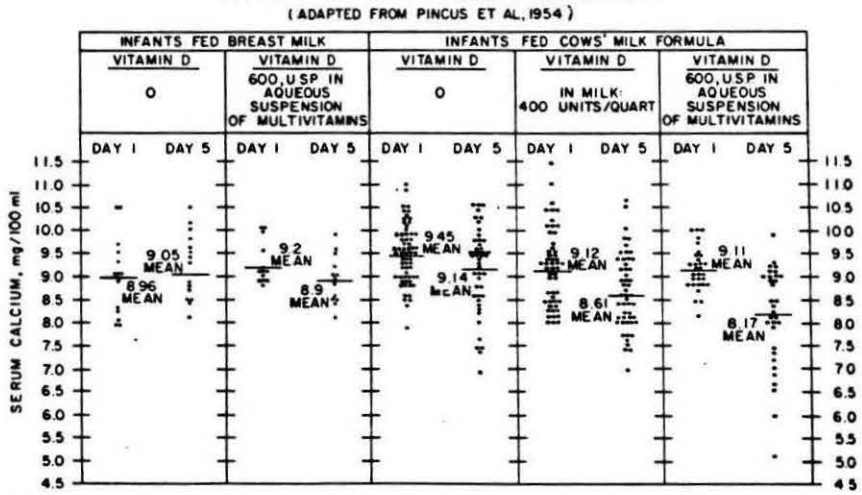


Fig. 12

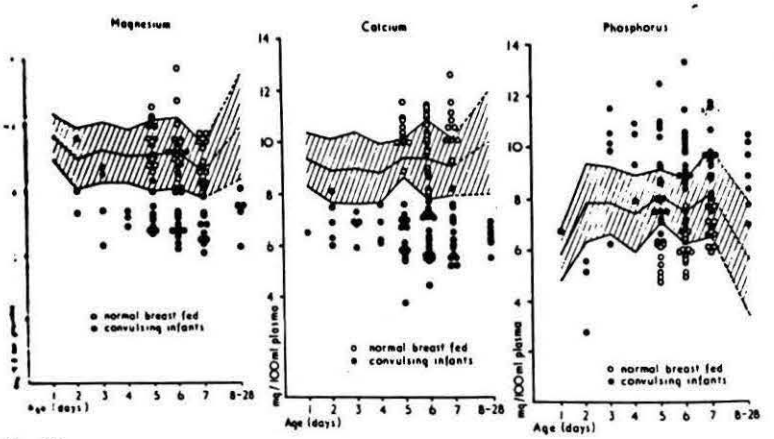


Fig. 13

cows' milk formula to resemble human milk more closely has partially corrected these abnormalities (Oppé and Redstone, 1968).

Hypocalcemic irritability, like infantile and premature adult cardiovascular diseases, has become more prevalent during this century. Only in the past 10 to 15 years has the dependence of plasma calcium levels in infancy on the magnesium status been accepted. The composite figure 13 (Cockburn et al., 1973) clearly depicts the lesser predilection of bottle-fed infants to convulsions, and the simultaneously low plasma magnesium and calcium and high phosphorus in the convulsing (bottle-fed) infants. The better response of hypocalcemic convulsions to magnesium than to calcium or barbiturate is depicted in Table 11. (Turner et al., 1977).

Infants that are particularly susceptible to falling magnesium levels after birth are those that suffer from IUGR (Tsang and Oh, 1970; Tsang, 1972) and infants of diabetic mothers (Tsang et al., 1972; Tsang and Brown, 1977). Diabetics are subject to magnesium deficiency (Martin, 1969). The nature of feeding these latter infants was not designated, but the mothers being American, formula was probably used.

DISCUSSION

The practice of medicine has changed substantially during the past 40 years, not only because of new diagnostic and therapeutic developments, but because new diseases have emerged or increased in incidence. In a commentary on the change in pediatric practice from the 1930s to the 1950s, Hutchison

Table 11. Pre- and Post-Treatment Plasma Magnesium, Calcium and Phosphorus in Response to Treatment of Neonatal Tetany*

Results of Treatment with Magnesium, Calcium, or Phenobarbitone (Mean ± SD)

	Magnesium Therapy (37)		*Calcium Therapy (34)*		*Barbiturate Therapy (33)*	
	Pre-Treatment	*Post-Treatment*	*Pre-Treatment*	*Post-Treatment*	*Pre-Treatment*	*Post-Treatment*
Plasma magnesium (mEq/L)	1.18 ± 0.34	1.75 ± 0.41	1.21 ± 0.18	1.27 ± 0.22	1.17 ± 0.22	1.28 ± 0.21
Plasma calcium (mg/100 ml)	6.16 ± 0.64	8.19 ± 0.97	5.80 ± 0.72	7.24 ± 1.12	6.11 ± 0.66	7.05 ± 1.06
Plasma phosphorus (mg/100 ml)	9.7 ± 1.05	9.02 ± 1.42	9.94 ± 1.04	8.94 ± 1.26	9.71 ± 1.32	8.53 ± 1.13
Number of seizures	1.86 ± 0.9	(After Rx started) 3.24 ± 4.23	1.72 ± 0.9	(After Rx started) 8.36 ± 10.2	1.67 ± 0.8	(After Rx started) 8.93 ± 9.4
Number of doses required for cure		2.31 ± 0.5		15.63 ± 5.9		12.48 ± 5.8

*Adapted from Turner, Cockburn and Forfar, 1977.

(1955) noted new renal and pancreatic diseases and considered the possibility that measures taken to abolish rickets might have resulted not only in infantile hypercalcemia (then prevalent in Great Britain–see Seelig, 1969b), but in new organic diseases. A variety of pediatric cardiovascular abnormalities has also been increasingly reported during the same era, and has persisted to the present. Direct and inferential evidence has been presented that the changed nutritional patterns since the 1930s might be to blame for a variety of cardiovascular and related or associated abnormalities that might be acquired during gestation and intensified during infancy, or that emerge during infancy or later life. Physicians who care for adults with IHD, atherosclerosis, hyperlipemia and hypertension, and epidemiologists and geneticists seeking explanations for the increased incidence of these disorders are increasingly looking to the infant years for clues as to origins and means of prevention of what has become a major epidemic.

Stress, in this paper, has been on magnesium deficiency–absolute and induced by dietary and other factors–as an important factor in sudden, unexpected cardiac death (during infancy, childhood, and early adult life–especially in men), and in chronic cardiovascular diseases. It is possible that the damage caused by vitamin D excess intensifies that produced by dietary magnesium deficiency, and that the primary lesion might be the cardiovascular necrosis and subsequent fibrosis, that can be produced experimentally by magnesium deficiency alone. Excess vitamin D increases blood pressure, the calcific process, and arterial fatty infiltration. Excess dietary fat further increases the tendency towards atheroma formation. The similarity of some of the cardiac and other defects and growth and mental retardation associated with the fetal alcohol syndrome (Hanson et al., 1976), and with the use of lithium (Weinstein and Goldfield, 1975) or of anticonvulsants (Speidel and Meadow, 1972; Anderson, 1976) to those seen with vitamin D excess suggests that each of these agents might cause the damage by means of a common mechanism. Anticonvulsants interfere with vitamin D metabolism (Christiansen et al., 1975), and cause hypomagnesemia (Christiansen et al., 1974). Alcoholism has long been known to cause magnesium depletion (Flink et al., 1954; Flink, 1980). Lithium alters magnesium metabolism, a subject discussed by Birch (1981) (in this symposium) as possibly related to the fetal cardiovascular damage in infants born to mothers receiving lithium during pregnancy. Thus, there is at least circumstantial evidence that several pharmacologic agents that adversely affect magnesium retention or metabolism can cause cardiac and related congenital diseases.

There is much still to be done before we understand the complete picture of nutritional factors involved in the pathogenesis of cardiovascular diseases. We hope that as investigations progress, nutritional intervention can be modified and new steps taken, so as to prevent some of the diseases that have reached epidemic proportions during the past 40 years.

REFERENCES

Anderson, R.C. Cardiac defects in children of mothers receiving anticonvulsant therapy during pregnancy. *J. Ped.* 89, 318–319 (1976).

Anderson, T. A new view of heart disease. *New Scient.* 9, 374–376 (1978).

Anderson, T.W. The changing pattern of ischemic heart disease. *Can. Med. Assoc. J.* 108, 1500–1508 (1973).

Anderson, W.R., Edland, J.F., and Schenk, E.A. Conducting system changes in the sudden death syndrome. *Am. J. Path.* 59, 35a (1970).

Ashe, J.R., Schofield, F.A., and Gram, M.R. The retention of calcium, iron, phosphorus, and magnesium during pregnancy: the adequacy of prenatal diets with and without supplementation. *Am. J. Clin. Nutr.* 32, 286–291 (1979).

Beuren, A.J., Apitz, J., Stoermer, J., Kaiser, B., Schlanger, H.V., Berg, W., and Jorgensen, G. Vitamin D-hypercalcemische Herz und Gefasserkrankung. *Mschr. Kinderh.* 114, 457–470 (1966).

Beuren, A.J., Schulze, C., Eberle, P., Harmanj, D., and Apitz, J. The syndrome of supravalvular aortic stenosis, peripheral pulmonary stenosis, mental retardation, and similar facial appearance. *Am. J. Card.* 13, 471–483 (1964).

Birch, N.J. The role of magnesium in the pharmacology of lithium and in development of fetal cardiovascular defects, in Proceedings of Symposium, American College of Nutrition, University of Minnesota, Minneapolis, 1978. SP Medical & Scientific Books, Jamaica, N.Y. (1982), pp. 295–300.

Blanc, W.A., Franciosi, R.A., and Cadotte, H. L'infarctus et la fibrose du myocarde en pathologie foetale et infantile. *Med. Hyg.* 24, 216–220 (1966).

Blumberg, R.W., and Lyon, R.A. Endocardial sclerosis. *Am. J. Dis. Child.* 84, 291–308 (1952).

Bogert, L.J., and Trail, R.K. Studies in inorganic metabolism. *J. Biol. Chem.* 54, 753–761 (1922).

Brehm, W. Potential dangers of viosterol during pregnancy with observations of calcification of placentae. *Ohio State Med. J.* 33, 990–993 (1937).

Bryan, C.S., and Oppenheimer, E.H. Ventricular endocardial fibroelastosis. Basis for its presence or absence in cases of pulmonic and aortic atresia. *Arch. Path.* 87, 82–86 (1969).

Burch, G.E., and Giles, T.D. The importance of magnesium deficiency in cardiovascular disease. *Am. Heart J.* 94, 649–657 (1977).

Byrne, P.A., and Cadell, J.L. The magnesium load test. I. Correlation of the clinical and laboratory data in neonates. *Clin. Ped.* 14, 460–465 (1975).

Caddell, J.L. The magnesium load test. I. A design for infants. *Clin. Ped.* 14, 449–459, 518–519 (1975).

Caddell, J.L., Byrne, P.A., Triska, R.A., and McElfresh, A.E. The magnesium load test. III. Correlation of clinical and laboratory data in infants from one to six months of age. *Clin. Ped.* 14, 478–484 (1975a).

Caddell, J.L., Saier, F.L., and Thomasen, C.A. Parenteral magnesium load tests in postpartum American women. *Am. J. Clin. Nut.* 28, 1099–1104 (1975b).

Charbon, G.A., and Hoekstra, M.H. On the competition between calcium and magnesium. *Acta Physiol. Pharm. Neerland.* 11, 141–150 (1962).

Christiansen, C., Nielsen, S.P., and Rodbro, P. Anticonvulsant hypomagnesemia. *Br. Med. J.* 1, 198–199 (1974).

Christiansen, C., Rodbro, P., Munck, O., and Minck, O. Actions of vitamins D_2 and 25-OH-D_3 in anticonvulsant osteomalacia. *Br. Med. J.* 2, 363–365 (1975).

Chu, H.I., Liu, S.H., Hsu, H.C., Choa, H.C., and Cheu, S.H. Calcium, phosphorus, nitrogen, and magnesium metabolism in normal young Chinese adults. *Chin. Med. J.* 59, 1–33 (1941).

Cockburn, F., Brown, J.K., Belton, N.R., and Forfar, J.O. Neonatal convulsions associated with primary disturbance of calcium, phosphorus and magnesium. *Arch. Dis. Childh.* 48, 99–108 (1973).

Coleman, E.N. Infantile hypercalcemia and cardiovascular lesions. Evidence, hypothesis and speculation. *Arch. Dis. Childh.* 40, 535–540 (1965).

Committee on Nutrition, American Academy of Pediatrics. The prophylactic requirement and the toxicity of vitamin D. *Pediatrics* 31, 512 (1963).

Coons, C.M., Schiefelbusch, A., Marshall, G.B., and Coons, R. Studies in metabolism during pregnancy. *Oklahoma Agric. Exp. Stat. Bull.* 223 (1935).

Craig, J.M. Congenital endocardial sclerosis. *Bull. Int. A.M. Mus.* 30, 15–67 (1949).

Danilevicus, Z. When does CHD start? *JAMA* 230, 1565–1566 (1974).

Dancis, J., Springer, D., and Cohlan, S.Q. Fetal homeostasis in maternal malnutrition. II. Magnesium malnutrition. *Pediat. Res.* 5, 131–136 (1971).

Davies, J.N.P., and Coles, R.M. Some considerations regarding obscure disease affecting the mural endocardium. *Am. Heart J.* 59, 600–631 (1960).

Dock, W. The predilection of atherosclerosis for the coronary arteries. *JAMA* 131, 875–878 (1946).

Elliott, G.B., and Elliott, J.D.A. Myocardial component in fibroelastoses scar. *Arch. Path.* 95, 321–324 (1973).

Esterly, J.R., and Oppenheimer, E.H. Some aspects of cardiac pathology in infancy and childhood. IV. Myocardial and coronary lesions in cardiac malformations. *Pediatrics* 39, 896–903 (1967).

Fanconi, G. Variations in sensitivity to vitamin D, in *Bone Structure and Metabolism.* G. Wolstenholme and C. O'Connor, eds. Little, Brown, Boston (1956), pp. 187–205.

Fangman, R.J., and Hellwig, C.A. Histology of coronary arteries in newborn infants. *Am. J. Path.* 23, 901–902, 1947.

Finola, G.C., Trump, R.A., and Crimson, M. Bone changes in the fetus following administration of dicalcium-phosphate and viosterol to the pregnant mother. *Am. J. Obst. Gyn.* 34, 955–958 (1937).

Flink, E.B. Clinical manifestations of acute magnesium deficiency in man, in *Magnesium in Health and Disease,* Proceedings of the Second International Symposium on Magnesium, American College of Nutrition; Society for Development of Research in Magnesium, University of Montreal, Montreal, Canada. M. Cantin and M.S. Seelig, eds. SP Medical & Scientific Books, Jamaica, N.Y. (1980), pp. 865–882.

Flink, E.B., Stutzman, F.L., Anderson, A.R., Konig, T., and Fraser, R. Magnesium deficiency after prolonged parenteral fluid administration and after alcoholism complicated by delirium tremens. *J. Lab. Clin. Med.* 43, 169–183 (1954).

Flowers, C.E., Jr. Magnesium sulfate in obstetrics. *Am. J. Obst. Gyn.* 91, 763–776 (1965).

Flowers, C.E., Jr., Easterling, W.E., Jr., White, F.D., Jung, J.M., and Fox, J.T., Jr. Magnesium sulfate in toxemia of pregnancy. *Obst. Gyn.* 19, 315–327 (1962).

Food and Nutrition Board, National Research Council, National Academy of Sciences. *Recommended Dietary Allowances: Mineral Elements,* 9th ed. U.S. Government Printing Office, Washington, D.C. (1980).

Franciosi, R.A., and Blanc, W.A. Myocardial infarcts in infants and children. I. A necropsy study in congenital heart disease. *J. Ped.* 73, 309–319 (1968).

Freeman, R.M., and Pearson, E. Hypomagnesemia of unknown etiology. *Am. J. Med.* 41, 645–656 (1966).

Friedman, W.F., and Roberts, W.C. Vitamin D and the supravalvular aortic stenosis syndrome. The transplacental effects of vitamin D on the aorta of the rabbit. *Circulation* 34, 77–86 (1966).

Friend, B. Nutrients in the United States food supply. A review of trends. *Am. J. Clin. Nutr.* 20, 907–914 (1967).

Gross, P. Concept of fetal endocarditis. *Arch. Path.* 31, 163–177 (1941).

Gruenwald, P. Necrosis in the coronary arteries of newborn infants. *Am. Heart J.* 38, 889–897 (1949).

Haddy, F.J., and Seelig, M.S. Magnesium and the arteries, in *Magnesium in Health and Disease.* Proceedings of the Second International Symposium on Magnesium, American College of Nutrition, Society for Development of Research in Magnesium, University of Montreal, Montreal, Canada, 1976. M. Cantin and M.S. Seelig, eds. SP Medical & Scientific Books, Jamaica, N.Y. (1980), pp. 639–657.

Hall, D.C. Serum magnesium in pregnancy. *Obst. Gyn.* 9, 158–162 (1957).

Hanson, J.W., Jones, K.L., and Smith, D.W. Fetal alcohol syndrome. Experience with 41 patients. *JAMA* 235, 1458–1460 (1976).

Harbert, G.M., Claiborne, H.A., McGaughy, H.S., Wilson, L.A., and Thornton, W.N. Convulsive toxemia. A report of 168 cases managed conservatively. *Am. J. Obst. Gyn.* 100, 336–342 (1968).

Harris, I., and Wilkinson, A.W. Magnesium depletion in children. *Lancet* 2, 735–736 (1971).

Hogg, G.R. Cardiac lesions in hemolytic disease of the newborn. *J. Ped.* 60, 352–360 (1962).

Horley, J.F. Foetal fibroelastosis. *Br. Med. J.* 1, 765–768 (1955).

Hummel, F.C., Sternberger, H.R., Hunscher, H.A., and Macy, I.G. Metabolism of women during the reproductive cycle. IV. Utilization of inorganic elements. (A continuous case study of a multipara). *J. Nutr.* 11, 235–255 (1936).

Hummel, F.C., Hunscher, H.A., Bates, M.F., Bonner, P., and Macy, I.G. A consideration of the nutritive state in the metabolism of women during pregnancy. *J. Nutr.* 13, 263–278 (1937).

Hurley, L.S. Magnesium deficiency in pregnancy and its effects on the offspring, in *Proceedings of the First International Symposium on Magnesium* I, Vittel, France, 1971. J. Durlach, ed. (1971), pp. 481–492.

Hutchinson, H.T., Nichols, M.M., Kuhn, C.R., and Vasicka, A. Effects of magnesium sulfate on uterine contractility, intrauterine fetus, and infant. *Am. J. Obst. Gyn.* 88, 747–758 (1963).

Hutchison, J.H. Some new diseases in pediatrics. *Br. Med. J.* 2, 339–342 (1955).

Johnson, F.R. Anoxia as a cause of endocardial fibroelastosis in infancy. *Arch. Path.* 54, 237–247 (1952).

Johnson, N.E., and Philipps, C.A. Magnesium contents of diets of pregnant women, in *Magnesium in Health and Disease.* Proceedings of the Second International Symposium on Magnesium, American College of Nutrition, Society for Development of Research in Magnesium, University of Montreal, Montreal, Canada, 1976. M. Cantin and M.S. Seelig, eds. SP Medical & Scientific Books, Jamaica, N.Y. (1980), pp. 827–831.

Kastor, J.A. Electrical disorders of the heart. *JAMA* 224, 1031–1033 (1973).

Kelly, J., and Andersen, D.H. Congenital endocardial fibroelastosis. *Pediatrics* 18, 539–555 (1956).

Kostopoulos, V., Seelig, M.S., Dolan, J., Berger, A.R., and Ross, R.S. Influence of parenteral administration of magnesium sulfate to normal pregnant and to pre-eclamptic women, in *Magnesium in Health and Disease.* Proceedings of the Second International Symposium on Magnesium, American College of Nutrition, Society for Development of Research in Magnesium, University of Montreal, Montreal, Canada, 1976. M. Cantin and M.S. Seelig, eds. SP Medical & Scientific Books, Jamaica, N.Y. (1980), pp. 839–848.

Lehr, D. The role of certain electrolytes and hormones in disseminated myocardial necrosis, in *Electrolytes and Cardiovascular Disease. I. Fundamental Aspects.* E. Bajusz, ed. Williams and Wilkins, New York (1965), pp. 248–273. [S. Karger, Basel, 1965].

Lehr, D., and Krukowski, M. About the mechanism of myocardial necrosis induced by sodium phosphate and adrenal corticoid overdosage. *Ann. N.Y. Acad. Sci.* 105, 135–182 (1963).

Lev, M., Croenen, J., and Lambert, E.C. Infantile coronary sclerosis with atrioventricular block. *J. Ped.* 70, 87–94 (1967).

Leverton, R.M., Leichsenring, J.M., Linkswiler, H., Fox, H., and Meyer, F.L. The metabolic response of young women to a standardized diet. *Home Economics Res. Report No. 16.* U.S. Department of Agriculture, Washington, D.C. (1962).

Lim, P., Jacob, E., Dong, S., and Khoo, O.T. Values for tissue magnesium as a guide in detecting magnesium deficiency. *J. Clin. Path.* 22, 417–421 (1969).

Linden, V. Correlations of vitamin D intake to ischemic heart disease, hypercholesterolemia and renal calcinosis, in *Nutritional Imbalance in Infant and Adult Disease.* Proceedings of the Annual Meeting of the American College of Nutrition, New York, 1975. M.S. Seelig, ed. SP Medical & Scientific Books, Jamaica, N.Y. (1977), pp. 23–42.

McGanity, W.J. Discussion of Flowers, C.E. *Am. J. Obst. Gyn.* 71, 775 (1965).

Martin, H.E. Clinical magnesium deficiency. *Ann. N.Y. Acad. Sci.* 162, 891–900 (1969).

Miller, R.A., Mehta, A.B., Rodriquez-Coronel, A., and Lev, M. Congenital atrioventricular block with multiple ectopic pacemakers. Electrocardiographic and conduction system correlation. *Am. J. Card.* 30, 554–558 (1972).

Mischel, W. Die anoganische Bestanteile der Placenta. *Arch. Gynaek.* 8, 11, 228, 384, 638 (1957).

Moller, J.H., Lucas, R.V., Jr., Adams, P., Jr., Anderson, R.C., Jorgens, J., and Edwards, J.E. Endocardial fibroelastosis. A clinical and anatomic study of 47 patients with emphasis on its relationship to mitral insufficiency. *Circulation* 30, 759–782 (1964).

Muller, P. La therapeutique magnésienne moderne en gynecologie et en obstetrique. *Strasbourg Med.* 19, 117–132 (1968).

Muller, P., Dellenbach, P., and Frenot, M. Deficit magnésique en pathologie gyneco-obstetricale, in *Proceedings of the First International Symposium on Magnesium II,* Vittel, France, 1971. J. Durlach, ed. (1971), pp. 459–480.

Naeye, R.L., Messmer, J. III, Specht, T., and Merrett, T.A. Sudden infant death syndrome temperament before death. *J. Ped.* 88, 511–515 (1976).

Neufeld, H.N., and Vlodaver, Z. Structural changes in the coronary arteries of infants. *Bull. Assoc. Card. Ped. Eur.* 4, 35–39 (1968).

Neufeld, H.N., and Vlodaver, Z. Structural changes of coronary arteries in young age groups. *Intl. Card.* 2, 56–78 (1971).

Oppé, T.E., and Redstone, D. Calcium and phosphorus levels in healthy newborn infants given various types of milk. *Lancet* 1, 1045–1048 (1968).

Oppenheimer, E.H., and Esterly, J.R. Cardiac lesions in hypertensive infants and children. *Arch. Path.* 84, 318–325 (1967).

Ornoy, A., Menczel, J., and Nebel, L. Alterations in the mineral composition and metabolism of rat fetuses and their placentas as induced by maternal hypervitaminosis D_2. *Isr. J. Med. Sci.* 4, 827–832 (1968).

Pincus, J.B., Gittleman, I.F., Sobel, A.E., and Schmerzler, E. Effects of vitamin D on the serum calcium and phosphorus levels in infants during the first week of life. *Pediatrics* 13, 178–185 (1954).

Potvliege, P.R. Hypervitaminosis D_2 in gravid rats. Study of its influence on fetal parathyroid glands and a report of hitherto undescribed placental alterations. *Arch. Path.* 73, 371–382 (1962).

Pritchard, J.A. The use of the magnesium ion in the management of eclamptogenic toxemias. *Surg. Gyn. Obst.* 100, 131–140 (1955).

Robertson, J.H. The significance of intimal thickening in the arteries of the newborn. *Arch. Dis. Child.* 35, 588–590 (1960).

Sabiston, D.C., Jr., Pelargonia, S., and Taussig, H.B. Myocardial infarction in infancy. The surgical management of a complication of congenital origin of the left coronary artery from the pulmonary artery. *J. Thor. Cardiovasc. Surg.* 40, 321–336 (1960).

Schornagel, H.E. Intimal thickening in the coronary arteries in infants. *Arch. Path.* 62, 427–432 (1956).

Scott, K.E., and Usher, R. Fetal malnutrition: its incidence, causes and effects. *Am. J. Obst. Gyn.* 94, 951–963 (1966).

Scoular, F.I., Pace, J.K., and Davis, A.M. The calcium, phosphorus, and magnesium balances of young college women consuming self-selected diets. *J. Nutr.* 62, 489–501 (1957).

Seelig, M.S. The requirement of magnesium by the normal adult. Summary and analysis of published data. *Am. J. Clin. Nutr.* 14, 342–390 (1964).

Seelig, M.S. Electrocardiographic patterns of magnesium depletion appearing in alcoholic heart disease. *Ann. N.Y. Acad. Sci.* 162, 906–917 (1969a).

Seelig, M.S. Vitamin D and cardiovascular, renal, and brain damage in infancy and childhood. *Ann. N.Y. Acad. Sci.* 147, 537–582 (1969b).

Seelig, M.S. Are American children still getting an excess of vitamin D? Hyperreactive children at risk. *Clin. Ped.* 9, 380–383 (1970).

Seelig, M.S. Human requirements of magnesium; factors that increase needs, in *Proceedings of the First International Symposium on Magnesium I,* Vittel, France, 1971. J. Durlach, ed. (1971), pp. 10–38.

Seelig, M.S. Myocardial loss of functional magnesium. II. In cardiomyopathies of diverse etiology, in *Recent Advances in Studies on Cardiac Structure and Metabolism. I. Myocardiology.* E. Bajusz and G. Rona, eds. University Park Press, Baltimore (1972), pp. 626–638.

Seelig, M.S. Magnesium deficiency with phosphate and vitamin D excesses. Possible role in pediatric cardiovascular disease. *Cardiovasc. Med.* 3, 637–650 (1978).

Seelig, M.S. *Magnesium Deficiency in the Pathogenesis of Disease.* L.V. Avioli, ed. Plenum Medical Book Co., New York (1980).

Seelig, M.S., and Bunce, G.E. Contribution of magnesium deficit to human disease, in *Magnesium in the Environment.* Proceedings of Symposium at Fort Valley State College, Georgia (1972), pp. 61–106.