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SOY IN HUMAN HEALTH - PART II

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SOYA IN HEART HEALTH

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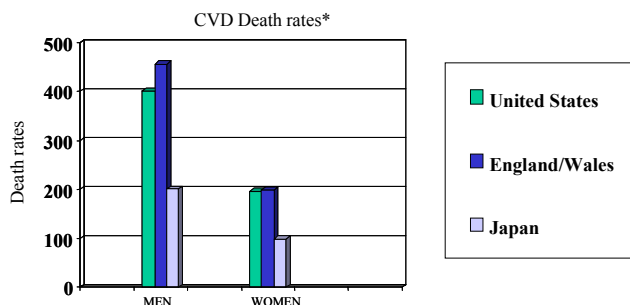
HEALTH PROFESSIONALS IN INDIA ARE FACED WITH A MAJOR PROBLEM

Look at the alarming statistics from India:

- Among the many health predictions for the new millennium, the most alarming is that of cardiovascular disease (CVD)— heart disease and stroke— topping the list for death and disability. Current projections suggest that by the year 2020 India will have the largest cardiovascular disease burden in the world.
- While there are undoubted regional differences between the developed countries and other economies, the predictions for India by 2015 show a steady increase since 1985. The projected rate per 100 000 for 1985 for all “circulatory diseases” was 145 males, 126 females; for 2000, 253 males and 204 females and for 2015, 295 males and 239 females, which is higher than that for other causes such as cancer.²
- One fifth of the deaths in India are from coronary heart disease. By the year 2020, it will account for one third of all deaths. Sadly, many of these Indians will be dying young.
- Heart disease in India occurs 10 to 15 years earlier than in the west.
- There are at least 20 million diabetics in India, which is the highest ever reported number from anywhere in the world. The prevalence of diabetes varies between 6-8% in urban and 2-3% in rural adults.
- Indians tend to be diabetic at a relatively young age of 45 years which is about 10 years earlier than in West
- There appears to be a steady increase in hypertension prevalence over the last 50 years, more in urban than in rural areas. Hypertension is 25-30% in urban and 10-15% in rural subjects.

Figure 1 compares CVD death rates for men and women from the United States, England/Wales and Japan.

Figure 1



* Number of deaths per 100,000 population, aged 35 to 74 years.

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CVD does not have one single cause. In an individual the risk for CVD is determined by a combination of risk factors – modifiable and not modifiable factors. Non-modifiable factors are inheritance, sex and age. Modifiable factors are elevated blood lipid levels, hypertension, cigarette smoking, lack of physical activity, obesity and diabetes.

Prevention is the mantra of the millennium. Primary prevention, especially in young subjects, is the need of the hour. Diet is a basic element in the development of CVD and the atherosclerotic process often underlying it. Dietary modification is the first step in the preventive treatment of several major modifiable risk factors for CVD such as hypercholesterolemia, hypertriglyceridemia, elevated LDL cholesterol, low HDL cholesterol, hypertension, obesity, and diabetes. A “heart healthy” diet is recommended by the National Cholesterol Education Program (NCEP),³ before initiating drug therapy, which can produce negative side effects and is expensive. In a country like ours, inexpensive options have to be considered first. A “heart-healthy” diet is an essential component of both prevention and treatment of CVD.

Most dietary guidelines have emphasized the role of dietary fat. The recommended low-saturated fat, low-cholesterol diet⁴ does help lower risk of CVD^{5,6}. However, other dietary factors may offer additional benefits.

The development of CVD is associated with the type of dietary protein consumed. This association was first advanced by Ignatowski of Russia in 1908. He proposed that proteins have the ability to reduce CVD risk⁷. In the early 1940s Meeker and Kestan^{8,9} showed that animal proteins was more atherogenic than plant protein in rabbits. The last twenty years have seen numerous studies in animals and in humans to determine the effects of proteins from animal and plant sources on blood cholesterol levels and other biological indicators of CVD risk. Soy proteins was the primary plant protein used in these studies because it is the only plant protein equal in protein quality to animal protein. However, most researchers now use soy protein as the plant protein in studies because of its unique ability to lower blood cholesterol and to favorably affect other biological parameters.

Soybeans were considered both a food and a medicine for centuries in Asia and were one of five “Sacred” crops named nearly five centuries ago by Chinese emperor Sheng-Nung. Soybeans first appeared in Japan in the eight century AD but did not appear in Europe until almost 1000 years later. In 1765 soybeans were introduced to North America. Soybeans did not begin to increase in importance as a crop until the end of the 19th century. Since the 1980s, there has been a great increase in the consumption both of traditional soy foods (tofu, soymilk, miso and tempeh) and the second and third generation products. In 1986 the American Dietetic Association¹⁰ recommended that school lunch programs incorporate tofu in their meals as an alternative to meat.

Within a period of two decades, world soybean production has more than tripled, from 40 MMT in 1970 to 120 MMT in 1992 (R) with the United States accounting for about half of the world’s total output (Fig. 2)

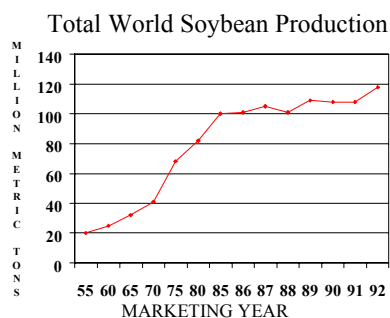


Figure 2a

World soybean production in 1993

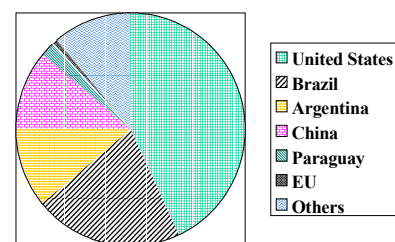


Figure 2b Source : In Pulse, 8, 1994

This increased production of Soy protein is a result of studies of Japanese diets. Japanese men who consume relatively large amounts of Soy have about one sixth the risk of CHD as US men. Magate et al¹² used information from an annual health check-up program in Japan in 1242 men and 3596 women. They found a significant trend between increasing intake of Soy products and decreasing total cholesterol concentration in both men and women.

Mechanisms of action

Although there is convincing evidence of soy protein's ability to decrease LDL cholesterol in hypercholesterolemic individuals, researchers are yet to identify exactly how this reduction is accomplished. It is highly possible that the cardio protective effects of Soy protein is the result of not one component or action, but of a number of individual or interrelated factors. The following components of Soy have been investigated for cholesterol lowering activity.

1. Amino Acids, peptides, and storage proteins: Animal studies^{13,14,45} indicated that certain amino acids, especially lysine, increase blood cholesterol levels, while arginine counteracts this effects. Soy protein provides a more favorable arginine to lysine ratio than casein.

Moreover, it was discovered that subjecting isolated soy protein to microbial proteases or pepsin resulted in the formation of 2 fractions – an insoluble high molecular weight fraction (HMF) and a soluble lower molecular weight fraction. HMF contains hydrophobic peptides that are very good at binding bile acids in vitro²⁸. Wang et al found that HMF increases steroid excretion and reduces serum cholesterol levels in humans.

Further, the two globulins 115 and 75, which are the major storage proteins in soybeans may be involved in direct up-regulation of liver or peripheral lipoprotein receptors (thus removing them from circulation). This would lead to a significant lowering of blood cholesterol. Lovali et al¹⁶ reported a seven fold increase in monocyte LDL receptor activity in hypercholesterolemic individuals who consumed Soy protein. LDL receptor mRNA levels in mononuclear cells were increased 75% in subjects consuming Soy protein compared with casein¹⁷.

2. Soy fiber: Soy fiber has a hypocholesterolemic effect when added to other foods.

3. Phytic acid: Soy rich diets provide phytic acid. Phytic acid chelates zinc strongly in the intestinal tract, thus decreasing its absorption¹⁸. A copper deficiency or a high ratio of zinc to copper results in a rise in blood cholesterol¹⁹. A theory propounded is that phytic acid may lower cholesterol levels by chelating zinc and allowing more copper to be absorbed, consequently decreasing the ratio of zinc to copper.

4. Saponins: Saponins are compounds consisting of carbohydrate moieties attached to steroidal molecule. Saponins are present in all Soy protein products, except those that are extracted with alcohol. These compounds may contribute to cholesterol lowering by increasing bile excretion²⁰.

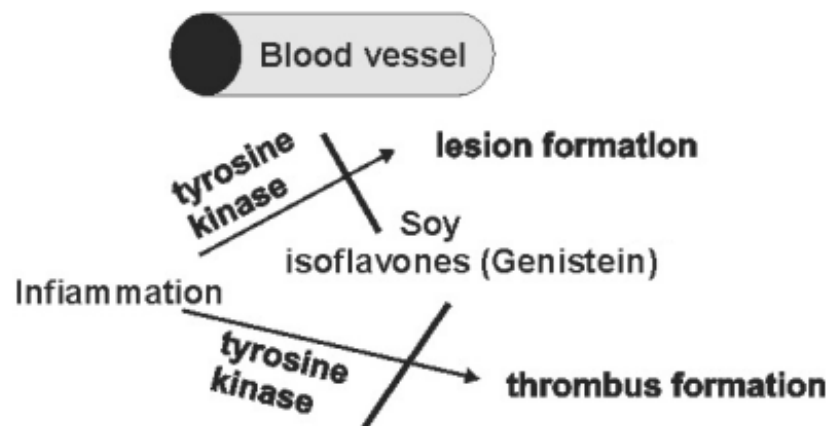
5. Trypsin inhibitors: All soy foods are heat-treated, which inactivates virtually all of the trypsin inhibitors. Heat-stable Bowman Birk inhibitor may increase the secretion of cholecystokinin, which in turn stimulates the gallbladder and increases secretion of bile into the gastrointestinal tract.

6. Isoflavanes: Phytoestrogens are only one group of compounds under the general term phytochemical, or plant chemical. Phytoestrogens vary greatly in both their estrogenic potency and physiologic effects. Isoflavones, which are primarily found in soybeans, are one class of phytoestrogens. Isoflavones have structures similar to mammalian estrogens. Isoflavones exert an estrogenic effect and bind to two types

of estrogen receptors (ER- α and ER- β). Isoflavones found in Soy include genistein, daidzein, and glycitein. Genistein binds rather weakly to ER- α (about 1/20 the affinity of 17- β estradiol) but with much higher affinity to ER- β (about 1/3 the affinity of 17 β - estradiol)²⁷. Estrogen has been shown to decrease LDL cholesterol and increase HDL cholesterol. They have a role in the up-regulation of depressed LDL receptors in the liver cells. This results in increased LDL uptake by the liver and lowering of serum LDL and hence lowering of serum cholesterol levels.

Soy protein containing isoflavones lowered cholesterol significantly more than soy protein without isoflavones in humans^{21,22,23}. Crouse et al²¹ concluded that the cholesterol-lowering effect of soy proteins is entirely due to isoflavones. Genistein is known to inhibit tyrosine kinase, an enzyme involved in the cascade of events leading to formation of thrombi and lesions²⁴. Isoflavones also act as antioxidants and can inhibit LDL oxidation²⁵.

Figure 3



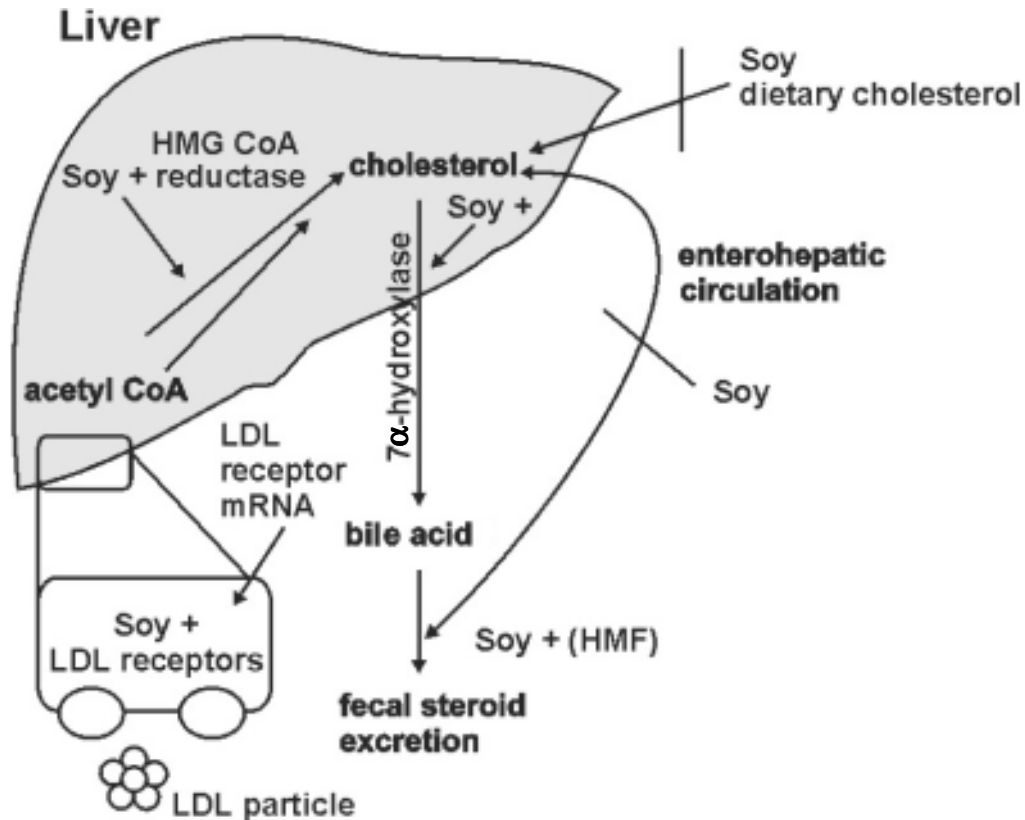
Isoflavone extract from soy improved systemic arterial elasticity in women without effects on blood lipid levels²⁶. These studies indicate that isoflavones and/or other ethanol-soluble soy phytochemicals may have direct effects on the vascular system, independent of lipid metabolism.

Amongst all these components, isoflavones are the major components by which soy lowers blood cholesterol levels. In fact, animal studies suggest that soy estrogens (i.e. isoflavones) may account for 60-70% of hypocholesterolemic effect of Soy protein.

Various mechanisms have been proposed to explain the hypocholesterolemic effect of consuming soy protein.

- 1. Stimulation of bile acid secretion:** There is an interruption in intestinal absorption of bile acids and dietary cholesterol when Soy protein is consumed. This results in enhanced bile acid secretion. This causes cholesterol to be removed from the body, resulting in increased liver synthesis of cholesterol for enhanced synthesis of bile acids and in greater LDL-cholesterol receptor activity.
- 2. Changes in liver metabolism of cholesterol:** The above causes the liver to convert more cholesterol into bile acids, thereby depleting its cholesterol pool. The liver responds by increasing the number of LDL receptors, causing fall in blood cholesterol.

Figure 4



- Hormone effects:** It is widely accepted that estrogens reduce risk for CHD. Estrogen decreases LDL-cholesterol, increase HDL-cholesterol, and improves vasomotor tone and vessel wall compliance. Soy isoflavones may act as an estrogen like compound and produce effects similar to those of estrogen. The higher arginine to lysine ratio of soy protein may decrease insulin secretion and increase glucagon secretion, which would then inhibit lipogenesis²⁹. These soy protein effects on insulin and glucagon levels have been reported in hypercholesterolemic humans³⁰. In animal studies, thyroxine levels increased with consumption of soy protein^{31,32}. High thyroxine levels were theorized to decrease cholesterol levels, but human studies have been inconsistent^{33,34}.
- Regulation of LDL receptors:** An increase in LDL receptors result in increased LDL cholesterol removal from blood. On the basis of several clinical studies, Sirton et al concluded that Soy protein up-regulates depressed LDL receptors in humans³⁴.

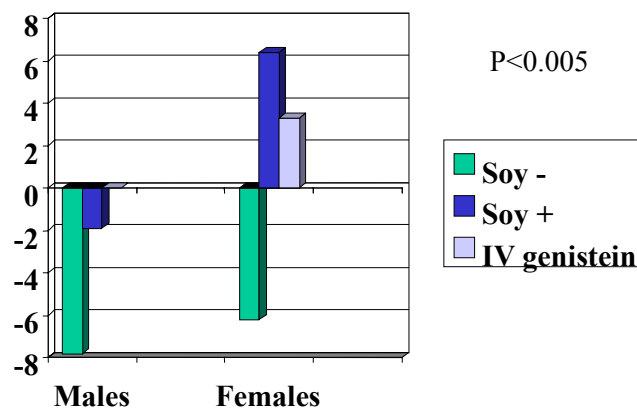
In addition to decreasing elevated levels of blood cholesterol, isolated soy protein has other positive effects on atherosclerosis.

- Antioxidant effect:** The hypothesis is now widely accepted that LDL cholesterol becomes atherogenic only after it has undergone oxidative modification. This proposes a role of antioxidant in preventing CVD. Studies show that genistein, and to a lesser extent, other isoflavones found in soy products have potential antioxidant activity.^{35,36}

2. **Effect on postprandial lipemia:** Postprandial lipemia resulting from dietary fat intake is considered to be associated with the development of CAD³⁷. Shige et al³⁷ concluded that consuming **20g/day** of isolated soy protein favorably affected post prandial remnant lipoprotein response.
3. **Effect on blood coagulation system:** One of the essential steps in the atherosclerotic process is the adherence of platelets to foam cells and the subsequent increase in growth factors released from platelets. In *in vitro* studies^{38,39}, genistein has been shown to
 - a. Interfere with the activation and accumulation of platelets.
 - b. Reduce the production of platelet-derived growth factors, which are believed to play an important part in the proliferation of smooth muscle cells in atherosclerotic plaque.
 - c. Inhibit the action of thrombin, an enzyme that converts fibrinogen into fibrin to form a blood clot.
4. **Effect on dilator response in atherosclerosis arteries:** In a study by Honore et al⁴⁰ constricted arteries in females monkeys dilated on feeding isoflavones intact Soy and IV administration of genistein.

Figure 5

Effects of Soy Diets either devoid of Isoflavones (Soy-) or with intact Isoflavones (Soy +) and of IV genistein on Coronary artery responses* to Acetylcholine in male and female rhesus monkeys



5. **Effect in restenosis:** Honore et al⁴¹ conducted research in which rhesus monkeys were fed atherogenic diets containing soy protein either with intact (Soy+) or with trace amounts (Soy-) of isoflavones. The animals then sustained a balloon injury to the iliac artery. They found that the Soy + diet inhibited the proliferation of cells that typically follows a balloon injury.
6. **Effect on atherosclerosis:** In a study on monkeys, Anthony et al⁴² found that Soy + group had the least coronary artery atherosclerosis lesions-90% less than in the casein group and 50% less than in the Soy- group.

CLINICAL AND EXPERIMENTAL STUDIES

In a meta-analysis⁴³ of 38 controlled clinical trials the relation between Soy protein consumption and serum lipid concentrations in humans were examined. In most of the studies soy protein intake averaged 47g per day.

The ingestion of diets containing soy protein, as compared with control diets, was accompanied by a significant reduction in serum concentrations of total cholesterol, LDL cholesterol, and triglycerides (Table 1).

TABLE 1. Net Change in Serum Lipids and Lipoprotein Concentrations In Subjects Ingesting the Soy-Containing Diets, as Compared with the Control Diets.*

INDEX	NO. OF STUDIES	NO. OF SUBJECTS	CHANGE (mg/dL)	95% CI	PERCENT CHANGE
Total cholesterol	38	730	-23.2	-32.9 to -13.5	-9.3
LDL cholesterol	31	564	-21.7	-31.7 to -11.2	-12.9
HDL cholesterol	30	551	+1.2	-3.1 to +5.4	+2.4
VLDL cholesterol	20	255	-0.4	-4.6 to +3.9	-2.6
Triglycerides	30	628	-13.3	-25.7 to -0.3	-10.5

*Net change is expressed as the change during the soy-containing diet minus the change during the control diet. CI denotes confidence interval.

Table-2 presents changes in serum cholesterol and LDL cholesterol concentrations according to quartiles of the initial cholesterol concentration. Subjects with normal cholesterol levels, who had initial values below 200 mg per deciliter, had non-significant reductions of 3.3 percent while receiving the soy protein diet. Those with mild hypercholesterolemia, who had initial values of 200 to 255 mg per deciliter (5.2 to 6.6 mmol per liter), had non-significant reductions of 4.4 percent. Subjects with moderate hypercholesterolemia, who had initial values of 250 to 333 mg per deciliter (6.70 to 8.61 mmol per liter), had significant decreases of 7.4 percent. Subjects with severe hypercholesterolemia, whose initial values were above 335 mg per deciliter (8.66 mmol per liter), had significant reductions of 19.6 percent.

The pattern of changes in serum LDL cholesterol concentrations, according to quartiles of the initial serum cholesterol concentrations.

Changes in serum HDL cholesterol concentrations were similar for all quartiles.

TABLE 2. Changes in Serum Cholesterol and LDL Cholesterol Concentrations According to Quartiles of the Study Group for Initial Cholesterol Concentration.*

VARIABLE	QUARTILE			
	1	2	3	4
Cholesterol (mg/dL) mg/dl				
Initial range	127.1 to 197.8	201.2 to 255.4	259.3 to 332.8	>335
Change	-5.2	-10.1	-22.2	-71.5
95% CI	-17.1 to +6.7	-21.8 to +1.7	-37.3 to -7.1	-86.6 to -56.5
% Change	-3.3	-4.4	-7.4	-19.6

VARIABLE	QUARTILE			
	1	2	3	4
LDL cholesterol (mg/dL)				
Change	-7.1	-10.7	-18.3	-68.1
95% CI	-20.0 to +6.0	-24.3 to +2.9	-35.3 to -1.3	-90.2 to -45.9
% Change	-7.7	-6.8	-9.8	-24.0

*Exact ranges are given for cholesterol and total cholesterol concentrations in the quartiles.

CI denotes confidence interval.

The meta-analysis indicated that the replacement of animal protein in the diet with Soy protein was associated with a significant decrease in serum cholesterol and LDL cholesterol concentrations. This was a fairly consistent finding, since decreases in serum cholesterol concentrations were reported in 34 of 38 studies; in the 4 studies that did not report such reductions, the subjects had fairly low initial serum cholesterol values (average, 185mg/dl). The meta-analysis also indicated that Soy proteins significantly decreased triglyceride concentrations and a non-significant increase in serum HDL cholesterol concentrations.

Generally persons with hypercholesterolemia are more responsive than normocholesterolemic subjects (Table 3,4). However Wong et al⁴⁴ found that regardless of plasma lipid status, the soy protein diet was associated with a statistically significant decrease in plasma concentrations of LDL cholesterol and the ratio of plasma LDL cholesterol to HDL cholesterol (P=0.005)

TABLE 3. Effects of soy-protein diets on plasma or serum cholesterol levels in human subjects with hypercholesterolemia

Reference	No. of subjects		Age (Years)	Days on diet	Mean Plasma or Serum Cholesterol level		Diff. %
	M	F			Control diet mmol/L	Soy-protein diet mmol/L	
Sirtori	10	10	22-68	21	8.66±0.75	6.67±0.52	-23
					8.09±0.44	6.57±0.34	-19
	25	16	49±2	21	8.72±0.34	6.98±0.34	-20
Descovich	29	36	20-69	28	9.08±0.18	7.37±0.21	-19
						7.86±0.18	-23
	67	60	47±11	56	9.10±0.49		-23
		52±11	56			-25	
Hodges	6		33-46	28	7.66±0.62	5.02±0.44	-34
Verrillo	4	9	41±22	112	8.80±0.40	6.20±0.20	-29
	4	2	59±11				
Verrillo	12	12	51±8	112	8.70±0.20	6.10±0.20	-30
	7	7	58±13				
Gaddi	8	7	3-12	28	9.31±2.87	7.55±2.46	-19
Grundy	4		32-69	30	5.84±0.98	5.46±0.72	-7
	10		29-64	3	5.74±0.36	5.64±0.44	-2

A very recent study done by Potter et al., University of Illinois, indicated that 25gm of Soy protein with or without soy fiber effectively lowered cholesterol levels in individuals with cholesterol levels of 5.7 mmol/L and higher. The decrease was attributed primarily to changes in LDL; the higher the initial cholesterol level, the greater the decrease.

TABLE 4. Effects of soy-protein diets on plasma or serum cholesterol levels in normocholesterolemic human subjects

Reference	No. of subjects		Age (Years)	Days on diet	Mean Plasma or Serum Cholesterol level		Diff. %
	M	F			Control diet mmol/L	Soy-protein diet mmol/L	
Carroll		6	21	36	4.94±0.28	4.53±0.26	-8
		5	20-25	37	4.47±0.13	4.16±0.10	-8
		5	10-22	41	4.29±0.08	4.16±0.07	-3
Giovannetti		12	20-28	28	3.39±0.21	3.41±0.21	+1
				28	3.49±0.21	3.39±0.21	-3
Van Raaij	46	30	18-28	28	3.96±0.59	3.88±0.59	-2
Van Raaij	22	27	29-60	28	5.30±1.03	5.09±1.10	-4
					5.14±1.03	5.17±0.98	+1
Miyazima	2	4	21-53	21	5.14±0.65	4.53±0.39	-12
	2	4	21-53	21	4.97±1.42	4.45±1.09	-10
Goldberg	3	1	20-59	42	4.19±0.16	4.14±0.59	-1
Sacks	9	4	21-40	20	3.23±0.16	3.26±0.13	+1

Anthony et al⁴² fed moderately atherogenic diets containing casein or soy protein with intact (Soy+) or with trace amounts (Soy-) of isoflavones to male cynomolgus monkeys. Table 5 shows that the levels of total cholesterol and LDL-cholesterol + VLDL-cholesterol were highest on the casein diet, somewhat lower on the Soy-diet, and significantly lower on the Soy+ diet. HDL cholesterol levels were lowest on the casein diet, significantly higher on the Soy-diet, and highest on the Soy+ diet.

TABLE 5. MEAN* PLASMA LIPIDS IN MALE CYNOMOLGUS MONKEYS FED DIETS WITH CASEIN, ISOLATED SOY PROTEIN WITH TRACE AMOUNTS OF ISOFLAVONES (SOY-), OR ISOLATED SOY PROTEIN WITH INTACT ISOFLAVONES (SOY+)

Lipid/Lipoprotein	DIET			ANCOVA P
	Casein (n=24)	Soy (-) (n=27)	Soy(+) (n=28)	
TC (mg/dL)	457.1±22.0	433.1±20.1	305.9±20.1	<0.001
LDL-C+VLDL-C (mg/dL)	416.9±24.0	387.1±22.0	250.2±22.0	<0.001
HDL-C (mg/dL)	37.9±3.1	46.0±3.1	58.0±3.1	<0.001
TC/HDL-C ratio	15.8±1.18	11.9±1.11	6.6±1.09	<0.001

*Means adjusted for baseline measure of that variable; within each variable, means with different letter superscripts are significantly different (P<0.05)

Adapted from Anthony MS et al. Soy protein versus soy phytoestrogens in the prevention of diet-induced coronary artery atherosclerosis of cynomolgus monkeys. *Arterioscler Thromb Vasc Biol* 1997; 17:2524-2531.

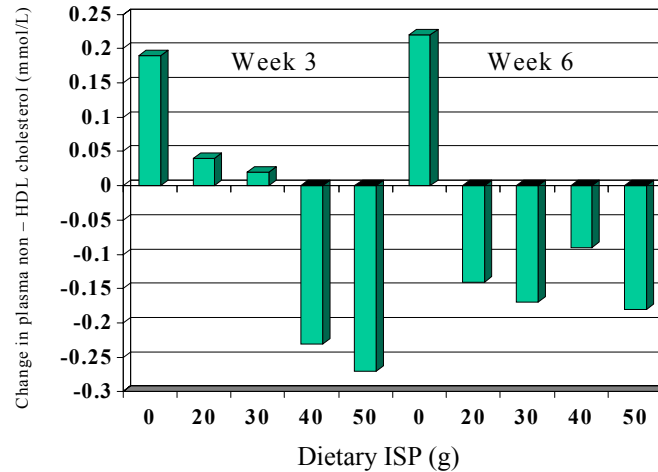
Teixeira et al⁴⁶ designed a dose-response study to determine the effects of graded amounts of dietary soy protein on plasma cholesterol and (a) lipoproteins concentrations in 81 moderately hypercholesterolemic men. After a 3-week lead-in on a Step I diet, total cholesterol was measured and subjects were randomly divided into 5 groups. For 6 weeks, each group received 50 g protein/d, which included isolated soy protein (ISP) and casein, respectively, in the following amounts: 50:0, 40:0, 30:20, 20:30, and 0:50 (control group). Blood was collected at baseline and weeks 3 and 6 of the intervention. Blood concentrations of lipids and apolipoproteins in each group at baseline and at weeks 3 and 6 are shown in Table 6. Non-HDL cholesterol concentrations were significantly reduced at week 6 in all groups that received ISP (Fig. 6). Adjusted mean changes of -0.139, -0.163, -0.095, and -0.182 mmol/L were found for the groups that received 20,30, 40 and 50g ISP, respectively. At week 3, significant reductions were found only when 40 and 50g ISP were consumed, with adjusted mean changes of -0.236 and -0.278 mmol/L, respectively. **At week 6, significant reduction was also observed in the group which received 20g ISP. Hence on long term basis even lesser consumption of ISP may help in reducing cholesterol levels.**

TABLE 6. Plasma lipid and serum apolipoprotein concentrations at baseline and weeks 3 and 6 of the intervention^a

	Group				
	0 g ISP (control) (n=16)	20 g ISP (n=16)	30 g ISP (n=16)	40 g ISP (n=16)	50 g ISP (n=16)
TC (mmol/L)					
Baseline	6.08±0.22 ^b	5.98±0.22	6.01±0.18	5.96±0.20	6.28±0.18
Week 3	6.24±0.24	5.99±0.26	6.03±0.18	5.74±0.19	6.02±0.21
Week 6	6.29±0.24	5.87±0.18	5.90±0.23	5.93±0.17	6.07±0.19
HDL cholesterol (mmol/L)					
Baseline	1.10±0.08	1.07±0.06	1.13±0.09	1.11±0.08	1.13±0.05
Week 3	1.08±0.07	1.03±0.07	1.12±0.08	1.11±0.09	1.17±0.07
Week 6	1.10±0.07	1.09±0.07	1.17±0.08	1.15±0.08	1.15±0.06
Non-HDL cholesterol (mmol/L)					
Baseline	4.98±0.24	4.91±0.21	4.88±0.19	4.86±0.20	5.15±0.19
Week 3	5.17±0.25	4.96±0.26	4.91±0.18	4.63±0.18	4.85±0.22
Week 6	5.19±0.25	4.78±0.18	4.74±0.21	4.78±0.18	4.92±0.18
TC:HDL cholesterol					
Baseline	5.89±0.42	5.84±0.37	5.86±0.49	5.73±0.36	5.71±0.31
Week 3	6.15±0.40	6.13±0.40	5.85±0.44	5.52±0.33	5.36±0.34
Week 6	6.02±0.37	5.68±0.34	5.37±0.34	5.50±0.33	5.47±0.30
Triacylglycerol (mmol/L)					
Baseline	2.14±0.28	1.77±0.12	2.52±0.31	2.05±0.22	2.18±0.28
Week 3	2.61±0.37	2.08±0.24	2.59±0.31	1.90±0.18	1.95±0.26
Week 6	2.32±0.25	1.93±0.16	2.27±0.24	2.13±0.26	2.54±0.40
Apo B (g/L)					
Baseline	1.40±0.08	1.34±0.05	1.47±0.08	1.41±0.07	1.47±0.07
Week 3	1.54±0.09	1.41±0.07	1.40±0.07	1.29±0.05	1.38±0.10
Week 6	1.50±0.10	1.31±0.05	1.34±0.08	1.36±0.07	1.39±0.07
Apo A-I (g/L)					
Baseline	1.38±0.05	1.34±0.05	1.43±0.07	1.29±0.03	1.40±0.06
Week 3	1.37±0.05	1.34±0.07	1.40±0.09	1.26±0.04	1.45±0.07
Week 6	1.39±0.06	1.35±0.07	1.43±0.09	1.32±0.05	1.36±0.05
Lipoprotein(a) (mmol/L)					
Baseline	42.8 ^c (1.0-340.4)	55.3 (7.6-266.4)	64.2 (3.1-310.7)	61.3 (8.4 - 672.7)	74.1 (3.3- 469.2)
Week 3	41.2 (1.3-406.7)	72.9 (7.1-322.6)	75.1 (3.7-283.6)	76.8 (10.1-605.4)	73.0 (3.1-595.6)
Week 6	43.9 (0.0-410.1)	52.3 (6.5-326.2)	75.7 (4.2-272.6)	59.0 (7.3-578.7)	68.0 (2.3-514.7)

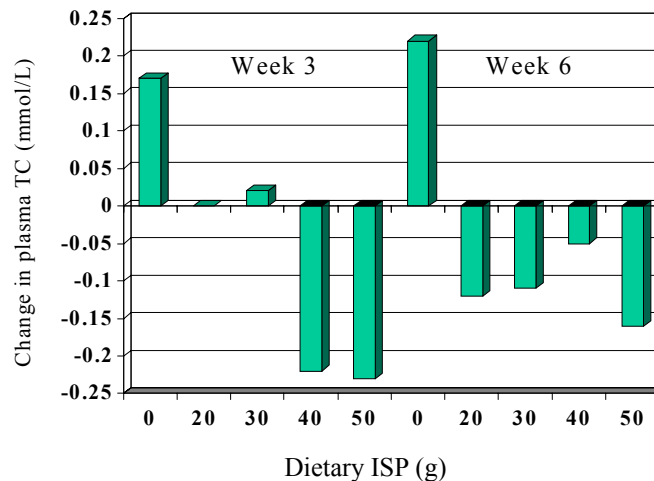
^aISP, isolated soy protein; TC, total cholesterol; apo, apolipoprotein.^bmean (SEM unless otherwise indicated). ^cMedian, range in parentheses

Figure 6



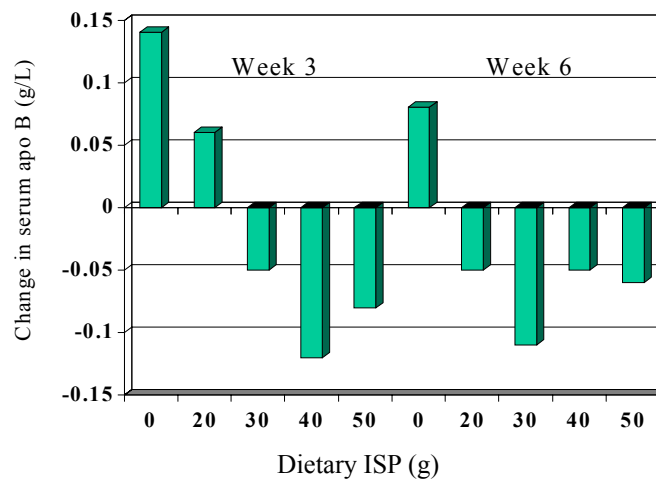
The reduction in plasma TC concentration (Fig. 7) was significant at week 6 for the groups that consumed 20, 30 and 50g ISP (adjusted mean changes of -0.126 , -0.115 , and -0.167 mmol/L, respectively). For the 40-g-ISP group, a non-significant reduction of 0.053 mmol/L was found. At week 3, the multiple R^2 for the multiple linear regression was not significant ($P=0.059$; fig. 7). However, there were identifiable trends when 40g ISP was consumed. The adjusted mean changes were -0.230 and -0.240 mmol/L ($P=0.01$ for both;) for the 40 and 50g ISP groups, respectively. This suggests that the effects identified at week 6 were also apparent at week 3 for the 40 and 50g ISP groups.

Figure 7



Serum apo B concentrations (Fig. 8) were significantly reduced at week 6 in all groups that consumed ISP. Adjusted mean changes of -0.055 , -0.113 , -0.055 , and -0.063 g/L were found for the 20-, 30-, 40-, and 50-g-ISP groups, respectively. At week 3, significant reductions were found when ≥ 30 g ISP was consumed. The adjusted mean changes were -0.059 , -0.116 , and -0.087 g/L for the 30-, 40-, and 50-g-ISP groups, respectively. At week 6, no significant changes were found for concentrations of HDL cholesterol, triacylglycerol, apo A-I, or lipoprotein(a) or TC:HDL cholesterol in any group that received ISP.

Figure 8



One of the greatest challenges for a physician is the treatment of a child with polygenic or familial hypercholesterolemia. Beginnings of adult atherosclerosis can be found in the fatty streaks that develop during the second decade of life⁴⁷. Dietary modifications is the initial treatment for children with hypercholesterolemia. Most physicians hesitate to start hypercholesterolemic children on a lifetime of drug therapy. A “heart healthy” step I NCEP diet achieves a 10% drop in total cholesterol. This translates into decrease of only 30mg/dL for a child with total blood cholesterol of 300mg/dL, the average level in a child with familial Hypercholesterolemia. Gaddi et al⁴⁸ achieved an average 21.8% lowering of blood cholesterol in children with familial Hypercholesterolemia when soy proteins was substituted for animal protein in a low fat low cholesterol diet. Thus soy protein makes diet therapy a much more potent tool than a low fat diet alone.

Wagner et al⁴⁹ proposed that protein may also act at the level of the artery wall to reduce LDL accumulation in male monkeys. Further, as diabetics are at an increased risk of atherosclerosis, they sought to determine if soy consumption would also improve plasma lipoproteins and disease arterial LDL accumulation in diabetic monkeys. The results are shown in Tables 7 & 8.

TABLE 7. Effect of Soy and Diabetes on Plasma Lipid and Lipoprotein Measures (mean±SEM)

Parameter	Soy (N=6)	Soy+DM (n=5)	CASEIN (n=6)	CASEIN+DM (n=6)	P (Prot/DM/PxDM)
TC (mg/dL)*					
Baseline	405±54	338±53	340±54	375±75	NS
14 weeks	211±30	288±33	304±30	384±30	.007/.02/.95
HDLC (mg/dL)*					
Baseline	39±6	35±9	42±7	37±8	NS
14 weeks	71±6	66±6	45±6	57±6	.01/.55/.15
LDLC (mg/dL)*					
Baseline	367±58	303±59	298±58	338±77	NS
14 weeks	139±33	223±36	259±33	326±32	.004/.03/.81
TC:HDLC*					
Baseline	12.5±3.0	12.3±3.1	9.9±2.4	12.8±3.6	NS
14 weeks	3.5±1.3	4.6±1.4	7.5±1.3	9.2±1.3	.005/.31/.85
Triglyceride (mg/dL)*					
Baseline	25±2	18±2	27±7	28±7	NS
14 weeks	27±18	84±20	21±18	34±18	.15/.08/.26
LDL molecular weight (µg/µmol)*					
Baseline	4.0±0.43	3.6±0.14	3.7±0.26	3.6±0.16	NS
12 weeks	3.9±0.18	3.9±0.20	3.6±0.18	3.5±0.18	NS
Lp(a)					
12 weeks	19±1	27±3	23±3	35±9	.29/.08/.68
Plasma LDL FCR (pools/h)					
14 weeks	.035±.002	.030±.003	.027±.003	.025±.003	.04/.2/.46

*Treatment measures and P values adjusted for baseline measures.

Diabetic animals had significantly higher TC and LDLC (P=.02 and P=.03, respectively) and tended to have higher Lp(a) and triglyceride (both P=.08) compared with non-diabetics. However, soy consumption resulted in a significant reduction in TC<LDLC, and the TC:HDLC ratio and a significant increase in HDLC in both diabetic and non-diabetic animals (all P≤.01; Table 3). The type of dietary protein also influenced the plasma LDL FCR. Monkeys consuming soy protein have significantly increased plasma LDL FCR compared with monkeys consuming casein protein regardless of their diabetic status. The plasma LDL FCR correlated negatively with plasma LDL concentrations in all animals (r= -.52, P<.02).

TABLE 8. Effect of Treatment on Arterial LDL Concentration ($\mu\text{g LDLC/g}$, mean \pm SEM)

Site	Soy (N=6)	Soy+DM (N=5)	CAS (N=6)	CAS+DM (n=6)	P (Prot/DM/ProtxDM)
Coronary artery	353 \pm 131	305 \pm 102	595 \pm 195	615 \pm 179	.10/.93/.84
Carotid	96 \pm 38	93 \pm 40	185 \pm 60	180 \pm 63	.11/.94/.98
Carotid bifurcation	82 \pm 26	69 \pm 18	215 \pm 48	230 \pm 81	.01/.98/.80
Internal carotid	33 \pm 8	28 \pm 5	76 \pm 18	86 \pm 26	.009/.90/.67
Thoracic aorta	128 \pm 53	71 \pm 21	164 \pm 38	227 \pm 71	.08/.96/.26
Abdominal aorta	97 \pm 23	67 \pm 14	141 \pm 34	182 \pm 49	.03/.87/.31
Iliac	100 \pm 45	58 \pm 21	139 \pm 46	157 \pm 41	.11/.78/.48
Femoral	138 \pm 34	131 \pm 47	154 \pm 36	269 \pm 70	.14/.29/.23

There was no significant difference in the baseline (biopsy) femoral artery cholesterol content among the groups. While the short treatment period (14 weeks) resulted in a significant increase in femoral artery cholesterol content ($P < .05$), there was no treatment effect. Due to the short period of study, chosen to allow evaluations of arterial LDL metabolism, there were no significant treatment effects in the arterial cholesterol content for any artery. However, there was a tendency ($P = .08$) for reduced cholesterol content in the abdominal aorta with soy and a tendency for an interaction effect ($P = .09$) between soy and diabetes.

The findings suggest that soy protein compared with casein reduces the progression of atherosclerosis by decreasing LDL delivery to the arteries of both control and diabetic male monkeys. These changes in arterial LDL metabolism would be expected to result in a decreased progression of atherosclerosis. It is interesting that the arterial sites associated with stroke (those found in the head and neck) seemed to have the greatest protection with Soy. Soy consumption also resulted in improved plasma lipoprotein concentration in diabetic monkeys. It is possible that with a longer treatment period, the arterial effects of diabetes would be more apparent. Thus, soy protein as compared with casein is as atheroprotective in adult male monkeys as it is in female monkeys⁵⁰. This may explain the decreased cardiovascular disease in Asian men compared with men eating a Western diet¹¹.

Conclusions

Traditionally, people have chosen totally or largely plant-based diets for a variety of philosophical, religious, or ecological reasons. They are now joined by a new breed of consumers interested in improving their health.

The US FDA recently published its final ruling on a food-labeling health claim for soy protein and cholesterol reduction stating that 25g/d of soy protein, as part of a diet low in saturated fat and cholesterol, may reduce the risk of heart disease⁵¹. These findings should provide physicians and dietitian with the motivation to recommend the increased consumption of soy protein as part of an integrated dietary approach to control Hypercholesterolemia. Increased interest in soy proteins is spurred by growing pressure to utilize all the non-pharmacological tools available to prevent and treat CVD and to minimize the necessity for drug therapy with its considerable cost and potential for side effects.

The incorporation of Soy protein into a health, low fat diet may provide a safe, inexpensive, proven method to help reduce elevated cholesterol levels and to otherwise decrease CVD risk. The growing number of food products containing soy protein and the increased use of a new generation of soy protein ingredients to develop familiar, good-tasting products will make it easier for the public to utilize this powerful weapon against CVD.

AHA recommends that it is prudent to include soy protein foods in a diet low in saturated fat and cholesterol to promote heart health.

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SOY IN INFANT NUTRITION

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Nutrition, growth & development and vaccination are the three most important issues of early childhood. Nutrition in absolute terms and specific to individual child's constitution, status of health, family background, geographical location and socioeconomic status is the most important basis of effective growth and development of a child. However, diseases like diarrhoeas, various exanthoses and enanthemas etc., sociocultural taboos and mis-beliefs; availability of food items on the backdrop of economic status and many other factors affect nutrition of the child in good or bad way.

Undoubtedly, breast milk is the best source of complete nutrition in first two years of life with gradual weaning starting from 4 – 6 months of age. However, because of multitude of factors e.g. mothers stepping out of home for jobs, serious illness in mother, protracted diarrhoeas (lactose intolerance and other causes) in children, etc., sometimes one has to think of alternate sources of nutrition and one food item emerges as clear victor in these situations and that is "SOYA".

Availability of refined "SOYA", & soya based infant formulae had been a problem in the past and it was aggravated to some extent by occasional reports of "Soy Allergy" and "Soy intolerance". However, many of these problems have been sorted out by modern technological advancement and research in the field of nutrition and hence soy can be considered as the best nutritional source in many of the situations mentioned above.

Here, we have attempted to put available information on soy in a proper frame so as to give the reader total perspective of the subject. However, all those dealing with nutrition of normal and challenged children should not forget the all time best dictum, i.e. "Breast is Best".

WHY INFANT FOODS?

Although the advantages and benefits of breast-feeding are well known, many Asian infants are bottle-fed, particularly in urbanized societies. Here is sharing of a report from Singapore: In Singapore it is unusual for mothers to exclusively breast-feed their babies beyond the third month of life. Wong (unpublished observations, 1971) surveyed the prevalence of breast-feeding in Singapore and noted that it had decreased over the years. In 1971, only ~ 28% of mothers breast-fed their babies at birth and just 4% did so at 3 months. The percentage of mothers breast-feeding their infants is still extremely low. In a recent study, Ng et al noted that only 6.3% of 14,778 infants were fully breast-fed at 4 months of age in Singapore.

Whether breast or bottle-fed, these infants are weaned to solid foods from ~ 4 months of age onward. Rice cereal is the first solid food most Asian infants are fed. Tofu, a form of bean curd, is commonly introduced at this time. Tofu is made by blending soybeans and boiling the blended beans in water. The suspension is then filtered and the fibrous content is discarded. The suspension is served as soymilk. To form bean curd, calcium salt is added to the soymilk. Depending on the various degrees of solidification and desiccation, various preparations of tofu can be made.

Many Asian mothers choose tofu for weaning because it is freely available at low cost. The soft consistency is also an important factor. Tofu can easily be mashed into a paste or gruel and mixed with rice cereal for feeding to babies. Asian infants accept tofu readily because it is highly palatable. The nutritional value of soy protein is well established and it is highly recommended by dieticians for weaning at this stage. In addition, the calcium content is high, which is good for children at this age.

Soy-based formulae and meat-based formulae are used as successful replacements for milk in the nutritional management of infants who are, or are suspected to be allergic to milk. Used most widely are soy-based formulae which eliminate the symptoms and ensure normal growth and well being of the infant. Soy-based formulae are made in both powdered and liquid forms, and the trend during the past decade has been to use a soy protein isolate to reduce or eliminate the presence of carbohydrates which cause flatulence and abnormal stooling.

Because of the wide variety of associated symptoms and the lack of a simple means for establishing diagnosis or immunologic pathogenesis, allergy to cow's milk in infants and children continues to be a perplexing problem for the physician. Perpetuation of the allergic syndromes can lead to general failure to thrive, slow or even retarded growth and other health problems. Consequently, implementation of a dietary management program that ensures both adequate nutrition and the elimination of symptoms becomes an important concern. Let us take a look at cow's milk Allergy.

Cow Milk Allergy

Incidence of allergy to cow's milk has been estimated to be from 0.3% to 7% in general infant and children groups and from 14% to 30% in "suspected allergic" infants and children. And, in general, cow's milk has been designated the food allergen most commonly affecting children.

Some of the symptoms and signs of cow milk allergy are shown in Table 1. The wide range of determined incidence is attributed to differences in diagnostic criteria, the groups studied, and the statistical methodology employed. Variances notwithstanding, the figures are considered sufficient to show that allergy to cow's milk is a very real problem in clinical medicine.

Soy-based formulae and meat-based formulae are used as successful replacements for milk in the nutritional management of infants who are allergic to milk or are suspected of milk allergy. Used most widely are soy-based formulae which eliminate the symptoms and ensure normal growth and well being of the infant.

Soy-based formulae are supplied in both powdered and liquid forms. The products can be obtained in powder form which require reconstitution with water and in two fluid forms, i.e. a ready to feed form and a concentrated liquid form, the latter usually requiring dilution with an equal volume of water prior to feeding.

For some children the formula is the sole source of nutrition for many days and perhaps several months of their lives. It is, therefore, imperative that the formula supply adequate and balanced nutrition, that it be microbiologically safe, and that it be free from toxic or antinutritional factors.

Table I. Symptoms and Signs of Cow Milk Allergy

Constitutional Failure to thrive Retarded growth Malnutrition	Gastrointestinal Diarrhoea Vomiting Colic Abdominal pain Malabsorption enteropathy Constipation	Central Nervous (Behavioral) Refuses milk Excessive crying Excessive sweating Headache Hyperirritability Hyperkinesis Listlessness
Dermatologic Eczema Urticaria Hives Angioneurotic Edema	Respiratory Rhinitis Bronchitis Asthma Sneezing Coughing Chronic nasal discharge Rattly respiration Excessive mucus in throat	Vascular Shock

IDEAL INFANT FOOD / FORMULA

Several governments have standards for infant formulae, while the standards of the Codex Committee on Foods for Special Dietary Use are generally used for those countries lacking their own specific regulations. In the United States, the standards of the Food and Drug Administration must be adhered to. The latter are based on various recommendations of the Committee on Nutrition of the American Academy of Pediatrics. The modern infant formula, therefore, meets the requirements of the growing child not only for protein, fat and carbohydrate, but for many vitamins and minerals as well.

All common vegetable proteins are deficient in one or more of the amino acids essential to man. Soy proteins are deficient in methionine. Infant formula regulations require that nutritional adequacy be demonstrated, and usually this takes the form of exceeding a specific protein efficiency ratio (PER) value. The Codex and Canadian standards are such that the PER value must be at least 85% of casein, while in the USA the FDA standard is 70% of casein. L-Methionine is therefore included in soy-based infant formulae to meet the PER requirement. Table II shows a comparison of the essential amino acid requirement for the human infant and levels found in a typical formula containing soy protein and methionine. Levels of essential amino acids in the formula exceed estimated requirements.

Table II. Essential Amino Acid Requirement of the Infant and Analysis of a Typical Soy Protein Infant Formula

Amino acid	Estimated amino acid requirement mg/100 Kcal	Levels in Infant formula mg/100 Kcal
Histidine	26	73
Isoleucine	66	132
Leucine	132	235
Lysine	101	173
Methionine	24	59
Phenylalanine	57	154
Threonine	59	106
Tryptophan	16	31
Valine	83	135
Cystine	23	28

A consideration of other vegetable proteins for infant feeding must, therefore, include an assessment of the required fortification with essential amino acids to meet the requirements of the infant and demonstration of nutritional adequacy in the PER assay.

Extensive clinical testing of a new infant formula is very desirable, and all reputable companies have their products tested in animals and then extensively in humans under strict supervisions before the product is marketed.

Infant formulae containing soy protein have been commercially available for almost 50 years. The first formulae contained full-fat soy flours and, as a consequence, were dark in color and had a beany flavor. The presence of soluble carbohydrates from the soybean was the cause of flatus in the infant and also yielded foul smelling stools.

With the development of more refined soy proteins, i.e. soy protein isolates, the manufacture of today's high quality soy infant formula is possible. Today's formulae are almost white or milk-like in color, are fairly bland tasting, and yield normal stools. Apart from nutritional concerns discussed earlier, commercial soy proteins for use in infant formulae should satisfy several other requirements. The protein content should preferably be greater than 90% of the dry weight. In this way the ash value is kept low, and it facilitates the addition of minerals to the formula so that nutritional requirements can be met while not allowing any mineral to reach harmful or toxic levels. The soluble carbohydrate content from the soybean should be low to prevent subsequent abnormal flatus and stool condition. The viscosity of an aqueous solution of the soy protein should be low so as to decrease the heat requirements for sterilization of the formula and thus minimize nutritional losses during hot fluid processing and sterilization. Soy protein should remain in solution during processing and sterilization. The protein should be white or very light tan in color and be bland tasting to permit manufacture of a formula that is as close to milk in aesthetic properties as possible.

Clearly the technology that yielded the high quality soy protein isolate of today enabled the infant formula industry to make great improvements over the formulae made from soy flours.

Although the details of manufacture of infant formulae is proprietary information, it is probably true to say that most formulae are made by first preparing the aqueous portion containing protein source, carbohydrates and minerals, and a separate fat portion, usually containing an emulsifier. These two portions are then mixed, homogenized, analyzed and formulation adjustments are made if necessary. Ingredients which are most heat and oxygen sensitive (e.g. vitamin C and the B vitamins) are then added together with the required amount of water to standardize the formula. The product is then either heat treated and spray dried to yield a powder, or filled into glass or metal containers and sterilized to yield a powder, or filled into glass or metal containers and sterilized to yield ready to feed or concentrated liquid products. The finished products are then subjected to chemical and microbiological analyses and must satisfy the manufacturer's product specifications for release.

Milk-based formulae contain lactose as the carbohydrates source. In a soy protein infant formula, the source of carbohydrate is usually sucrose, corn syrup (hydrolyzed corn starch), or a mixture of sucrose and corn syrup. Therefore, not only are soy protein formulae recommended for infants who are allergic to milk protein but they are appropriate for feeding infants who exhibit lactose intolerance or have lactase deficiency.

Of constant concern to the infant formula manufacturer is the possibility that toxic or antinutritional factors might enter the formula. Such undesirable agents might not only come with the protein, but might also come from other ingredients or the process water. The manufacturer therefore must subject all ingredients to stringent analyses before acceptance for use in the formula.

The ingredients must satisfy the specifications set for such items as heavy metals, pesticides and herbicides, as well as microbiological specifications which usually include total standard plate count, aerobic and anerobic thermophile content, yeasts and molds and pathogens.

Soy protein contains factors which are of concern to the formula manufacturer, for example, trypsin inhibitor. If the formula is made from soy protein isolate, the inhibitor content of the formula will be low and analysis has shown that over 90% of the original trypsin inhibitor is destroyed during the aqueous heat processing of the formula. Furthermore, when a soy protein formula was incorporated in a rat diet, no incidence of pancreatic hypertrophy or hyperplasia was observed histologically, and weight gain was equivalent to rats on a diet containing casein as the source of protein.

Soy protein isolates contain approximately 20 mg of phytic acid/g, and therefore the effect of this phytic acid on mineral availability from the formula must be determined and shown to be adequate for the infant. Approximately 90% of the phytic acid of one such soy protein was removed by ultra-filtration. Three formulae, each containing a different calcium and phosphorous level but with similar calcium/phosphorous ratios and similar zinc, iron, copper and magnesium levels, were prepared from the phytate-reduced soy protein isolate and three formulae from phytate containing isolate. Weaning male rats, ten per diet group, received these formulae as their sole source of diet for four weeks. The protein and calorie efficiencies, bone and carcass ash, calcium, phosphorous and zinc of rats receiving the phytate containing formulae were not significantly different from the rats receiving corresponding phytate-reduced formulae. The results suggest that, regardless of the calcium and phosphorous levels of the formulae, phytate does not interfere with calcium, phosphorous and zinc utilization from soy formula for the rat.

ROLE OF SOY IN INFANT FOOD/FORMULAE

1. HISTORICAL ASPECTS

Soybeans have been cultivated and consumed in Asia for a long time. Soybeans may have been cultivated in China as early as 2838 BC. More definite evidence about soy farming was recorded in Chinese literature between the 7th and 11th centuries BC. Soybeans were first cultivated in northern China and later in central and southern China. Around 100 BC, the cultivation of soybeans spread to the Korean peninsula, Japan, Southeast Asian countries, and the Indian subcontinent.

Because soy cultivation has a long history in Asian countries, soy products are staples in most Asian families. Products include soy cooking oil, soy flour, soy sauce, soy beverages, various forms of soybean curd (tofu) and soy infant formulae. Soy is a major source of protein for many vegetarians living in Asia.

Asian children are exposed to soyfoods from a very young age. In a study of daily lactose intake by Singaporean children, Tan et al found that ~ 10% of the children were not consuming dairy products but were consuming soy formulae. This observation was confirmed by Tan and Quak in a more recent study. As shown in Figure 1, in a group of 248 healthy children <10 years of age, ~ 19% did not consume cow milk and consumed mainly soymilk. The main reasons cited for soymilk consumption were lactose intolerance or aversion to cow milk.

We recently conducted a survey on the consumption of soy by healthy Asian children. Of the children studied, 90% had consumed some soy products. Of these, >95% had consumed soyfoods before the age of 18 months. These foods included soy sauce, tofu, and soy formulae.

2. SOY BASED FORMULAE

NUTRITIONAL ADEQUACY OF SOY-PROTEIN FORMULAE

The distribution of nutrients in Soy Protein Formulae (SPFs) is quite similar to that in cow-milk formulae. SPFs and cow-milk formulae contain the same amount of proteins, lipids derived from vegetable oil and carbohydrates in the form of maltodextrins, corn starch or sucrose. Commercial SPFs differ from one another most markedly in carbohydrate content. Inclusion of 2 different carbohydrates (sucrose and corn syrup hydrolysates) affords the theoretical advantage of maximizing carbohydrate digestion and absorption. All SPFs are lactose free, fortified with L-methionine, and contain added taurine, carnitine and iron.

Several clinical studies showed that feeding SPFs to full-term infants is associated with normal growth, protein nutritional status, and bone mineralization. One study performed in infants exclusively fed SPFs during the first 6 months of life showed no immunologic abnormality or increase in infection morbidity as was reported previously. No differences in the proportion of infants who seroconverted to oral poliovirus immunization were found between the types of feeding.

COMPOSITION OF ISOLATED SOY PROTEIN-BASED FORMULAE

The isolated soy protein-based formulae currently on the market are all free of cow milk protein and lactose, and prepared so that they provide 67 kcal/dL. All are iron-fortified and meet the vitamin, mineral, and electrolyte specifications addressed in the 1976 guidelines from the American Academy of Pediatrics for feeding full-term infants and established by the US Food and Drug Administration.

The protein is a soy isolate supplemented with L-methionine, L-carnitine, and taurine to provide protein at 2.45 to 3.1 g/100 kcal or 1.65 to 2.1 g/dL. The harvested soybean is processed by removal of the hull to yield a pulp that is then refined to soybean oil and soybean flake. The defatted flakes are processed into soy flour, soy protein isolate, or soy co-tyledon fiber. Soy protein isolate is extracted in a slightly alkaline solution and precipitated at the isoelectric point of 4.5 to yield a purity of at least 90% soy protein on a dry basis.

Supplementation with L-methionine began by the early 1970s. In 1979, Fomon et al demonstrated improved biological quality of the protein with the addition of sulfur containing amino acids. Subsequent studies in 1986 demonstrated that at a protein intake of 1.8 g/100 kcal, methionine was required to improve nitrogen balance, whereas at intake of 2.2 and 2.6 g/100 kcal, methionine supplementation improved weight gain, urea nitrogen excretion, and albumin synthesis. Before the routine supplementation of soy protein formulae with methionine, infants with undiagnosed, untreated cystic fibrosis were particularly at risk for severe hypoalbuminemia and edema when fed soy proteins, a risk that remains in soy, cow milk, and breastfed infants with cystic fibrosis until the initiation of pancreatic enzyme therapy.

Carnitine, which is required for the optimal mitochondrial oxidation of long-chain fatty acids, is deficient in foods of plant origin and is added to soy formula to the level in breast milk, as is taurine, an amino acid that is abundant in human milk. Taurine functions as an antioxidant and, along with glycine, is a major conjugate of bile acids in early infancy.

The fat content of soy protein-based formulae is derived primarily from vegetable oils. The quantity of specific fats varies by manufacturer and is usually similar to those in the corresponding cow milk-based formula. The fat content ranges from 5.3 to 5.5 g/100 kcal or 3.6 to 3.8 g/dL. The oils used include soy, palm, sunflower, olein, safflower and coconut.

Carbohydrate is provided lactose free, as corn starch, corn starch hydrolysate, tapioca starch, or sucrose, with content ranging from 10.0 to 10.2 g/100 kcal or 6.7 to 6.9 g/dL. Polysaccharide, in the form of supplemented soy fibre, has been added to one soy protein-based formula.

Until 1980, mineral absorption from soy formulae was erratic because of poor stability of the suspensions and the presence of excessive soy phytates in the formula. Not surprisingly, conflicting results of studies addressing the adequacy of bone mineralization were reported. With the present formulations, bone mineralization, serum levels of calcium and phosphorous, and alkaline phosphatase levels in full-term infants through 6 to 12 months of age are equivalent to those seen with cow milk-based formulae. Because soy protein isolate formulae still contain 1.5% phytates and upto 30% of the total phosphorous is phytate-bound, the total phosphorous and calcium content of the formulae is ~ 20% higher than in cow milk-based formula, while still maintaining the mandated calcium to available phosphorous ratio (1.1 to 2.0:1).

The soy phytates and fiber oligosaccharides also bind iron and zinc. All soy-based formulae thus are iron-fortified and have proved as effective as iron-fortified (12 mg/L) cow milk-based formulae in the prevention of iron deficiency in infants. With radiolabeled zinc, the highest absorption of zinc is from human milk (41%) and the lowest is from soy formula (14%). All soy protein-based formulae thus are zinc-fortified. In one infant, the phytates may have interfered with the uptake of exogenous thyroid hormone, binding the T4 within the lumen, increasing fecal loss, and reducing the efficacy of oral thyroid hormone.

Early studies revealed that the full nutritional value of soybean protein is achieved only after heat has been applied. Subsequent studies confirmed the presence of a number of heat-labile factors with biological

activity in soybean-based products. The most prominent of these factors is a soybean protease inhibitor with the properties of an antitrypsin, antichymotrypsin, and antielastin. Soybean protein isolate, as heated for infant formulae, removes 80% to 90% of this protease inhibitor activity and renders it nutritionally irrelevant. There also are heat-stable factors that remain in the soy protein isolate, including the low-molecular-weight fibres, phytates, saponins, and phytoestrogens.

The phytoestrogens demonstrate physiologic activity in rodent models and, per unit of body weight, the infant's potential intake of phytoestrogen from isolated soy protein-based formula is higher than that demonstrated to influence the menstrual cycle of humans. Very limited human data to date, however, suggest that soy phytoestrogens have a low affinity for human postnatal estrogen receptors and low potency in bioassays.

In 1996, the American Academy of Pediatrics issued a statement on aluminum toxicity in infants and children and discussed the relatively high content of aluminum in soy-based formula. Although the aluminum content of human milk is 4 to 65 ng/ml, that of soy protein-based formula is 600 to 1300 ng/ml. The source of the aluminum is the mineral salts used in formula production. Aluminum, which makes up 8% of the earth's crust as the third most common element, has no known biological function in humans. The toxicity of aluminum is traced to increased deposition in bone and in the central nervous system, particularly in the presence of reduced renal function in preterm infants and children with renal failure. Additional potential sources of aluminum include total parenteral nutrition solutions, renal dialysis fluids, and aluminum containing antacids. Because aluminum competes with calcium for absorption, increased amounts of dietary aluminum from isolated soy protein-based formula may contribute to the reduced skeletal mineralization (osteopenia) observed in preterm infants and infants with intrauterine growth retardation. Term infants with normal renal function do not seem to be at substantial risk for aluminum toxicity from soy protein-based formulae.

SOY PROTEIN-BASED FORMULAE IN TERM INFANTS

Numerous studies have documented normal growth and development in term neonates fed methionine-supplemented isolated soy protein-based formulae. Average energy intakes in infants receiving soy protein formulae also are equivalent to those achieved with cow milk formula. The serum albumin concentration, as a marker of nutritional adequacy, also is normal and bone mineralization also is equivalent to that documented with cow milk-based formula. Additional studies confirm that soy protein formulae do not interfere with the normal immune responses to oral immunization with polio vaccine.

SOY PROTEIN-BASED FORMULAE IN PRETERM INFANTS

Preterm infants who weighed from 1500 to 1800 g and were fed methionine-supplemented soy protein-based formulae demonstrated significantly less weight gain, less length gain, and lower serum albumin levels than that achieved with cow milk-based formulae. With lower birth weights, i.e. <1500 g, data conflict; one study demonstrated equivalent growth and plasma protein levels, whereas another demonstrated significant reductions in body.

All three studies of preterm infants agreed, however, that serum phosphorous levels were lower in the preterm infants fed soy protein-based formula and, when measured, the alkaline phosphatase levels were higher. As anticipated from these observations, the osteopenia of prematurity is reportedly increased in low birth weight infants receiving soy protein-based formulae. Even with supplemented calcium and vitamin D, radiographic evidence of increased osteopenia was present in 32% of 125 preterm infants fed soy protein based formula.

When combined with concerns about aluminum toxicity, the failure to achieve equivalent growth rates or albumin levels consistently and the reduced bone mineralization lead to the conclusion that soy protein based formulae should not be fed to low birth weight preterm infants. The newer cow milk protein-based formulae designed for preterm infants are clearly superior.

USE IN ACUTE DIARRHOEA AND SECONDARY LACTASE DEFICIENCY

Because of the role of lactose-free soy protein-based formulae in the management of long-term lactose restriction, a number of studies have addressed the role of these formulae in the recovery from acute infantile diarrhoea complicated by transient lactase deficiency. After immediate rehydration, most infants can be managed successfully with continued breastfeeding or standard cow milk or soy formula. In an extensive review, Brown noted that the dietary failure rate of lactose-containing formulae was 22%, whereas that of lactose-free formulae was 12%. In a study comparing breast milk, cow milk-based formula, and soy protein-based formula, no difference was found in the rate of recovery from rotavirus or non rotavirus diarrhoea based on nutritional therapy. Although not significant from the perspective of nutritional compromise, the duration of diarrhoea has been reported to be shorter in infants receiving soy protein-based formula. The duration of liquid stools may be reduced further by adding additional soy polysaccharide fiber or by resuming a mixed-staple diet.

A recent study by Santosham et al. showed that the early introduction of soy is safe and, indeed, associated with a shorter duration of diarrhoea than delayed introduction of formula. The longer duration of diarrhoea observed among the infants receiving cow's milk formula did not have a negative impact on weight gain. However, the prolongation of diarrhoea may result in longer hospital stays and lost wages on the part of the parents who must take time away from work in order to attend to their children excluded from day-care. In this regard, it should be noted that the cow's milk group had, on an average a one-day longer hospital stay compared to the soy group.

Soy-based formulae shorten the duration of diarrhoea when compared to cow's milk formulae in non-breast-fed infants with mild to moderate diarrhoea. Thus, as far as this particular outcome is concerned, a soy-based formula has advantages over a cow's milk formula. Studies are also needed of re-feeding with severe diarrhoea.

It is also known that with hospitalized infants the introduction of a soy-based, lactose-free formula during the acute phase of diarrhoeal illness resulted in reduction of stool output and in duration of diarrhoea.

Many pediatricians continue to recommend a clear liquid diet consisting of fluids such as fruit juices or gelatin water. Such solutions contain relatively high carbohydrate concentrations. The higher carbohydrate concentrations in these fluids are not optimal for the absorption of sodium and water from the gut. They may actually exacerbate diarrhoea by imposing a high osmotic load and may ultimately lead to hypernatremic dehydration. There is evidence supporting the recommendation of early feeding with a soy-based, lactose-free formula, instead of clear liquids, in the acute phase of diarrhoeal illness in children.

It is probable that the reduction in duration of diarrhoea in patients fed early in the course of their treatment is the result of enhancement of sodium and water absorption by the products of digestion of the soy formula (glucose and amino acids) in the gut. Such enhanced sodium transport forms the physiologic basis for oral rehydration itself. Substances besides glucose serve as substrates for facilitated cotransport of sodium (e.g. certain amino acids) and have been proposed to be useful in improving the absorption of oral rehydration solution.

It can be concluded that for outpatients with diarrhoea, the early introduction of a soy-based, lactose-free formula is safe and may shorten the duration of diarrhoea while maintaining adequate caloric intake.

USE IN DISORDERS OF CARBOHYDRATE METABOLISM

When strict dietary lactose elimination is required in the management of infants with galactosemia or primary lactase deficiency, the soy protein formulae are safe and cost-effective. Soy protein-based formulae with sucrose as the carbohydrate are contraindicated in sucrase-isomaltase deficiency and in hereditary fructose intolerance.

Results of studies in animal models using a diabetes-prone rat suggested an increased frequency of diabetes when ingesting a soybean meal diet. However, when soy protein isolate or hydrolyzed soy protein feedings were used, no significant increase in diabetes was noted. This suggests that the factor contributing to the increased frequency of diabetes in this animal model is not the soy protein present in infant formulae.

SOY-PROTEIN FORMULA FOR TREATMENT OF COW-MILK ALLERGY (CMA).

SPF was first described as a cow-milk substitute in 1909 but was not used for feeding babies with CMA until 1929. Since then, SPFs have been widely used for feeding babies with CMA. These formulae were the only available cow-milk substitute in 1929, and such products ensured a normal life for many children who were affected by the large spectrum of clinical manifestations of CMA. In addition, SPFs have been given to genetically atopic, allergy-prone infants for the prevention of atopic diseases when breast milk was not available.

More recently, other special formulae derived from the hydrolysis of cow-milk protein (extensively and partially) have become available on the market, and a debate on the allergenicity of SPFs has been increasing. However, in all these studies, the definition of soy allergy was anecdotal and not based on scientific diagnostic criteria: no challenge to soy was made, nor were data on IgE specific to soy available.

In 1990, the Committee on Nutrition of the European Society for Pediatric Gastroenterology and Nutrition reported that available data did not support the use of SPFs in infants with suspected or proven adverse reactions to cow-milk protein. To support this recommendation, the committee should have referenced studies on CMA. Surprisingly, the committee referenced studies that were not appropriate because these studies dealt with the use of SPFs for the prevention of atopic diseases and not with the management of adverse reactions to cow milk.

Another common bias is the incorrect quotation of the conclusions of previous studies to support the assumption that SPFs are allergenic. For example, Eastham et al reported that soy proteins are as antigenic and not as allergenic as cow-milk proteins. However, the conclusion of this study is commonly misinterpreted or misunderstood. The authors showed an antibody response (hemoagglutinins that are mainly IgG) to soy proteins in SPF-fed infants that was similar to that found to cow-milk proteins in infants fed cow-milk formula and concluded that soy protein is as antigenic as cow-milk protein. IgG antibodies to food antigens are physiologically produced and there is no evidence that they are involved in the development of atopic disease. Therefore, Eastham et al's conclusion that soy is as allergenic as cow milk is incorrect, as are similar conclusions by other authors.

Several authors have quoted other studies without checking the reliability of the statements. Kahn et al, in their work devoted to sleep disturbance and CMA, comment that "soya milk may not be the best choice for replacement of cow milk since up to 5% of allergic infants can also suffer from soy protein intolerance".

However, their comment was based on information from a book, not on the results of a study double-blind, placebo controlled, oral food challenge. Pekki et al stated "When are used as a substitute for cow-milk allergy, allergy to soy proteins develops in a far higher number of infants. To support this statement, the authors again referenced the studies by Kuitunen et al. Jakobsson and Lindberg and Gerrard et al, the flaws of which were discussed above. Estham, in a review on the topic of soy-protein allergy, claimed that this intolerance develops in 15-50% of cases, and quotes findings on soy antigenicity; however, the data were not from a double-blind, placebo-controlled oral food challenge. Wilson and Hamburger, in their review article on CMA in the first year of life, state that one of the primary disadvantages of SPFs is antigenicity. Approximately 25% of patients with CMA are also allergic to soy. In addition, soy proteins are irritating to the gastrointestinal tract of the infants, especially during or after an acute episode of gastroenterogenesis. Thus, SPFs will not be of value in these two groups of patients". References for this statement were the book by Bahna and Heiner and the study by Gerrard et al, which do they support the data and the conclusion of the authors. In the same article, the authors stressed that children with CMA should be given partially hydrolyzed formula. On the basis of other studies these products are not recommended in such patients and can trigger severe anaphylaxis.

Of the studies in which soy allergy was diagnosed, few used a challenge test to make the diagnosis. Sampson found that only 5% of 204 patients with atopic dermatitis showed soy sensitivity, as evidenced by double-blind, placebo controlled challenge tests. Bock and Atkins reported that only 4 children out of 54 (7%) with CMA had symptoms after a double-blind, placebo-controlled food challenge with soy. In another study, no child with severe CMA had a positive result after a double-blind, placebo controlled food challenge to SPF.

There is growing evidence that soy proteins can induce enteropathy in young infants with and without cow-milk intolerance with atrophy of the villi similar to that caused by cow-milk protein intolerance. Colitis induced by soy protein and cow-milk protein is clinically and pathologically similar. Clinical features of colitis are nonspecific and include fever, leukocytosis, vomiting, blood-tinged mucoid diarrhoea, carbohydrate intolerance, dehydration, and metabolic acidosis, shock may occur as a consequence. The more chronic reactions may also involve anemia and hypoproteinemia as a result of enteric loss of iron and protein. These symptoms usually are described in infants who experience intestinal difficulties after ingestion of cow milk. Histologically, colitis, related lesions are indistinguishable from those seen in untreated celiac disease.

Freier et al estimated that gastrointestinal symptoms occur in ~ 30% of infants fed soymilk in the treatment of gastrointestinal cow-milk hypersensitivity. On the basis of this observation, they do not recommend the use of SPFs in infants <6 months of age with cow-milk hypersensitivity manifested by gastrointestinal symptoms. They do use SPFs in infants >6 months of age and have not noticed any adverse effects. Hill et al described several children with intolerance to multiple food proteins. The children with CMA had slowly evolving, adverse, late reactions (irritability, diarrhoea, vomiting, and eczema) within several days of consuming not only to cow milk but also soymilk, casein hydrolysate, and other foods.

Other manifestations, such as atopic dermatitis, may occur in some SPF-fed children. Anaphylaxis after the ingestion of soy protein appears to be an extremely rare phenomenon.

SOY-PROTEIN FORMULAE USED FOR PREVENTION OF COW-MILK ALLERGY

In 1953 it was reported that SPFs given to atopic, allergy-prone babies prevented the onset of allergic disease, mainly eczema. However, the results of this study were criticized because of the lack of a control group. A prospective, long-term study that included a control group was then done. A large cohort of 292

infants with family histories of atopic disease were randomly assigned to receive either an SPF or a cow-milk formula; 10 year later, 235 of 295 children were followed up by a physician. Allergic disease had occurred in 18% of the soy group and in 50% of the control group, the difference being attributable to asthma and perennial allergic rhinitis. Surprisingly, no significant difference occurred in the prevalence of eczema, which was low in both groups. Three years later, Brown et al did not confirm these optimistic results: allergy occurred in 10% of the children assigned to the soy group and in 13% of the control children, but the difference was not significant.

Encouraging results on the preventive effect of SPF were shown in the elegant study in infants of allergic parents by Matthew et al; 23 breast-feeding mothers adhered to a dietary regimen in which dairy products, fish, and eggs were excluded for the first 6 months postpartum. SPF supplements were given to the infants as necessary. Nineteen mothers who declined to follow the prescribed dietary regimen formed the control group. The incidence of eczema was significantly lower in the regimen group at both 6 and 13 months. However, the diagnosis of eczema was not blind with regard to dietary group.

In a small but intense study in children with a biparental history of atopic disease, 48 children were randomly assigned to receive SPF or cow-milk formula from weaning to age 9 months. Two thirds of the children developed atopic disease by age 4 years and there was no significant difference between groups.

Of the other studies published, some have recommended the use of SPFs because their subjects showed fewer allergic reactions to them than to cow-milk formulae, whereas others found a similar frequency of allergic manifestations with either formula. Businco et al, in prospective studies of at-risk infants, confirmed the efficacy of preventive dietary measures (defined as exclusive breast-feeding for the first 6 months supplemented as necessary with SPFs and a diet free of cow milk and eggs for breast-feeding mothers) and preventive environmental measures (i.e., elimination of dust mites, smoking, and pets in the house). More recently, these authors observed 174 high risk infants for <52 months; the prevalence of atopic disease at the last follow-up was low: 1% food allergy, 0.5% atopic dermatitis, and 9% asthma.

Miskelly et al in their study of 487 at-risk infants, concluded that the allergy symptoms manifested by the intervention group (fed breast milk, as SPF, or both) were similar to those of the control group (fed breast milk, cow-milk formula, or both). Bardare et al confirmed the preventive effect of SPF in a large prospective study including 391 atopic, allergy-prone infants. Breast-feeding was recommended for the first 6 months of life, and SPF was given when breast milk was not available; selected weaning was also advised. At the end of the first year of life, 13% of the infants in the study group and 29% of the children in the control group had atopic disease ($P < 0.01$).

TREATMENT OF COLIC WITH SOY PROTEIN-BASED FORMULA

Colicky discomfort, apparently abdominal in origin, is described by the parents of 10% to 20% of infants during the first 3 months of age. Although many factors have been implicated, parents frequently seek relief by changing infant formula. Although some calming benefit can be attributed to the sucrose and fibre content, controlled trials of cow milk and soy protein-based formulae have not demonstrated a significant benefit from soy. The value of parental counseling as to the cause and duration of colic seems greater than the value of switching to soy formula. Because most colicky behavior diminishes spontaneously between 4 to 6 months of age, any intervention at that time can be credited anecdotally.

ANTIGENICITY OF SOY PROTEIN-BASED FORMULAE

Any ingested large molecular weight protein is a potential antigen to the intestinal immune system. In soy

protein isolate, 90% of the pulp-derived protein resides in two major heat-stable globulins: β -conglycin, with a molecular weight of 180000, and glycinin, with a molecular weight of 320000. The former has three subunits, and the latter has six. After enteric digestion, the number of potential antigens generated at the mucosal surface is enormous. As a result, the in-vitro demonstration of antigen-specific antibody can be difficult. The antigenicity of soy protein, suspected since 1934, was documented in low-risk infants by Eastham et al in 1982. Intrauterine sensitization has been documented by demonstrating antigen-specific antibody in human amniotic fluid.

Severe gastrointestinal reactions to soy protein formula have been described for >30 years and encompass the full gamut of disease seen with cow milk protein in infancy: enteropathy, enterocolitis, and proctitis. Small-bowel injury, a reversible celiac-like villus injury that produces an enteropathy with malabsorption, hypoalbuminemia, and failure to thrive, has been documented in at least four studies. To date, those afflicted have responded to the elimination of soy protein-based formulae and are no longer sensitive by 5 years of age. Severe enterocolitis manifested by bloody diarrhoea, ulcerations, and histologic features of acute and chronic inflammatory bowel disease also has been well described in infants receiving soy protein-based formulae. They respond quickly to elimination of the soy formula and introduction of a hydrolyzed protein formula. Their degree of sensitivity to soy protein during the first few years of age can remain dramatic; thus, casual use of soy-based formula is to be avoided. Most children, but not all, can resume soy protein consumption safely after 5 years of age. In addition, up to 60% of infants with cow milk protein-induced enterocolitis also will be equally sensitive to soy protein. It is theorized that the intestinal mucosa damaged by cow milk allows increased uptake and, therefore, increased immunologic response to the subsequent antigen soy. Eosinophilic proctocolitis, a more benign variant of enterocolitis, also has been reported in infants receiving soy protein-based formula.

These dietary protein-induced syndromes of enteropathy and enterocolitis, although clearly immunologic in origin, are not immunoglobulin E-mediated, reflecting instead an age-dependent transient soy protein hypersensitivity. Because of the reported high frequency of infants sensitive to both cow milk and soy antigens, soy protein-based formulae are not indicated in the management of documented cow milk protein-induced enteropathy or enterocolitis.

ALLERGENICITY OF SOY PROTEIN-BASED FORMULAE

Recognizing that soy protein is antigenic does not mean that soy protein is highly allergenic. To address immunoglobulin E (IgE)-mediated hypersensitivity to soy protein-based formula, three types of studies have been performed. The first addresses the frequency with which proven allergy develops in healthy infants fed cow milk or soy protein-based formulae. The second addresses the same question in infants at high risk according to a family history of allergic responses to dietary protein. The symptom is usually eczema, and the high risk history usually includes a family history of atopic disease (e.g. asthma, allergic rhinitis, or eczema). The third type of study addresses the response of infants with proven cow milk allergy to subsequent ingestion of soy protein-based formula. The problem with these studies is with the definition of allergy, which included fussiness, colic, emesis, a positive RAST antibody, and/or a positive double-blind, placebo-controlled challenge.

In a prospective study of healthy infants fed breast milk, cow milk formula, or soy-based formula. Halpern et al documented allergic responses to soy in 0.5% of infants and to cow milk in 1.8%. The frequency is consistent with the summary by Fomon that in 3 decades of study of soy-based formulae, <1% of soy

formula-fed infants had adverse reactions. In a national survey of pediatric allergists, the occurrence of allergy to cow milk was reported at 3.4%, whereas allergy to soy protein was reported to be 1.1%. Two large studies of infants with atopic dermatitis addressed the frequency with which a double blind, placebo-controlled challenge with soy protein was positive. Sampson documented soy positivity in 5% of 204 patients, whereas Businco et al implicated soy in 4% of 143 children.

Prospective studies of high risk infants suggest that soy protein based formula has no relative value over cow milk formula in the prophylaxis or prevention of allergic disease. Furthermore, the use of soy protein-based formula during the first 3 months of age does not reduce the frequency of positive antibody responses to cow milk formula introduced later in infancy. When human milk feeding is supplemented with soy formula in high risk infants, the anticipated frequency of eczema by 2 years of age is not significantly reduced. Interpretation of these data is obscured by multiple alterations in the maternal diet and by environmental stimuli. The issue of delay in allergic disease, as opposed to the prevention of allergic disease, awaits the result of long-term investigations. Fortunately, true anaphylaxis after soy protein exposure has been reported only once. According to the data now available, isolated soy protein-based formula has no advantage over cow milk-based formula for supplementing the diet of a breastfed infant.

Two studies documented the frequency of tolerance to soy protein in a small number of children with documented allergy to cow milk protein as defined by a positive skin test and positive double-blind, placebo-controlled challenge. The rate of combined positivity to cow milk and soy approximated 10%.

CONCLUSIONS AND RECOMMENDATIONS

1. In term infants whose nutritional needs are not being met with breast milk or cow milk-based formulae, isolated soy protein-based formulae are safe and effective alternatives to provide appropriate nutrition for normal growth and development. Isolated soy protein-based formula has no advantage over cow milk protein-based formula as a supplement for the breastfed infant.
2. Because soy protein-based formulae are lactose-free, they are appropriate for use in infants with galactosemia and hereditary lactase deficiency.
3. Parents seeking a vegetarian-based diet for a term infant can be advised to use isolated soy protein-based formula.
4. Most previously well infants with acute gastroenteritis can be managed after rehydration with continued use of human breast milk or standard dilutions of cow milk-based formulae. Isolated soy protein-based formulae are indicated when lactose intolerance has been documented.
5. The routine use of isolated soy protein-based formula has no proven value in the prevention or management of infantile colic.
6. The routine use of isolated soy protein-based formula has no proven value in the prevention of atopic disease in healthy or high risk infants.
7. Infants with documented cow milk protein-induced enteropathy or enterocolitis frequently are as sensitive to soy protein and should not be given isolated soy protein-based formula routinely. They should be provided formula derived from hydrolyzed protein or synthetic amino acid.
8. Most infants with documented IgE-mediated allergy to cow milk protein will do well on isolated soy protein-based formula.
9. Soy protein-based formulae are not designed or recommended for preterm infants who weigh <1800g.

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