INOVERA BIOSCIENCES, INC.

INOVERA Bioscience, Inc. is located near Philadelphia in Ambler, PA. Our mission is to develop products for the medical and nutritional needs of patients to the highest quality standards and deliver those products as cost effectively as possible. Our products must provide a patient benefit not available in any other single product.

INOVERA's unique, patented product **Forvia®** is the first and only daily multivitamin/mineral tablet formulated for people with malabsorption of nutrients due to Inflammatory Bowel Disease (IBD), celiac disease or surgeries that may interfere with nutritional absorption such as weight-loss surgeries. The Chewable tablet formulation adds convenience and an option where difficulty swallowing, rapid transit of intestinal contents due to ostomy or other surgeries, such as gastric bypass, may be problems.

Forbones® ***Xtra D*** calcium supplement tablets with vitamin D provide calcium as dicalcium phosphate, a non-gassy form of calcium that additionally provides phosphorous, the other major mineral in bone. Get information on bone health, calcium and vitamin D.

All INOVERA products are developed on the basis of sound medical information in consultation with clinical experts in the field. Our products use the finest quality raw materials and are manufactured and packaged in modern facilities. All products are laboratory-tested to assure potency and stability.

Contact us for more information about INOVERA. To order Forvia, click here. To order Forbones, click here.

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Forvia

What is Forvia?

FORVIA is a multivitamin/mineral product that provides nutritional support for patients with reduced ability to absorb vitamins and minerals from diet due to gastrointestinal conditions such as

- Inflammatory bowel disease (IBD), including Crohn's disease and ulcerative colitis
- Celiac disease
- Other malabsorption conditions including weight-loss and other gastrointestinal surgeries.

  FORVIA Tablets and Chewables were developed on the basis of growing medical knowledge about the effects of disease on the body's ability to absorb and use nutrients.

  The vitamins and minerals selected for FORVIA Tablets and Chewables are based on current clinical findings about the common nutritional deficiencies and daily vitamin and mineral needs of patients with malabsorption. Just as important, certain ingredients commonly found in general purpose vitamin supplements are not in FORVIA products because they can interfere with absorption of more important nutrients or aggravate symptoms of disease.
- FORVIA contains the fat-soluble vitamins A, D, E and K in water-miscible form to enable good absorption and utilization. People with malabsorption conditions from disease or weight loss surgery are at increased risk for low levels of these vitamins. Vitamin D, important for maintaining bone mass, is supplemented at 2 times the Daily Value because it is not optimally absorbed in people with IBD or who have undergone gastric bypass surgery.
- FORVIA contains folic acid, the daily administration of which has been found in a number of studies to be associated with a reduced risk for the development of colorectal cancer or dysplasia in individuals with ulcerative colitis.
- FORVIA contains vitamin C and iron in the ratio and amounts shown to increase iron absorption when given together. Iron is provided as ferrous fumarate, which is highly soluble in the gastrointestinal tract, is well-tolerated orally, and was less toxic then ferrous sulfate or ferrous gluconate in laboratory studies.
- FORVIA contains 1000 mcg of vitamin B12 (cyanocobalamin). B12 may be poorly absorbed in patients with IBD, particularly in extensive Crohn's disease, or malabsorption from other diseases or from surgery.
- FORVIA contains zinc, important for wound healing and immune function, at 150% of the Daily Value because it may be lost through increased excretion in individuals with IBD.
- FORVIA contains calcium diphosphate, a "non-gassy"/non-carbonate form of calcium for improved bone health.

- FORVIA does not contain magnesium as an active ingredient because magnesium can promote diarrhea.
- FORVIA is lactose-free and gluten-free (important for people allergic to gluten due to celiac disease), and contains no sugars, dyes, artificial sweeteners or flavorings.
- FORVIA Chewables offer an additional dosing option to FORVIA Tablets. The natural orange flavored Chewables have the same multivitamin and mineral content as FORVIA Tablets and are a convenient choice for people who may have difficulty swallowing tablets or who have an ostomy or other surgeries. Chewables may be a good choice for people with gastric bypass procedures who need high potency supplementation in a chewable form.

  See Complete Product and Use Information for a full description of active ingredients. FORVIA is a non-prescription product. However, daily administration of FORVIA is designed to be one component of a comprehensive medical and nutritional program. Patients are urged to consult their physician about their individual treatment program and discuss the role of FORVIA in meeting their individual nutritional needs.

  FORVIA Tablets and Chewables are manufactured in modern U.S. facilities using the highest quality ingredients and are inspected and laboratory-tested to assure compliance with specifications before leaving the factory. Our confidence in the quality of our product is reflected in our money-back guarantee.

Complete Product and Use Information

Forvia FAQs

What makes FORVIA Multivitamin/mineral Tablets and Chewables different from other vitamin products?

FORVIA Tablets are specially designed to address the deficiencies most often seen in nutrient malabsorption conditions such as Inflammatory Bowel Disease (Crohn's disease and colitis) or weight-loss surgery. FORVIA is different from general purpose products in 3 ways. First, FORVIA Tablets and Chewables have the vitamins and minerals most often deficient in IBD or weight loss surgery. Second, the forms of the individual vitamins and minerals were selected to promote good absorption and reduce stomach distress. Third, ingredients often found in general purpose products that can cause distress are not in FORVIA. For example, there is no lactose or gluten in FORVIA, and no magnesium because magnesium may cause diarrhea.

What vitamins and minerals are in FORVIA Tablets and Chewables?

For a complete listing of each nutrient, click here.

I have celiac disease and can't tolerate gluten. Is there gluten in FORVIA?

No, FORVIA Tablets and Chewables do not contain gluten.

Should the two tablet dose be taken both at once?

You can take both at once or separately, such as one in the morning and one at night with a glass of water or juice. Either way, you'll get the full nutritional benefit.

Do the tablets break down quickly in the body?

The manufacturing specification for FORVIA Tablets is for disintegration within 45 minutes in the test specified in the US Pharmacopeia, a manual of pharmaceutical testing methods and standards. Actual experience with batches to date indicates disintegration times in 20 to 35 minutes, and for most people the tablets will disintegrate completely before the stomach empties. Some individuals may have faster transit times if there has been extensive bowel surgery or there is an ostomy in place. If rapid transit is a problem, we recommend taking FORVIA Chewables. An alternative would be to take FORVIA Tablets with a meal or snack (since food in the stomach tends to slow emptying time) as well as a glass of water or juice.

Do FORVIA Tablets and Chewables supply all the vitamins and minerals I need, or do I have to take other products as well?

Your physician or health professional is in the best position to judge your individual needs. However, for most people, FORVIA Tablets and a reasonably balanced diet will provide the necessary vitamins and minerals. An important exception is calcium – FORVIA provides 200 mg of the 1000 mg daily requirement, but some IBD patients have a higher daily requirement or may not be able to maintain a diet rich in calcium. These people should consider an additional supplement of calcium such as Forbones tablets.

How much iron is in FORVIA?

Each FORVIA Tablet contains 15 mg of elemental iron as ferrous fumarate. Absorption of iron is improved when taken in the right ratio with vitamin C, and FORVIA Tablets contain vitamin C in the amount and ratio shown to improve iron absorption.

I'm taking other medications. Does FORVIA interfere with other medications?

Your physician or pharmacist is in the best position to answer questions about specific medications you may be taking. If you take anticoagulants or blood thinners, you should discuss taking FORVIA with your doctor because FORVIA Tablets contain vitamin K, which may affect the dose of anticoagulant needed. If you are taking antibiotics, you should not take FORVIA and antibiotics within two hours of each other because iron-containing products such as FORVIA may interfere with absorption of some antibiotics.

Do I need a prescription for FORVIA?

No, FORVIA Tablets and Chewables are available without prescription. Click here to order them direct over the website, or call 1-866-619-7705 toll-free or write us at Inovera, PO Box 790, Spring House, PA 19477-0790. Our operators take calls 9:00 – 5:00 ET Monday – Friday.

Is FORVIA FDA-approved?

Oral vitamin and mineral products like FORVIA which are intended for maintaining or improving nutritional status rather than treating an underlying disease do not require pre-marketing approval from the US Food and Drug Administration (FDA). However, manufacture is subject to plant inspection and manufacturing and labeling regulations. FORVIA Tablets and Chewables are manufactured and packaged in facilities that comply with all applicable FDA cGMP (current Good Manufacturing Practice) guidelines and regulations.

I have a hard time swallowing large tablets. How big are FORVIA Tablets?

FORVIA Tablets are capsule-shaped, about 5/16″ across and ¾" long, but for people who have a hard time swallowing, FORVIA Chewables are a good choice. The vitamin and mineral content is the same with either Chewables or regular Tablets.

My child is 10 and has IBD – would FORVIA Chewables be suitable for her?

For children under 12, you should discuss FORVIA with your child's physician. Nutritional needs and physical size of children vary with age and extent of disease. Her doctor is in the best position to judge the dose and appropriateness of FORVIA to her individual case.

Forvia Medical Information

Read the Product Label now

Read the Physician’s Roundtable now

3 Important Medical Conditions that cause vitamin and mineral deficiencies

Inflammatory Bowel Disease

Inflammatory Bowel Disease (IBD) is the general term for a group of chronic inflammatory processes of known etiology involving the gastrointestinal tract. The two major IBD subgroups are 1) chronic nonspecific ulcerative colitis and 2) Crohn’s disease, with the latter disease occurring either in the small bowel (regional enteritis) or the colon (Crohn’s disease of the colon or granulomatous colitis).1

The Crohn’s and Colitis Foundation of America estimates there are about 1 million persons with IBD in the U.S. Syndicated market data indicate the prevalence of IBD patients under medical care to be approximately 800,000 in the U.S. and 1.5 million in the 7 major world markets.

Among the many medical problems encountered in IBD are multiple derangements of vitamin and mineral absorption and excretion that can complicate patient management. Patients with IBD are at high risk of developing hypovitaminosis as well as deficiencies of certain minerals and electrolytes; however, these problems can be addressed by appropriate nutritional strategies.

Celiac Disease

Celiac disease, also known as celiac sprue and gluten enteropathy, is an allergic response to gluten. Gluten is a family of proteins found in wheat, barley and rye. In individuals with celiac disease, eating gluten results in inflammation and destruction of the intestinal villi. The villi are the site of absorption of nutrients so their destruction leads to malabsorption of food and deficiencies of vitamins and minerals. Celiac disease can be of varying intensity and can also have confusing symptoms. Two organizations with information on celiac disease are the National Foundation for Celiac Awareness and the Celiac Disease Foundation.

Gastrointestinal Surgery

Surgeries on the gastrointestinal tract that remove portions of the stomach or small intestine have the potential to reduce absorption of vitamins and minerals from food. Weight-loss, or bariatric, surgery procedures can result in malabsorption and significant deficiencies of vitamins and minerals. Weight-loss surgery procedures include those that reduce stomach volume such as stapling or lap band and bypass procedures, which reduce stomach volume and also bypass segments of the small intestine. The bypass procedures result in the most profound weight loss but also lead to serious vitamin/mineral deficiencies without daily

supplementation with a high potency vitamin/mineral product. FORVIA Tablets and Chewables meet recommendations of the American Society for Metabolic and Bariatric Surgery committee on Nutrition. For non-commercial information about bariatric surgery, try **this website**.

Read the Product Label now

Read the Physician’s Roundtable now

Forvia Product Label

FORVIA® Tablets and Chewables
(for' vee-uh)

High-Potency Multivitamin / Mineral Tablets and Chewables
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DESCRIPTION:
FORVIA® is a medical food formulated as oral multinutrient tablets and chewable wafers to meet the special nutrient needs of individuals who do not obtain sufficient quantities of certain essential vitamins and minerals from diet, especially because of poor absorption or increased excretion of nutrients or dietary restrictions due to gastrointestinal conditions such as inflammatory bowel disease (IBD), celiac disease and bariatric or other surgeries.

PROPERTIES:
The adult dose of two tablets or chewable wafers daily has the following properties (see Composition listed below for detailed information on tablet and wafer composition):

- FORVIA contains the fat-soluble vitamins A, D, E and K in water-miscible forms to promote good absorption and utilization. Water-miscible forms more easily mix with body enzymes and bile salts to create absorbable particles called micelles. Vitamin D, important for maintaining bone mass, is supplemented at 2 times the Daily Value because is not optimally absorbed in IBD and absorption may be inhibited by steroids used in the treatment of IBD.
- FORVIA contains vitamin C and iron in the ratio and quantities shown to increase iron absorption when given together. Iron is provided as ferrous fumarate, which is highly soluble in the gastrointestinal tract, well tolerated orally and was less toxic than ferrous sulfate or ferrous gluconate in laboratory studies.
- FORVIA contains folic acid, the daily administration of which has been found in a number of studies to be associated with a reduced risk for the development of colorectal cancer or dysplasia in individuals with ulcerative colitis.
- FORVIA contains 1000 mcg of vitamin B 12 (cyanocobalamin). B 12 may be poorly absorbed in patients with IBD, particularly in extensive Crohn's disease, because B 12 in diet is absorbed by an active transport mechanism in the terminal ileum (lower part of small intestine). A small percentage of a large oral dose such as in FORVIA Tablets can be absorbed passively throughout the small intestine and maintain B 12 levels in IBD patients. Patient B 12 status should be monitored when switching from parenteral B 12 injections to FORVIA Tablets.
- FORVIA contains zinc, important for wound healing and immune function, which is supplemented at 150% of the Daily Value because zinc may be lost through increased excretion in individuals with IBD.

- FORVIA contains dicalcium phosphate, a “non-gassy”/non-carbonate form of calcium.
- FORVIA is lactose-free and contains no sugars (except fructose in the Chewables), dyes, artificial sweeteners or flavorings.
- FORVIA contains no gluten and may be suitable for patients with Celiac Disease.

COMPOSITION:

	1 Tablet or Chewable Contains	2 Tablets or Chewables Provide	
Vitamins	(Amount)	(Amount)	% Daily Value
Vitamin A	2,500 IU	5,000 IU	100
Vitamin D	400 IU	800 IU	200
Vitamin E	75 IU	150 IU	500
Vitamin K	40 mcg	80 mcg	100
Vitamin C	100 mg	200 mg	330
Vitamin B1	5 mg	10 mg	670
Vitamin B2	5 mg	10 mg	590
Vitamin B6	5 mg	10 mg	500
Vitamin B12	500 mcg	1,000 mcg	16670
Folic Acid	0.2 mg	0.4 mg	100
Niacin	10 mg	20 mg	100
Biotin	0.15 mg	0.3 mg	100
Pantothenic acid	5 mg	10 mg	100
Minerals			
Iron (elemental)	15 mg	30 mg	170
Calcium (elemental)	100 mg	200 mg	20
Zinc	11.25 mg	22.5 mg	150

Selenium	35 mcg	70 mcg	100
Copper	1.0 mg	2.0 mg	100
Iodine	75 mcg	150 mcg	100
Manganese	1.0 mg	2.0 mg	100

*Percent Daily Values are based on a 2,000 calorie diet.

INGREDIENTS:

Tablets – Vitamin A acetate, cholecalciferol, dl-alpha tocopherol acetate, phytonadione, ascorbic acid, thiamine mononitrate, riboflavin, pyridoxine hydrochloride, cyanocobalamin, folic acid, niacinamide, biotin, D- calcium pantothenate, ferrous fumarate, dicalcium phosphate, zinc oxide, selenium yeast, cupric oxide, potassium iodide, manganese sulfate, calcium stearate, calcium silicate, silicon dioxide, crospovidone, zinc stearate, croscarmellose sodium, hydroxypropyl methylcellulose, titanium dioxide, microcrystalline cellulose, stearic acid.

Chewables – Vitamin A acetate, cholecalciferol, dl-alpha tocopherol acetate, phytonadione, ascorbic acid, thiamine mononitrate, riboflavin, pyridoxine hydrochloride, caynacoablamin, folic acid, niacinamide, biotin, D- calcium pantothenate, ferrous fumarate, dicalcium phosphate, zinc oxide, selenium yeast, cupric oxide, potassium iodide, manganese sulfate, dextrates,fructose,vegetable stearine, natural orange flavor, silicon dioxide, magnesium stearate.

INDICATIONS:

FORVIA tablets are indicated for use under medical supervision in individuals who do not obtain sufficient quantities of certain of the essential vitamins and minerals from diet, especially due to poor absorption or increased excretion of nutrients, or dietary restrictions associated with gastrointestinal conditions such as inflammatory bowel disease (IBD) (ulcerative colitis; Crohn’s disease), celiac disease and bariatric or other surgeries.

DOSAGE:

Adults: Two tablets daily in a single or divided dose, or as directed by physician
Children under age 12: As directed by physician

PRECAUTIONS:

Do not exceed recommended dosage. FORVIA is not intended for the treatment of pernicious anemia, and the treatment of any anemic conditions should be under the advice and supervision of a physician. Intake of folic acid from all sources should be limited to 1.0 mg/day or less to prevent the masking of vitamin B 12 deficiencies. Vitamin K interferes with the action of anticoagulant drugs. Individuals taking anticoagulants should consult

their physician before taking FORVIA. Excessive quantities of vitamin A may be hazardous to the embryo or fetus when taken during pregnancy. Women of childbearing potential should consult their physician concerning their total daily vitamin A intake. Because oral iron products interfere with oral absorption of tetracycline antibiotics, these products should not be taken within two hours of each other. Serious deficiencies of individual vitamins or minerals require medical evaluation and may require treatment and monitoring. Dermatitis herpetiformis is a rare hereditary skin disease linked to celiac disease. Dermatitis herpetiformis patients should not consume FORVIA® or other iodine-containing supplements or foods high in iodine while rash is present.

WARNINGS: Accidental overdose of iron-containing products is a leading cause of fatal poisoning in children under 6. Keep this product out of the reach of children. In case of accidental overdose, call a doctor or poison control center immediately.

ADVERSE REACTIONS: FORVIA Tablets are generally well-tolerated. There have been occasional reports of stomach distress or diarrhea. Individuals who are particularly sensitive to vitamin and mineral formulations may wish to divide the daily dose and take one tablet in the morning and one in the afternoon or evening with a meal or snack. There have been two reports of discolored stools, possibly due to iron in the formulation.

HOW SUPPLIED: Ivory capsule-shaped tablets imprinted FORVIA in bottles of 60 and 180 tablets with child-resistant safety cap. Off white natural orange flavor chewable wafers imprinted FORVIA 05 in round bottles of 60. Do not use if safety seal under cap is broken or missing.

STORAGE: Store at controlled room temperature, 59o – 86oF (15o – 30oC)

MANUFACTURED FOR:
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Forbones Xtra D

About Forbones *Xtra D*

Forbones Xtra D is a calcium supplement designed particularly for people that need additional calcium but don’t like the excess gas that can come from calcium carbonate supplements.

Each Forbones Xtra D tablet:

Contains dicalcium phosphate. Forbones provides both calcium and phosphorus, the two major minerals in bone. Forbones is gas free, unlike calcium carbonate supplements that produce carbon dioxide gas and can cause pain or discomfort from intestinal distension, belching and flatulence.

Provides 400 mg of elemental calcium and 300 mg of elemental phosphorus. 2-3 tablets daily provide the calcium and phosphorus needed by most people. People with certain gastrointestinal conditions or who are taking corticosteroid drugs such as prednisone may need additional calcium and should consult their physician regarding daily calcium intake.

Provides 200 International Units of vitamin D (cholecalciferol), essential to absorption and utilization of calcium. The vitamin D in each tablet is in water-miscible form to promote good absorption in people who may not digest fats and oils well. Gastric bypass surgery and gastrointestinal conditions such as pancreatitis, Crohn’s disease and ulcerative colitis can interfere with digestion of fats.

Contains no gluten, lactose, or sweeteners.

Forbones Xtra D FAQs

How is Forbones Xtra D calcium supplement different from other calcium supplements?

The source of calcium in Forbones Tablets is dicalcium phosphate. Unlike calcium carbonate, the most common source of calcium in supplements, the calcium ingredient in Forbones does not react with stomach acid to form carbon dioxide (CO_2) gas.

How many Forbones Xtra D Tablets should a person take, and when is the best time to take them?

The Daily Value for calcium is 1000 mg per day, although some people, including nursing mothers, adults over 50 and individuals who take oral steroids or who have had certain weight loss procedures, may require more. Your doctor or dietician is in the best position to advise on your total intake. Two Forbones Tablets daily provide 800 mg and a third tablet daily would provide 1200 mg. A person also taking two FORVIA Tablets or Chewables daily would receive an additional 200 mg of calcium. The best time to take Forbones Tablets is with meals, but the most important factor in dosing is to develop a good daily routine that works for you. Missing a dose has more impact than timing.

Forbones Xtra D Medical Information

Read the Product Label

Calcium Supplementation

The objective of daily calcium supplementation is to assure adequate calcium intake because inadequate calcium intake can lead to osteoporosis and osteomalacia. While osteomalacia is relatively rare in the U.S., osteoporosis is a significant problem in people over 65 because of the risk of bone fracture. Dairy products are the main source of dietary calcium in the U.S. diet1, but individuals who do not consume sufficient dairy products may be at risk. Efficiency of calcium absorption declines with age, and certain gastrointestinal diseases, surgeries, and drugs may also decrease absorption or increase excretion.

Functions of Calcium and Phosphorus

Calcium and phosphorus have multiple functions throughout the body, although about 99% of body stores of calcium1 and 80% of phosphorus4 are in bone. In the skeleton, calcium and phosphorus (as phosphate) provide most of the mineral content and are responsible for the strength and rigidity of the bony skeleton. Non-skeletal calcium is present in plasma and its concentration is controlled tightly via endocrine control over absorption through the intestines and excretion through the kidneys in urine. Calcium ion (Ca++) is essential to muscle contraction, including cardiac muscle, and for conduction of electrical impulses in the heart. Calcium ion is also involved in neurotransmitter release, cell membrane integrity and blood coagulation.2 Phosphorus is essential to energy transfer within cells and in transferring nutrients and other materials into and out of cells.4

The calcium in the skeleton serves not only as the structural mineral in bone along with phosphate but as a pool available to maintain circulating calcium levels. There is a constant turnover of bone, with old bone being resorbed and new bone deposited. The calcium and phosphorus freed by resorption are available in the circulating pool for deposition as new bone and to fulfill the additional roles of calcium in cell function throughout the body. A portion of circulating calcium is lost daily through excretion via the kidneys and the intestinal tract. Calcium lost from the body must be replaced from diet or supplementation to assure there is adequate calcium present for deposition of new bone. Phosphate, too, must be replaced from diet, although phosphorus is widely distributed in foodstuffs as opposed to calcium, which comes mostly from dairy products in North America.1,2,4

Calcium Absorption and Excretion

Calcium is absorbed through the intestinal tract via two mechanisms. A vitamin D-dependent active transport mechanism operates in the duodenum and proximal jejunum, the part of the small intestine just below the stomach. This area has the highest rate of absorption, about 3 times that of the remainder of the gut.5 A second mechanism for absorption is diffusion, which occurs throughout the small and large intestine.3

The dual absorption mechanism helps compensate for varying amounts of calcium in diet because the efficiency of absorption depends on the amount of calcium consumed. Efficiency of absorption goes down when calcium intake is high and increases when intake is low. Unfortunately, increasing age tends to reduce absorption efficiency.[2,5] In addition, certain drugs, such as steroids and phenytoin depress calcium intestinal transport. Diseases, such as inflammatory bowel disease (ulcerative colitis and Crohn's disease), where fat malabsorption, diarrhea and chronic intestinal inflammation are present increase calcium loss through feces. Surgical procedures for weight reduction that involve bypass of the duodenum may reduce absorption efficiency, since the portion of the intestinal tract with highest absorption efficiency is the duodenum and proximal jejunum. Foods which contain oxalates or phytates can form complexes with calcium that can't be absorbed.[1]Phytates are present in unsprouted seeds, grains and legumes and in raw nuts. Oxalates are present in spinach and seeds.

Calcium is excreted from the body in feces, urine and to a small extent in sweat. During lactation, mothers secrete significant levels of calcium into breast milk. Fecal loss of calcium makes up the bulk of excreted calcium under normal conditions, with the excreted volume made up of unabsorbed dietary calcium and calcium contained in mucosal cell sloughing from the intestinal tract. Urinary calcium excretion accounts for almost all other calcium loss, except, as noted above, during lactation or extensive sweating. Calcium loss in urine is influenced by parathyroid hormone, which regulates reabsorption of calcium in the kidney. Medical conditions affecting parathyroid hormone therefore can impact calcium loss in urine. Some diuretic drugs ("water pills") can increase calcium loss by partially blocking reabsorption of calcium in the kidney. Corticosteroid drugs such as prednisone, which are often used to treat inflammation, also increase loss of calcium and increase the need for intake of calcium in diet or through supplements.

Role of Vitamin D

The body obtains Vitamin D from diet and through exposure to sunlight. However, various population studies show vitamin D insufficiency persists in North America and Europe, particularly during winter months when sun exposure is reduced. Once absorbed from diet or generated in the skin, vitamin D is converted in the liver to a metabolite, 25 hydroxy vitamin D. This metabolite is inactive, but circulating 25 hydroxy vitamin D is converted in the kidney and possibly other sites to the active metabolite 1,25 dihydroxy vitamin D.6 The level of the 1,25 dihydroxy metabolite is tightly controlled by feedback mechanisms based on calcium levels in blood. As calcium levels in blood increase, conversion of vitamin D to its active metabolite decreases.[7]

Vitamin D facilitates active absorption of calcium and phosphate in the intestine through the actions of 1,25 dihydroxy vitamin D, which stimulates active calcium uptake by the cells lining the intestine. The mechanism for facilitating absorption involves binding the vitamin D metabolite to the vitamin D receptor in the cells and subsequent opening of the calcium channel in the cell membrane in the intestinal wall, stimulation of the cell calcium binding protein (calbindin), which transports calcium through the cell, and stimulation of the plasma membrane calcium ATPase, which pumps calcium from the cell to the blood stream.[7,8]

Vitamin D also has a role in maintaining levels of calcium in circulation in the blood through interaction with parathyroid hormone in mobilizing calcium (and phosphate) from bone and reducing excretion in urine through the kidneys.[2]Vitamin D stimulates bone cells to form new bone but, at higher levels, increases calcium mobilization from old bone.[9]

Malabsorption of Vitamin D

Diseases and surgeries of the digestive tract can impair Vitamin D absorption. Since Vitamin D is fat soluble, any disease that interferes with breakdown and digestion of fats can reduce absorption of Vitamin D (and the other fat-soluble vitamins – A, E and K). Some diseases impacting fat absorption are Inflammatory Bowel Disease (Crohn's disease and ulcerative colitis), cystic fibrosis, chronic pancreatitis, and short bowel syndrome. Certain surgeries for weight reduction, especially bypass surgery, can impair fat absorption and thus Vitamin D absorption.

Forbones contains a water-miscible form of Vitamin D that promotes good absorption. The water-miscible form more easily forms the small particles necessary to pass through the gut wall compared to oily forms of Vitamin D for people with fat malabsorption.

Forms of Calcium

The most frequently found form of calcium in dietary supplements is calcium carbonate. Other forms of calcium used in supplements are calcium citrate, calcium gluconate and calcium phosphate. The carbonate form is the most frequently used because it is inexpensive and not as bulky as some other forms. The principal drawback to carbonate is that it releases carbon dioxide gas on contact with stomach acid and can cause abdominal distension, pain and discomfort. Gluconate and citrate forms of calcium are more bulky, creating problems for making tablets of a size that can be swallowed. For that reason and because they are more water soluble, these forms are more often used in liquid or chewable products. Calcium phosphate does not produce carbon dioxide in stomach acid and can be formed into tablets of reasonable size, making it a good choice where excess gas can be an issue.

1. Weaver CM, Heaney RP, Calcium (Ch 7) in Modern Nutrition in Health and Disease (Shils ME, Olson JA, Shike M, Ross AC, Eds.),Williams & Wilkins, Baltimore 1999:141-155

2. Marcus R, Agents Affecting Calcification and Bone Turnover (Ch 62) in Goodman & Gilman's Pharmacological Basis of Therapeutics (Hardman JG, Limbird LE, Gilman AG, Eds), McGraw-Hill, New York, 2001:1715-1743

3. Bronner F, Intestinal Calcium Transport: The Cellular Pathway, Miner Electrolyte Metab 1990;16:94-100

4. Knochel JP, Phosphorus (Ch 8) in Modern Nutrition in Health and Disease (Shils ME, Olson JA, Shike M, Ross AC, Eds.),Williams & Wilkins, Baltimore 1999: 157-167

5. Civitelli R, Avioli LV, Calcium, Phosphate and Magnesium Absorption (Ch 65) in Physiology of the Gastrointestinal Tract, 3rd Ed (Johnson LR, ed), Raven Press, NY; 1994: 2173-2181

6. Holick MF, Vitamin D (Ch 18) in Modern Nutrition in Health and Disease (Shils ME, Olson JA, Shike M, Ross AC, Eds.),Williams & Wilkins, Baltimore 1999:329-345

7. Heaney RP, Functional Indices of Vitamin D Status and Ramifications of Vitamin D Deficiency, Am J Clin Nutr;Vol 80, No 6, Dec 2004:1706S-1709S.

8. Merck Manual, 17th Edition Beers MH, Berkow R, eds), Merck Research Laboratories, 1999: 141

9. op. cit., p35

Forbones Xtra D Product Label

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Forbones Xtra D
Calcium Supplement
with Vitamin D & Phosphorus

Supplement Facts		
Serving Size 1 Tablet		
	Amount per Serving	% Daily Value
Vitamin D	200 IU	50%
Calcium	400 mg	40%
Phosphorus	300 mg	30.00%

Ingredients: dicalcium phosphate, cholecalciferol, cellulose, stearic acid, silicon dioxide, croscarmellose sodium, calcium stearate, hydroxypropyl methylcellulose, titanium dioxide (color).

Some gastrointestinal conditions and medications can interfere with calcium absorption or increase loss of calcium. Consult your physician regarding appropriate daily intake of calcium if you have inflammatory bowel disease or other gastrointestinal conditions.

SUGGESTED USE:
Take two or three tablets per day (one tablet two to three times per day) with food or as directed by your physician.

Do not use if safety seal under cap is broken or missing
Keep out of reach of children.
Keep bottle tightly closed.
Store at room temperature, 59° to 86° F (15° – 30° C)

Order direct from INOVERA Bioscience by mail, phone or internet or ask your pharmacist. To order by phone, call 1-866-619-7705 or visit the website at www.inovera.com.

Distributed by: INOVERA Bioscience, Inc.
PO Box 768, Ambler, PA 19002 USA
1-866-619-7705 www.inovera.com

Important information* about Forbones:

- Forbones contains dicalcium phosphate, a less ‘gassy’ form of calcium than calcium carbonate.
- Forbones provides 400 mg per tablet of calcium, the main building block of bone. The body constantly replaces old bone with new, so it is important to maintain a daily intake of calcium to replace lost calcium.
- Forbones provides Vitamin D, essential to absorption and utilization of calcium. Taking vitamin D with calcium helps assure adequate vitamin D is available to promote good absorption.
- Forbones provides phosphorus, an important constituent of bone along with calcium. About 80% of the body’s phosphate stores are in bone.

  *These statement have not been approved by the Food and Drug Administration. This product is not intended to diagnose, treat, cure or prevent any disease.

Shop

(Currently just the product images, though you have the option of giving a general introduction to the shop or list brief product descriptions with Forvia/Forbones Xtra D)

Button Text: “Select Options”

(Shop) Forvia

Multivitamin formulated for persons with malabsorption conditions.

Tablets or Chewables?

Quantity

Product Description

FORVIA is a multivitamin/mineral product that provides nutritional support for patients with reduced ability to absorb vitamins and minerals from diet due to gastrointestinal conditions such as

- Inflammatory bowel disease (IBD), including Crohn’s disease and ulcerative colitis
- Celiac disease
- Other malabsorption conditions including weight-loss and other gastrointestinal surgeries.

FORVIA Tablets and Chewables were developed on the basis of growing medical knowledge about the effects of disease on the body’s ability to absorb and use nutrients.

Additional Information

Tablets or Chewables?	Chewable, Tablet
Quantity	30 days supply, 60 days supply, 90 days supply, Six months supply

(Shop) Forbones Xtra D

$11.95–$33.95

Calcium Supplement with Vitamin D & Phosphorus

Quantity

Product Description

Contains dicalcium phosphate. Forbones provides both calcium and phosphorus, the two major minerals in bone. Forbones is gas free, unlike calcium carbonate supplements that produce carbon dioxide gas and can cause pain or discomfort from intestinal distension, belching and flatulence.

Provides 400 mg of elemental calcium and 300 mg of elemental phosphorus. 2-3 tablets daily provide the calcium and phosphorus needed by most people. People with certain gastrointestinal conditions or who are taking corticosteroid drugs such as prednisone may need additional calcium and should consult their physician regarding daily calcium intake.

Provides 75 International Units of vitamin D (cholecalciferol), essential to absorption and utilization of calcium. The vitamin D in each tablet is in water-miscible form to promote good absorption in people who may not digest fats and oils well. Gastric bypass surgery and gastrointestinal conditions such as pancreatitis, Crohn’s disease and ulcerative colitis can interfere with digestion of fats.

Contains no gluten, lactose, artificial colors, dyes or sweeteners.

Additional Information

Tablets or Chewables?	Tablet
Quantity	30 Tablets, 60 Tablets, 90 Tablets

My Account (login page)

(Notice in blue) Welcome to our new site! If had an account on our old site your information is still here, but you must. On that page just enter the email you used to register and you'll recieve an email with a reset link shortly!

If you encounter any difficulties, please don't hesitate to call us at (215) 646-7705 and we can reset your password manually.

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Hello (not ? **Sign out**)

From your account dashboard you can view your **recent orders**, manage your **shipping and billing addresses** and **edit your password and account details**.

- Dashboard
- Orders
- Downloads
- Addresses
- Account Details
- Logout

ROUNDTABLE DISCUSSION

Bret A. Lashner, M.D. and Joel B. Mason, M.D.
October 12, 1998, Boston, MA

(NOTE: I'm going to reformat this considerably. My plan is to break this up into pages based on the vitamins being discussed, remove the "roundtable discussion" page headers, and add a table of contents style navigation, etc. The only editing this *might* need is a read through for typos.)

Moderator: This discussion with Dr. Lashner and Dr. Mason will address current information about the existence of vitamin and mineral deficiencies in Inflammatory Bowel Disease (IBD), as well as strategies to meet the particular nutritional requirements of IBD patients. To start, perhaps you could introduce yourselves.

Dr. Lashner: I'm Bret Lashner, Director of the Inflammatory Bowel Disease Center at the Cleveland Clinic in Cleveland. Previously, at the University of Chicago, I worked with some renowned inflammatory bowel disease experts including Dr. Joseph Kirsner and Dr. Irwin Rosenberg. I have a very busy clinical practice but also pursue some areas of clinical research. In particular, I'm looking at the risk factors for colorectal cancer and ulcerative colitis, especially as that may relate to folic acid deficiency and also whether supplementation may prevent the occurrence of cancer or dysplasia in ulcerative colitis.

Dr. Mason: I'm Joel Mason. I trained alongside Bret at the University of Chicago and have now been at Tufts University for twelve years. I am an Associate Professor of Medicine and Nutrition and head of the Adult Nutrition Support Service, which is an inpatient consultation service in the hospital. I am Chief of the Division of Clinical Nutrition and also Director of the Vitamin and Carcinogenesis program at the USDA Human Nutrition Research Center on Aging at Tufts University. I am a member of the Division of Gastroenterology in the medical school as well. Due to the influence of common mentors at the University of Chicago, both Bret and I have an interest in the prevention of colon cancer and both of us have published studies pertaining to this issue.

Moderator: The first topic today is the general basis of vitamin mineral deficiencies in inflammatory bowel disease. Perhaps you could both discuss that.

Dr. Lashner: The two main inflammatory bowel diseases are Crohn's disease and ulcerative colitis, each having distinguishing features relative to inflammation of the gastrointestinal tract and distinct types of vitamin and mineral deficiencies. Crohn's disease can affect any segment or area of the gastrointestinal tract, and, depending on which areas are affected, a particular type of deficiency is likely to occur.

The most common area of involvement of Crohn's disease is disease of the terminal ileum, an area that is particularly suited to the absorption of B_{12}. People with severe terminal ileal disease or resection of the terminal ileum have a problem with B_{12}

deficiency. Crohn's disease can also involve extensive areas of the small bowel, leading to a generalized malabsorption of fat and other nutrients and, in turn, to further vitamin deficiencies. The fat-soluble vitamins A, D, and E are particular problems when there is fat malabsorption. Folic acid and the other water-soluble vitamins are mostly absorbed in the proximal small bowel, so, if there is disease there or a patient has a short bowel syndrome where most of the small bowel has been resected, there will be major vitamin deficiencies.

Ulcerative colitis always involves the colon. When it is severe, there will be intestinal losses through diarrhea and bleeding, and with that there will be problems with iron deficiency. From diarrhea, you may have certain mineral and electrolyte deficiencies, such as potassium and bicarbonate. A principal medication we use to treat ulcerative colitis, sulfasalazine, is an inhibitor of folic acid absorption, another reason why people might have vitamin deficiency.

Finally, there are many foods rich in vitamins that make people with inflammatory bowel disease feel worse. Fruits and vegetables might exacerbate symptoms of the disease, making abdominal pain and diarrhea somewhat worse, and patients naturally will avoid these, another problem and reason to be vitamin deficient.

Dr. Mason: I would just like to underscore the point that it is not just the direct effect of disease on the gastrointestinal tract and the subsequent inability to assimilate nutrients that causes deficiencies. In many ways it is the general effects that inflammatory bowel disease has on a patient that lead to micronutrient deficiencies. For instance, Bret was pointing out the fact that the inhibition of appetite or the inhibition of a desire to eat certain types of foods that are rich in micronutrients plays an important role in some of the deficiencies that appear in this disease. Similarly, the physician taking care of a patient may recommend a diet that can lead to vitamin or mineral deficiencies. For example, a diet that has few or no fresh fruits or vegetables will severely curtail the intake of necessary nutrients. So there are a lot of factors other than the direct effect of these illnesses on the integrity of the intestine that actually lead to micronutrient deficiencies in IBD patients.

Dr. Lashner: I agree. Another frequent dietary recommendation is that patients avoid milk and milk products. And indeed, those who are lactase deficient will have an exacerbation of abdominal pain and diarrhea with milk, but meanwhile they lose the valuable nutrients from milk when it's removed from the diet. Another factor that should be mentioned is corticosteroid therapy that is frequently used for both diseases. Steroids carry a major risk for bone demineralization, osteoporosis and osteomalacia, especially when there is fat malabsorption that may directly lead to vitamin and mineral deficiencies.

Moderator: We wanted to talk a little bit about folate and the B vitamins. Dr. Lashner, you've done some important work with folate and I wondered if you could discuss that.

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Dr. Lashner: I have published four studies in this area, looking at the role of folic acid supplementation to prevent cancer and dysplasia in ulcerative colitis. Dysplasia is a premalignant lesion, and since the risk of cancer and cancer mortality is so high in ulcerative colitis, we recommend cancer surveillance colonoscopy. Patients have periodic, often every one to two years, colonoscopy with extensive biopsy sampling of their colon, and colectomy is recommended if dysplasia or asymptomatic cancer is found.

You can imagine that after more than twenty years of performing cancer surveillance in this country we've collected an incredible amount of data. The first study published in Gastroenterology in 1989 was a case control study that looked at patients with cancer or dysplasia followed in our surveillance program and compared them to people without cancer or dysplasia. The principal exposure of interest was folic acid supplementation. At the University of Chicago, at that time about 30% of patients were supplemented with folic acid. These were mostly people who were on sulfasalazine, and from the work that was done at the University of Chicago at the time, mostly by Dr. Rosenberg, folic acid was supplemented to people with sulfasalazine but still at a rate of about 30% of patients. In any case, those patients who were supplemented with folic acid had a lower risk for cancer or dysplasia; not statistically significant, but the risk was quite reduced.

Another study also was done at the University of Chicago on cancer surveillance colonoscopy patients as they came in for their colonoscopy. I drew blood and measured red blood cell folate levels as well as serum folate and some other vitamin levels to see if they were associated with cancer. It turned out that higher folic acid levels had a protective effect on the development of cancer or dysplasia. This was statistically significant. For every 10 nanogram per milliliter (mL) increase in red blood cell folate there was an 18% reduction in risk of cancer or dysplasia. Other vitamins and minerals that were studied did not show a statistically significant effect, although there seemed to be a small protective effect from increased vitamin A and vitamin D levels.

A third study done at the Cleveland Clinic was a cohort study that looked at a large group of patients followed in a cancer surveillance colonoscopy program. Charts were reviewed, and when it was mentioned that folic acid supplementation was taken for at least 6 months, that was considered the positive exposure, and indeed folic acid had a protective effect but it was not statistically significant. It is interesting to note that by this time, by the mid to late 1990's, about 60% or more of our ulcerative colitis patients were taking folic acid. In an earlier era, maybe 10 years ago, only 30% of patients were supplemented. So the word is out that folic acid may be beneficial and many more people are taking it now than were previously.

In these studies, we've also looked at the dose of folic acid that might be protective. Typically, 0.4 mg is given in a multivitamin and 1 mg as a sole vitamin supplement. It turns out that any supplementation of either 0.4 mg or 1 mg was sufficient to reduce the

risk. There was no dose response. You didn't get necessarily more protective effect from folate beyond 0.4 mg.

The fourth study, which was published in the American Journal of Gastroenterology, also looked at patients with ulcerative colitis having cancer surveillance colonoscopy. This time we looked not just at their folic acid use; we also looked at an intermediary marker of malignancy, p53 mutations. It seems that p53 mutations were associated with cancer or dysplasia and folic acid deficiency. If patients were supplemented with folic acid, they were less likely to have a p53 mutation in their mucosa, less likely to develop dysplasia and less likely to develop cancer.

Moderator: Dr. Mason, you've also published some work, I believe, on folate and the effects of folate depletion on certain metabolic pathways.

Dr. Mason: I have been concentrating a lot more on mechanistic issues over the past 7 or 8 years and only more recently have started to venture into clinical studies as Dr. Lashner was describing.

Similar to what Bret describes, we have found adverse effects on the p53 gene in animal models of folate deficiency. We have found that modest folate depletion in laboratory animals causes several aberrations of the p53 gene. Interestingly, not only does it seem to be specific for the p53 gene but also it seems to be specific for that region of the p53 gene that is most highly associated with the evolution of colorectal cancer. There is a so called "hyper-mutable region" of p53 that seems to be particularly sensitive to the adverse affects associated with folate depletion, and this region is also the one that is most frequently disrupted in cancerous lesions.

There are a few other things I'd like to comment on or qualify in regard to Bret's remarks. Bret was really the first one to appreciate the inverse relationship between dietary folate and the risk of colorectal neoplasia and he did so in patients with ulcerative colitis. Since 1989, when Bret published his initial observations, a whole host of findings (now amounting to over 15 epidemiologic studies) have established an identical effect in the general population. There is increasing interest not only in utilizing folate as a cancer protective agent in the setting of ulcerative colitis or Crohn's disease, but also for the problem in the general population of colorectal cancer, which presently is the second biggest cancer killer in the Western world. We don't know yet whether the potential beneficial effects of folate in the setting of inflammatory bowel disease are similar in nature to the potential benefits in the general population. Some of the larger epidemiologic studies in the general population have seen a stepwise increase in protection as one proceeds from a small dose of dietary folate (200 micrograms per day) all the way up to about 1 mg per day. This contrasts a bit with some of Bret's studies in inflammatory bowel disease, which suggest there is a threshold effect at 0.4 mg. I should note

parenthetically that you have to be circumspect when you're supplementing a patient with inflammatory bowel disease with large does of folate. Particularly when you're dealing with someone with Crohn's who may have a subtle B_{12}

deficiency, you have to be a bit cautious giving large doses of folate in that setting because you might mask B_{12} deficiency.

Moderator: You mentioned in one of your articles the effects of folate on concentration of homocysteine. What are the implications of that?

Dr. Mason: Homocysteine is an amino acid that circulates in the blood of all people and interestingly, the disposal of homocysteine in the body is largely conducted through a folate-dependent pathway. Homocysteine is converted to methionine through a folatedependent reaction, and, like most biochemical reactions, if you limit one of the substrates (in this instance, folate) you cause an accumulation of the precursor compounds. So in this situation, folate deficiency results in an accumulation of one of the precursors, homocysteine, and that is used clinically as an indicator of folate deficiency. In fact, in the last 5-7 years, tests for serum homocysteine levels have become commercially available and are being used increasingly as a very sensitive indicator of folate deficiency.

In my clinical practice, I use homocysteine quite a bit as a very sensitive indicator of folate deficiency, in fact more sensitive than blood measurements of folate, whether that is serum or red cell folate. In a study that we published in the American Journal of Clinical Nutrition, we looked at indicators of folate status in people who harbor precancerous polyps (so-called adenomatous polyps), versus people who harbor nonprecancerous polyps, (so-called hyperplasic polyps). We found that blood levels of folate were identical in these two groups (both serum and red cell folate). We then looked at colonic folate levels of these people. We took biopsies of the colon, some distance away from the polyp itself so there wasn't any local effect of the polyp and we found that there was about a 40% decrease in colonic folate levels in those people who harbor the precancerous polyps, indicating that even in the absence of blood indications of folate deficiency there was some indication of folate depletion in those people who harbor precancerous polyps. This suggests perhaps a particular sensitivity of the colonic mucosa to folate depletion that might not necessarily be reflected in systemic indicators. Now to get back to homocysteine, we also measured homocysteine in these two groups, and interestingly, the group that harbored the precancerous polyps did have a small but statistically significant increase in serum homocysteine compared to the group who did not harbor precancerous polyps, suggesting that even though blood concentrations of folate were not indicative of a difference in folate status between these two groups, there indeed was a very subtle indication of differences in systemic folate status, at least as reflected by homocysteine levels.

Dr. Lashner: Both groups were in the normal range. How do you define 'normal range' of homocysteine?

Dr. Mason: Bret brings up a very interesting point. No one yet knows what a normal homocysteine level is. Certainly one can go by the conventional definition of "normality", which usually

is defined as the mean of a "normal population" plus or minus 2 standard deviations. But let me remind you that homocysteine has only recently been implicated as an independent risk factor in cardiovascular disease. In this regard it is very comparable to our understanding about serum cholesterol levels back in the early 1960s. In those days, a normal cholesterol level was assumed to be about 240 mg per deciliter, because if you looked at the mean cholesterol level in the United States in an ambulatory healthy population and added 2 standard deviations, it was approximately 240 mg per deciliter. It was only 10 or 20 years later that we came to appreciate that what we were defining as normal, still represented a level that was associated with a very substantial risk of cardiovascular disease. Nowadays, a "normal cholesterol level" is usually defined as one that is under 180-200 mg per deciliter, because that is at a level that minimizes the risk of cardiovascular disease.

Dr. Lashner: In that same line, do people who take multivitamins (0.4 mg of folic acid) consistently have lower homocysteine levels? Can you push down your homocysteine levels with folate supplementation?

Dr. Mason: You can. In fact, one of the most effective ways of reducing serum homocysteine levels in almost any population is by taking additional dietary folate. There are several large intervention trials now, not with cancer risk necessarily, but more with cardiovascular risk, where investigators are selecting people who have moderately high elevations of homocysteine and supplementing them either with folate alone or with folate in addition to B6 and B_{12}, since B6 and B_{12} are also cofactors in the disposal of homocysteine from the body.

Moderator: I just picked up a news article last week referring to a paper on a large population study by Giovannucci et. al., in the Annals of Internal Medicine. This is one of the studies I think you were talking about.

Dr. Mason: Right. Dr. Giovanucci is at the Harvard School of Public Health. This is his third publication pertaining to folate and cancer arising from either the Health Professionals Longitudinal Study or the Nurses Health Study. This most recent one is from the Nurses Health Study. This is the third study in which he has demonstrated in these very large prospective cohorts that increasing doses of folate intake are associated with a very substantial reduction in the risk of colorectal neoplasia. Interestingly, Bret, who we already mentioned was the first one to make this observation in the ulcerative colitis population, found about a 60% reduction in his very first paper.

Dr. Lashner: The odds ratio was 0.38, which means about a 62% reduction.

Dr. Mason: I'd like to point out that there are now 17 epidemiologic studies, some of which are in inflammatory bowel disease such as the ones that Bret had done. The rest are in the

general population. In all of these studies, you find a risk reduction in the 40-60% range. It is amazing how consistent these studies are.

Dr. Lashner: The consistency is amazing. Some are not statistically significant but, even so, virtually anyone who has looked at folate has found a protective effect.

Dr. Mason: In fact, in the many studies that have been done in the general population, all but a few show a statistically significant benefit or protection of increasing levels of dietary folate. There are rarely fields in medicine with evolving fields of knowledge where there is so much consistency amongst epidemiologic studies.

Moderator: Thank you. I think we can move to the next topic, vitamin B_{12}. Who would like to start?

Dr. Lashner: B_{12} absorption is complex. We eat B_{12} and it is bound in our stomach to dietary Rproteins. The stomach also secretes intrinsic factor and, in the duodenum, pancreatic enzymes cleave the R-proteins from the B_{12} and free it to bind with the intrinsic factor. The B_{12}-intrinsic factor complex is subsequently absorbed in the terminal ileum, leading to normal B_{12} absorption. Disruption anywhere along that pathway will lead to B_{12} deficiency.

In Crohn's disease, the most common place for that pathway to be interrupted is in the terminal ileum where there is active disease or after there's been a resection. The other common place is the pancreas. Pancreatic insufficiency from acute or chronic pancreatitis is rare, but it's occurring often enough in patients with Crohn's disease that we're thinking that it might be an extraintestinal manifestation of IBD. Other reasons for pancreatic disease are duodenal Crohn's disease with obstruction of the pancreatic duct and pancreatic damage from some medications used for IBD, namely azothiaprine or 6-mercaptopurine. Steroids are thought to have an effect for induction of pancreatitis. Then, of course, disease of the gastric antrum where intrinsic factor can't be adequately secreted is another reason why people might have B_{12} deficiency. Joel, are you going to talk about oral supplementation?

Dr. Mason: The prevalence of B_{12} deficiency that has been reported in IBD largely depends upon whether you look at ulcerative colitis or patients with Crohn's disease. The reasons are inherent to the nature of where the disease affects the intestine: B_{12} deficiency in ulcerative colitis is rarely reported. When it occurs, it is usually thought to be due to an illness or disease condition that is independent of the ulcerative colitis. However, in Crohn's disease (because it so commonly affects the ileum), the prevalence of B_{12} deficiency is reported anywhere from 5-50%.

The risk of someone developing B_{12} deficiency is largely related to the extent of the disease in the ileum and there have actually been studies done where they look at the radiologic extent of disease in a patient with Crohn's ileitis. Those patients who have

more than 100 cm of disease almost invariably develop B_{12} deficiency. Those who have less than about 40 cm of disease almost invariably don't have B_{12} deficiency, while, in between, people may or may not develop B_{12} deficiency.

Traditionally, B_{12} deficiency both as a result of pernicious anemia as well as a result of a diseased ileum has been treated with parenteral B_{12}. However, one thing that physicians often forget is that studies done over the years demonstrate in both these settings that a high percentage of patients can be very suitably treated just by giving vitamin B_{12} in large oral doses, usually 500 micrograms to 1,000 micrograms a day. Even if you lose a large portion of the ileum or your ability to secrete intrinsic factor, about 1% of ingested B_{12} gets across the intestinal wall and into the blood stream. So if you are taking a large dose, even though the absorption might be very inefficient, enough gets in that it actually meets the needs of the person. The needs of B_{12} are minuscule, amounting to about 2 micrograms per day. Therefore, there is reason to consider the use of an oral supplement containing either 500 or 1,000 micrograms of B_{12}. The advantage of this is that even though it represents a huge amount of B_{12}, it is inexpensive and it is associated with absolutely no side effects.

Dr. Lashner: How long does it take to get B_{12} deficient? Don't we have body stores that will last several years?

Dr. Mason: It does take a long time. Because the needs of B_{12} are so low, much lower than most vitamins, and because the liver does contain a fair amount of B_{12} and because there is an enterohepatic circulation, it does take a long time to develop B_{12} deficiency; or at least that has been the conventional thinking.

I just came back from a meeting, the 6th Biannual Conference on Folate, B_{12} and One Carbon Metabolism. There were data presented at that meeting suggesting this traditional way of thinking (that it takes so long to become depleted of B_{12}) might be somewhat misguided. The investigators selected a group of people who require parenteral B_{12} due, I believe, to ileal disease. The B_{12} status of those subjects was followed using a very sensitive indicator of cellular B_{12} status, called serum methylmalonic acid. Like homocysteine, methylmalonic acid levels rise very early on in B_{12} deficiency because B_{12} is a cofactor in the disposal of methylmalonic acid. This is also a commercially available assay and one that is used extensively in my clinical practice. In this study, which was performed by Bob Allen and Sally Stabler at the University of Colorado, they showed that some people (and this

varies from person to person), actually start developing biochemical evidence of B_{12} deficiency in as little as one month after their last B_{12} injection.

Dr. Lashner: That's interesting. So now the next question is, if you have virtually no B_{12} absorption capacity for whatever reason, how often do you have to give parenteral B_{12}?

Dr. Mason:

That is exactly the clinical question addressed by this study. As you are well aware, Bret, physicians traditionally give B_{12} injections to people either every month or every three months because the thought is that you don't have to give it any more frequently because B_{12} stores last so long. What Allen and Stabler were asking is, is this really adequate? It is not clear why, but in some people the traditional regimen doesn't seem to be adequate because when they return for their monthly or every three month injection, their methylmalonic acid levels were already on the rise.

Dr. Lashner: So is oral supplementation to these people who have B_{12} malabsorption likely to keep levels up?

Dr. Mason: When you identify someone who you're convinced has true B_{12} deficiency, I think you're obliged to give them a series of parenteral injections to quickly replete them. This is because the neurologic and psychiatric complications of B_{12} deficiency can become irreversible after a certain point, and one shouldn't be awaiting the potential benefits of oral therapy, which are slow compared to the immediate benefits of parenteral therapy. So, once identified, I immediately give these people 3-5 parenteral injections of B_{12} each amounting to 500-1000 micrograms. That will quickly replete their stores. Then one can go on an oral regimen.

Even though oral therapy is going to work for many people, there are clearly some people for whom it is not going to work, and I think as a physician you should monitor their B_{12} status on a fairly regular basis for the first year or two when they are on oral therapy, just to be sure that they are being adequately repleted. If you convince yourself as their physician that oral therapy is working fine for them after the first year or two, then you can probably feel assured that is going to continue to work for them unless they have progression of their disease. But as reflected in some of the studies that have been done in pernicious anemia, there is a significant minority of people who still need parenteral therapy.

Moderator: Is there a fairly simple test for B_{12}?

Dr. Mason: There is a very simple test, plasma B_{12}. Increasingly, people are using serum methylmalonic acid levels as a more sensitive indicator of B_{12} deficiency. In years past it was said that anyone who had a B_{12} level greater than 200 picograms/mL was B_{12} sufficient. Interestingly, studies

published in just the last 10 years indicate that, although the majority of people whose serum B_{12} levels are greater than 200 picograms/mL are B_{12} sufficient, approximately 7-10% of people in the lownormal range, which is 200-400 picograms/mL, actually develop both biochemical, (i.e. methylmalonic acid elevation) and clinical sequelae of B_{12} deficiency. It is not known why a small percentage of people who live in this low normal range develop frank symptoms of B_{12} deficiency. These people somehow have an altered B_{12} "thermostat", if you will. They require higher serum B_{12} levels to maintain normal physiologic functions.

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Moderator: Just to complete this part of the discussion, the literature shows deficiencies of B1, B2 and B6 reported in IBD. Do these have significance for you, and do you have any comments?

Dr. Mason: There are certainly reports of deficiencies of a variety of B vitamins in the setting of IBD. They're not as well defined as some of the other deficiencies that we have already discussed, in part because one B vitamin deficiency appears frequently in conjunction with other B vitamin deficiencies. Most investigators haven't bothered to dissect out all of the different B vitamin deficiencies that appear. In general, the administration of a single multivitamin tablet is usually enough to ward off most of these B vitamin deficiencies that you are speaking of.

Moderator: We can then move on to the fat-soluble vitamins A, D, E and K. Dr. Lashner, some comments?

Dr. Lashner: The fat-soluble vitamins for the most part require intact dietary fat absorption for their absorption to occur. Fat malabsorption will occur in IBD with extensive mucosal disease, with short bowel syndrome and, once again, with pancreatic disease where there are insufficient enzymes or bile to form the appropriate micelles for the fat absorption.

Dr. Mason: Certainly there are reports indicating a significant minority of patients with IBD develop low fat-soluble vitamin levels. There are reports of approximately 20% of patients with low serum retinol levels relating to vitamin A status. There are reports indicating occasional episodes of vitamin E deficiency and flagrant neurologic decompensation based on that.

One other comment that I would make is that in general, a modest supplementation with these fat-soluble vitamins is usually sufficient to overcome results of any mild fat malabsorption, even though there are occasional patients with flagrant fat malabsorption that require upwards of 5-10 times the recommend daily allowance to remain in a vitamin-sufficient state.

Another comment that I would like to make is that one would have to be somewhat cautious in the use of vitamin A because there certainly are occasions where people have made themselves vitamin A toxic, which is primarily on a chronic basis and presents as hepatic toxicity. More recently, it has been identified that as little as 15,000 international units (IU) a day of vitamin A might be teratogenic in pregnant women, so nowadays we certainly have to be attentive to the vitamin A needs of IBD patients.

Particularly because this tends to be a disease of young adults involving many women in the childbearing years, one has to be careful not to be overzealous with the supplementation of vitamin A.

Dr. Lashner: By the same token, there is a risk of night blindness with low levels of vitamin A; something that is easily correctable if recognized.

Dr. Mason: Absolutely, Bret, and one of the nice things about this whole discussion is that most of these vitamin and mineral deficiencies are eminently treatable conditions. These are things that, if a physician takes the time to think about them and diagnose them, they can be attended to in a very easy fashion.

I think that one of the fat-soluble vitamins that we are most concerned about in IBD is vitamin D. If there is going to be a fat-soluble vitamin deficiency, it frequently is vitamin D. There seems to be a particular sensitivity in the human body to vitamin D depletion compared to depletion of the other fat-soluble vitamins. In fact, I think the consensus of the literature is that anywhere from 20-60% of patients with IBD are noted to have low circulating vitamin D levels. Just to underscore the importance of that, the prevalence of significant bone disease in patients with low vitamin D levels is much higher than in those patients with normal vitamin D levels.

Moderator: Would it be your feeling that about two times the RDA might be a good level at which to supplement?

Dr. Mason: As I indicated: in this setting of IBD, routine supplementation with about 2-4 times the RDA is probably a reasonable goal. There are studies primarily in postmenopausal women where up to 800 IU (which is 4 times the RDA) can be administered with complete safety. There are no reports of vitamin D toxicity with this range of vitamin D supplementation.

Dr. Lashner: The biggest problem we see with mineral metabolism in IBD is with steroid use. Steroids are used for both Crohn's disease and ulcerative colitis. They work very well, and because they work so well patients are reluctant to stop them and frequently we find prednisone-dependent patients or patients who take prednisone for a very long time. When that happens, there are severe consequences with bone demineralization either through osteoporosis or osteomalacia. The effects of steroids on vitamin D and calcium are still being elucidated, but we know there is a decrease in the absorption of calcium, a decrease in activation of vitamin D and there are direct effects on bone demineralization itself from steroids. These people with chronic steroid use are very much prone to avascular necrosis of the bone as well as osteopenic syndromes. Joel, you might want to talk about supplementation of patients on and off steroids with vitamin D and calcium.

Dr. Mason: Bret, all my patients with IBD are on a multivitamin/multimineral tablet but I would agree with you that one has to be particularly attentive to patients on chronic steroids in regard

to their vitamin D and bone status. These are patients who I am very careful about making sure that they are also taking a generous amount of calcium in their diet; I am frequently aiming toward somewhere between 800-1200 mg per day. Parenthetically, recently there was a large study that effectively demonstrated that one of the bisphosphonates is very effective in attenuating or even preventing corticosteroidinduced bone disease. Therefore, in addition to the nutritional approach to preventing corticosteroid-induced disease, we now have a pharmacological approach. These may prove to be highly complementary.

One of the other things I would add is that because sclerosing cholangitis sometimes complicates these diseases, one occasionally sees patients with IBD that have chronic cholestasis. There are studies that indicate that, if one has a serum bilirubin level chronically above 5 mg/dl, one is more prone to these fat-soluble vitamin deficiencies, probably because you're putting insufficient amounts of bile into the intestine to consistently maintain the critical micellar concentration for fat absorption.

Dr. Lashner: What kind of doses of vitamin D and calcium do you recommend to people on steroids?

Dr. Mason: I have been usually asking people to take 400-800 IU of vitamin D a day as well as somewhere between 800-1200 mg of calcium. It is pretty hard for most people to get 800-1200 mg of calcium in their diet through foodstuffs alone. Frequently attaining that level requires some type of calcium supplementation.

Dr. Lashner: If patients are not on steroids, you would still recommend the calcium, I assume, but what about vitamin D?

Dr. Mason: I guess I am less rigorous in that setting, but please recall that all my patients with IBD are on a multivitamin/multimineral supplement that at the very least contains 200 IU of vitamin D, and, since the average adult American intake of vitamin D is somewhere on the order of 100-200 IU, these people are getting a total of somewhere around 300-500 IU per day.

Moderator: Perhaps we can move on to iron, then. This is something that both of you have discussed quite a bit. Your comments on iron, Dr. Mason?

Dr. Mason: I think that Bret would certainly agree that anemia is exceedingly common in IBD, and in most cases it's due to either anemia of chronic disease and/or iron deficiency. Iron deficiency is exceedingly common in IBD for obvious reasons.

Dr. Lashner:

Anemia is virtually universal. Certainly this is true for ulcerative colitis when the bleeding becomes severe and in Crohn's disease when the inflammation becomes severe. For the most part, it's iron deficiency anemia for patients with ulcerative colitis and chronic disease for people with Crohn's disease, but there is a fair amount of overlap.

Moderator: Can you discuss prevention and management?

Dr. Lashner: What you really need to do is to control the underlying disease. Stop the bleeding in ulcerative colitis or deal with the inflammation in Crohn's. Frequently the hemoglobin will rise and that's good, that would avoid supplementation. Iron supplementation orally at corrective doses can have a fair number of GI side effects; it can be constipating, cause abdominal pain, and can actually exacerbate symptoms of IBD. Because of that, we will tend to give lower doses that aren't necessarily therapeutic or parenteral iron which I don't like giving but I have to give in certain circumstances.

Moderator: Dr. Mason you've talked about doses of up to 40 mg a day as being pretty well tolerated.

Dr. Mason: Yes. I would agree with Bret that conventional therapeutic doses of iron in a person who has been identified as having an iron deficiency anemia is usually about 60 mg of elemental iron three times a day. That is usually given as a 325 mg tablet of ferrous sulfate three times a day. That amount of iron is frequently, in my experience as it is with Bret's and other gastroenterologists', enough to cause significant GI symptoms. Sufficiently significant, mind you, that those patients just stop taking their medicine. So, like Bret, except in particularly dire circumstances, I frequently supplement people in a more gradual fashion using lower doses. In many instances, if you can stop the bleeding as Bret indicates and give them a more modest dose, it might take a little bit longer for them to replete but nevertheless you get to the point you want to reach. It just might take you a few extra months to get to that point.

Dr. Mason: One other comment I would like to make on iron: we physicians frequently associate iron depletion solely with the development of iron deficiency anemia but it is also important to keep in mind that iron deficiency anemia is just the end result of iron depletion. Iron constitutes a component of many important proteins in the body other than hemoglobin. There are a number of other heme containing proteins such as myoglobin and the cytochromes.

It is fairly clear that iron depletion that is not severe enough to cause anemia can still result in certain constitutional symptoms such as fatigue and lassitude, and this is important to keep in mind when one sees patients in clinic who complain of fatigue. That might be due to chronic inflammation, which is a common cause of lassitude in IBD patients, but one also must keep in mind that this might be, at least in part, a result of

iron depletion that is not severe or prolonged enough to be causing iron deficiency anemia, but nevertheless sufficiently severe to cause effects on muscles and other organs resulting in fatigue.

Moderator: The next topic is vitamin C.

Dr. Lashner: Vitamin C is a water-soluble vitamin that is easily absorbed, and frankly I can't imagine that this has ever been a problem with people with IBD, although I haven't measured it.

Dr. Mason: I am sure that there are occasional reports of vitamin C deficiency, because if one has severe dietary restrictions, one is going to get vitamin C deficient eventually. I would agree with Bret that it is vanishingly rare in my experience. I think one thing that is worth mentioning, though, is that vitamin C, since it is a mild organic acid, does enhance the absorption of inorganic iron, which is the form of iron that is present in virtually all of the nutritional supplements. Some people when they give iron supplementation to patients with iron deficiency actually co-administer large doses of vitamin C to enhance the absorption.

Moderator: In the next section, I grouped calcium, magnesium, phosphate and potassium together. We talked a little bit already about calcium, so perhaps we can talk nextabout magnesium.

Dr. Lashner: Magnesium is an essential mineral. Its absorption very much follows calcium. When there is calcium malabsorption there will be magnesium malabsorption and when there is no calcium malabsorption there will be no magnesium malabsorption.

One problem with magnesium is that very little of it is absorbed. If you give it, it acts as an osmotic agent to promote diarrhea. In fact, that is the reason citrate of magnesium and magnesium hydroxide, otherwise known as milk of magnesia, actually act as cathartics. So supplementing IBD patients daily with magnesium, especially magnesium oxide, is fraught with the problem of diarrhea as a side effect.

Moderator: A review article mentioned something to the effect that it probably was not worthwhile to supplement magnesium orally as part of a multivitamin/multimineral regimen because 1) it's cathartic, and 2) if patients develop serious magnesium deficiency you probably have to go the injectable route anyway to correct it. Does that make sense to you?

Dr. Lashner: Calcium supplementation to preserve bone health is very worthwhile. If you are giving calcium and vitamin D so the calcium is absorbed, the dietary magnesium follows right

along with it and is very much tied into it. It can be problematic to have magnesium in a daily supplement, and serious magnesium depletion may require parenteral magnesium anyway.

Moderator: How about potassium? I think in an earlier discussion a point was made that if a patient can develop a potassium deficiency this is a serious situation that requires some urgent medical attention.

Dr. Lashner: Potassium is one of the electrolytes that is low when there is dehydration and diarrhea. When potassium is exceedingly low, it's life threatening, and it has to be dealt with parenterally or certainly aggressively orally. There is no reason why potassium has to be put into a multivitamin supplement. There is plenty of potassium in the diet and unless the diarrhea is severe enough to cause worry and imminent hospitalization, then I don't think that it needs to be supplemented.

Dr. Mason: I would agree with that and the same thing with bicarbonate.

Dr. Lashner: Bicarbonate is lost in diarrhea, but still for the most part it doesn't need to be supplemented orally on a regular basis.

Dr. Mason: Again, I would agree with Bret, when a patient with IBD becomes particularly ill on an acute basis, their needs can become extraordinary for a variety of things including nutrients. In that setting one has to cater the delivery of nutrients in a very selected fashion to these people based on their particular needs.

Moderator: Any more comments on that, or should we move on to zinc?

Dr. Lashner: There are a whole host of trace elements that can be deficient in IBD. The biggest ones are zinc, selenium and chromium. The latter two deficiencies in my experience are exclusively seen in patients with short bowel syndrome who are on total parenteral nutrition. This is something that is just not seen in IBD patients who do not require total parenteral nutrition. I don't take care of home TPN patients but I do think there is a weekly supplement of trace elements, isn't there?

Dr. Mason: In the vast majority of TPN formulas there is a standard mix of trace elements that includes zinc, selenium and chromium. I would agree with Bret that selenium and chromium are required in such small amounts that the development of deficiency of those in conventional IBD is uncommon. Zinc turns out to be the only trace mineral that appears with any reasonable frequency as a deficiency in patients with IBD.

Moderator: The percentage of IBD patients with zinc deficiency is fairly high, is it not?

Dr. Mason: Low zinc levels have been seen in approximately 40-50% of hospitalized patients with IBD, although this is obviously a biased sampling because those statistics reflect particularly ill patients who are hospitalized. One has to realize also that serum zinc levels, particularly in the setting of acute illness, are fairly unreliable because serum zinc is a "negative acute phase reactant." The more systemic inflammation there is, the lower the serum zinc levels go, partly because there is a redistribution of zinc in the body in the setting of acute illness and a lot of zinc gets redistributed from the intravascular compartment into the liver.

Having said that, there still does seem to be occasional occurrences of flagrant zinc deficiency in patients with IBD. The reason is that about half of the zinc excreted from the body under normal

circumstances is through the stool, and when one has chronic diarrhea the losses of zinc on a daily basis go up tremendously. In fact, in a study done some years ago, it was found that in patients with diarrhea due to IBD the average dose of zinc required was about three fold the normal level that is required.

Zinc is necessary for a number of things because it is involved in a number of metalloproteins. It seems to be very important in maintaining adequate wound healing, which is obviously important in the recovery from IBD. It seems to be important in maintaining fertility, and infertility amongst male patients with IBD is an occasional problem, especially with sulfasalazine where the sperm counts are sometimes reversibly inhibited. As a clinical presentation, zinc deficiency usually presents as a rather nonspecific rash. It can be on various parts of the body.

My particular habit is to supplement people with voluminous diarrhea or at least those having chronic diarrhea, because zinc deficiency is sometimes hard to diagnose, and as I mentioned serum levels are not very good indicators. The only qualification I would make is that one has to be careful not to use too much zinc because before the days of ipecac, the most common way to induce vomiting in the emergency room was by giving huge doses of zinc. It's a very good agent for creating nausea when given in large doses.

Moderator: 1-2 times the RDA would not be a problem?

Dr. Mason: No. Not at all. That is far below the amount necessary to induce any kind of GI symptoms.

Moderator: We've seen some reports on deficiencies of biotin in patients with IBD. Have either of you looked at that or have any comments? I'm not sure if that has any clinical significance at all.

Dr. Mason: I've also seen those reports. I think that only under exceptional circumstances does biotin deficiency probably appear. As I indicated before, if one gives a comprehensive mix of B vitamins, one is probably not going to become significantly biotin deficient.

Moderator: Dr. Mason, in your article you mentioned that there is considerable rationale for placing all patients with IBD on a multivitamin/multimineral supplement.

Dr. Mason: My personal belief is that the prevalence of micronutrient deficiencies (vitamin and mineral deficiencies) in patients with IBD is so high, the potential benefits of supplementation great enough and the potential adverse effects so low that it warrants the use of a multivitamin/multimineral preparation in all patients with IBD.

Dr. Lashner: I fully agree. I ask everybody to take it. Frequently they don't, mainly because they don't believe me. They don't think that vitamin supplementation is important to their care despite what I say. Education is very important. I think they do need to take multivitamin/mineral supplements.

Moderator: Given what has been learned in recent years concerning the nutritional deficiencies commonly associated with IBD, do you feel it would be feasible to develop and make available a non-prescription multivitamin/mineral supplement that would more closely match the needs of most IBD patients than the currently available general supplements?

Dr. Lashner: Yes, if attention is given to important points of our discussion including the need for daily folate, fat-soluble vitamins and calcium supplementation, and the appropriate use in this group of oral doses of iron, B_{12} and vitamin D that are above the RDA for the general adult population.

Moderator: Thank you both for coming today and for your discussion of this important aspect of the management of Inflammatory Bowel Disease.