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IATROGENIC NUTRITIONAL DEFICIENCIES

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CONTENTS

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INTRODUCTION

Clinicians and biologists are most familiar with nutritional deficiencies that result from poor diets or a conditioning illness—e.g. protein-calorie malnutrition in Third World nations, and pernicious anemia, respectively. Diagnosis and specific treatment by health professionals correct the deficiency. It is increasingly apparent, however, that many types of therapy by physicians can provoke nutrient deficiencies. This chapter reviews several categories of such iatrogenic nutrient deficiencies (iatrogenic—induced inadvertently by a physician or his treatment).

Although severe deficiencies have been unintentionally induced during parenteral nutrition and by use of certain new therapeutic diets, this chapter does not review these.

SURGERY

Surgical Stress and Tissue Trauma

Immediately following major surgery there is considerable urinary loss of nitrogen, potassium, magnesium, and zinc (69, 205, 206). Hypercalcuria may result from immobilization, soft tissue injury of surgery, and skeletal trauma due to either surgery or accident (205). Such nutrient losses vary with age, with the nature of the underlying injury, and with site and magnitude of trauma. Poor nutritional status preoperatively may interfere with recovery through impaired wound healing, but postoperative megadoses of vitamins do not protect against surgical complications (73).

Gastric Surgery

B_{12} DEFICIENCY Removal of the stomach eliminates the source of intrinsic factor and therefore leads to deficiency of vitamin B_{12}.The reported

Table 1 Nutrient deficiencies resulting from gastrectomy

Nutrient	References
Vitamin B_{12}	32, 57, 62, 98, 104, 106, 119, 121, 166–171, 174
Vitamin D and calcium	34, 35, 39, 58, 65, 77, 78, 81, 129, 131, 132, 134–137, 159, 175, 176, 190, 199, 210
Folate	104
Iron	9, 11, 57, 106, 121, 210
Protein	141, 204
Thiamine	20, 26

incidence of B_{12} deficiency following gastrectomy for peptic ulcer disease has ranged from 14 to 57% (32, 57, 98, 106, 174). This variation reflects differences in the surgical procedures used—i.e. anastomosis with duodenum or jejunum and presence or absence of associated vagotomy, as well as differences in the duration of follow-up. Johnson & Hoffbrand (104) studied 223 cases and concluded that as a cause of subsequent B_{12} deficiency the extent of gastric resection is more important than ulcer site, type of anastomosis, or inclusion of vagotomy. The deficiency often does not develop until six years following surgery, and new cases still develop after 10–15 years (32). This long depletion period for development of clincially evident deficiency of vitamin B_{12} is consistent with the earlier observations of Darby et al (55) in patients with pernicious anemia who were permitted to relapse under observation. On the other hand, development of low serum B_{12} postoperatively is not related to age or sex. In Buxton's (32) study, about 5% of gastrectomized patients developed evidence of B_{12} deficiency each year between postoperative years 5 and 15.

Multiple mechanisms may be involved. Most of the gastrectomized patients studied by Mahmud et al (121) and Lous & Swartz (119) displayed normal absorption of crystalline B_{12}, and fewer than 30% had abnormal B_{12} absorption tests indicating deficient intrinsic factor activity. In gastrectomized patients Doscherholmen & Swain (62) demonstrated impaired absorption of B_{12} when the vitamin was fed mixed into eggs, but not of crystalline B_{12}. This observation is consistent with a role of impaired acid and/or pepsin secretion in producing deficient utilization of dietary B_{12}. The effect may be additive with that of intrinsic factor deficiency, when present. Other proposed mechanisms for postgastrectomy B_{12} deficiency include bacterial overgrowth of the small intestine and disturbed enterohepatic circulation.

Buxton et al (32) noted that mean cell volume did not increase until serum B_{12} had fallen. They noted "obvious" macrocytosis in only 3 of 35 post-gastrectomy patients at the time when low B_{12} levels in the blood were documented. Iron nutriture was not examined in this series. Mahmud et al (121), on the other hand, reported "moderate" or "large" numbers of macrocytes in peripheral blood smears of 16 of 22 patients with low serum B_{12}; concomitant deficiency of bone marrow iron stores appeared to prevent the development of frank megaloblastosis.

Roos (166–171) found evidence of neuropathy in 34% of 128 gastrectomized patients after 12 years. The patients had primarily a peripheral sensory neuropathy, often associated with some myelopathy, affective changes, and dementia. Myelopathic signs did not respond to B_{12} replacement therapy. Affective improvement with treatment occurred in the majority of cases with intellectual impairment, but cognitive functioning at follow-up was not documented.

FOLATE More than 30% of the gastrectomized patients reported by Johnson & Hoffbrand (104) had low folate values. Mean serum folate levels were 30% lower in patients who underwent "radical" gastric resection than those who had partial resections, but this difference was not significant because of scatter in the data. Neither ulcer site, presence or absence of vagotomy, nor type of anastomosis significantly differentiated serum folate levels. No data concerning preoperative diet were reported. The stomach is not thought to have a major role in folate absorption, but there are complex interactions between the metabolism of folate and of B_{12}, that do depend on the gastric mucosa. Thus the pathogenesis of folate deficiency after gastrectomy requires further investigation, including its relationship to preoperative nutriture.

VITAMIN D BONE DISEASE Metabolic bone disease has been recognized as a late complication of gastric surgery since 1941 (175). By the tenth year following surgery the incidence has been judged to be 5–15% (134–137) to as high as 41% (64). Osteomalacia is the most prevalent syndrome described (9, 129), but osteoporosis has also been noted. Osteomalacia may be clinically apparent, with bone pain, low serum calcium and phosphorus, elevated alkaline phosphatase, and radiologic abnormalities (159). Clinically silent bone disease of moderate severity has, however, frequently been detected by bone biopsy. The disorder is most common after subtotal gastrectomy and gastrojejunostomy (Billroth II) and less common after a Billroth I procedure (78) or after vagotomy with gastric drainage (131, 132, 176, 210). The mechanism of the osteomalacia is controversial. Low 25-hydroxy-vitamin D levels have been detected following gastric surgery. Impaired absorption of vitamin D (190) and response to vitamin D therapy have been reported.

Chalmers (35) and Gertner et al (81) proposed that an important etiologic factor is poor dietary intake of vitamin D due to discomfort induced by eating fatty foods. Gertner found normal absorption of 25-hydroxycholecalciferol (25-OHD) in 5 of 6 patients with postgastrectomy osteomalacia but a history of dietary insufficiency in 4 of the 6. Destruction of vitamin D by intestinal bacteria has also been suggested but has not received direct support (199).

Osteoporosis can occur alone or in combination with osteomalacia following gastrectomy (34, 39). Reported incidence increases with increased duration of follow-up; changes become manifest more than six years following operation (58). The effect is also age-related, gastrectomy appearing to enhance age-dependent bone loss (77). These changes have been attributed to decreased calcium absorption and increased fecal excretion.

IRON Iron deficiency and associated anemia are commonly reported following gastric surgery (9, 11, 57, 106, 210), with rates as high as 44% among men and 84% among women (210) depending on the surgical procedures as well as the measures and criteria applied. In Mahmud's series (121) 87% of gastrectomized patients had decreased bone marrow stores of iron. In addition to defective absorption, hemorrhage and dietary deficiency have been considered to be contributing mechanisms.

THIAMINE Cases of "wet beriberi" following gastrectomy in alcoholics have been reported by Brigden & Robinson (26) and Bjornsson & Jonsson (20). Alchoholics are at risk for thiamine deficiency and for alcholic cardiomyopathy even without gastrectomy. Since the stomach is not known to play a major role in thiamine absorption, knowledge of the preoperative thiamine nutriture and intake of the vitamin during hospitalization is necessary before assessing the significance of gastrectomy per se on absorption and metabolism of thiamine in these patients with symptoms attributed to thiamine deficiency.

PROTEIN-CALORIE MALNUTRITION Neale (141) reviewed 27 cases of protein-calorie malnutrition following gastrectomy, in all of which surgery was complicated by contaminated bowel syndrome, pancreatic insufficiency, or anorexia. In a case reported by Waldram (204) surgery was complicated by alcoholism, depression, and poor dentition.

Small Bowel Resection or Bypass

B_{12} DEFICIENCY Impaired absorption of vitamin B_{12} was noted by Booth & Mollin (23) and Valman (200) following ileal resection, and following jejunoileal bypass by others (12, 107). Best (18) and Baker & Bogoch (13) described subacute combined degeneration of the spinal cord after ileal resection for Crohn's disease followed by folate therapy; low serum B_{12} was documented in both cases. Rodgers et al (162) reported abnormal Schilling tests in 3 of 13 children 10–26 months after replacement of the esophagus with a bowel segment that included colon and terminal ileum; serum B_{12} levels were still normal at that time.

VITAMIN D BONE DISEASE Osteomalacia has been observed following gastrojejunostomy (93, 144), jejunoileal bypass for morbid obesity (46, 139, 148), and resection of jejunum, ileum, or both (43).

The incidence of histological osteomalacia was nearly 50% in an un-

Table 2 Nutrient deficiencies resulting from intestinal bypass or resection

Nutrient	References
Vitamin A	27, 164, 208
Vitamin B_6	100
Vitamin B_{12}	12, 13, 18, 23, 107, 162, 200
Vitamin D and calcium	7, 43, 44, 46, 47, 48, 54, 93, 120, 139, 144, 148, 164, 177, 185
Vitamin E	164, 208
Thiamine	82
Magnesium	46, 72, 117, 143, 146, 195
Trace metals	8, 130, 209
Carnitine	75, 140
Potassium	59, 83, 120, 151
Carbohydrate	151, 177
Protein	140, 179, 182, 211
Fat	102, 120, 178

selected group of patients 3–6 years after jejunoileal bypass (43). Low plasma 25-OHD concentrations suggest vitamin D malabsorption (44, 159). In addition, low serum 1,25-dihydroxy-vitamin D was documented by Mosekilde et al (139). Malabsorption of bile acid following bypass (54) may play a role in the malabsorption of vitamin D and of enterohepatically circulating 25-OHD (7). Bacterial contamination of the bypassed segment and lack of exposure of the patient to sunlight may also contribute to the deficit. Liver disease occurring after bypass may impair 25-hydroxylation of vitamin D (185). Mild, asymptomatic hypocalcemia occurred in 48% of one series (185) and secondary hyperparathyroidism was observed; bone disease was not found preoperatively in 4 morbidly obese subjects studied.

One to 14 years following jejunal, ileal, or combined resections, osteomalacia occurred in 9 of 25 patients (43). Abnormal bone biopsy occurred often in absence of symptoms or other biochemical or radiologic changes. The authors suggested that preoperative inflammatory bowel disease contributed to the bone changes. A history of poor dietary intake of vitamin D and of little exposure to sunlight were not uncommon, and cholestyramine therapy may also have contributed (see also 46) in some cases. The response to parenteral or oral vitamin D supplements varies (47, 48).

PROTEIN DEFICIENCY Protein malnutrition frequently follows jejunoileal bypass (140, 179, 182, 211). Moxley et al (140) and White et al (211) reported a pattern of blood amino acid changes commonly seen in protein-

calorie malnutrition: Low plasma concentrations of essential amino acids (valine, isoleucine, leucine, phenylalanine, threonine and lysine) as well as of nonessential amino acids (alanine, citrulline, cystine, tyramine, ornithine, and arginine) were associated with rapid weight loss during the first four months after surgery. Plasma levels of glycine and serine were elevated. Following stabilization of weight at 12–36 months after surgery, moderate depression of plasma valine, isoleucine, leucine, lysine, tyramine, ornithine, and arginine persisted. Oral amino acid tolerance tests consistent with impaired absorption immediately postoperatively improved by 12 months. Tryptophan was not measured. Normal blood glucose and liver glycogen and absence of ketones were documented throughout the postoperative course.

Liver disease secondary to the small bowel bypass may contribute to the picture of deficiency. Experimentally, hepatic fatty metamorphosis has been attributed to protein deficiencies. During the immediate postoperative period White et al (211) found that SGOT was elevated in 12 of 18 patients, most of whom had marked hepatic steatosis. By 12–36 months hepatic fat diminished and SGOT normalized. Improved amino acid tolerance with time in these patients was attributed to adaptive increases in absorption.

In 44 bypass patients studied by Shizgal et al (182) by multiple isotope dilution techniques, loss of body cell mass in addition to loss of body fat occurred in 4 cases. Increased extracellular mass, characteristic of protein malnutrition, was documented. Six subjects experienced malaise, anorexia, weakness, hypokalemia, abnormal liver function tests, and frequent hospitalizations. Symptoms remitted and abnormal laboratory values were corrected after infusions of amino acids. A high protein diet was necessary to sustain the remission of symptoms and maintenance of normal body composition.

VITAMINS A, E, AND K Jejunoileal bypass can lead to deficiencies in these fat soluble vitamins (27, 164, 208). Rogers et al (164) found vitamin A levels of less than 30 μg/dl in 17 of 40 patients (42%) studied an average of 17 months after surgery. Abnormal dark adaptation was documented in 4 of 9 patients at least 18 months after surgery; this responded to oral supplementation. The degree of deficiency did not correlate with the time elapsed since surgery or with dietary intake; the weight of the 4 patients was stable. In the case reported by Wechsler (208), dermatologic changes and night blindness developed two years after surgery and were associated with a serum vitamin A level of 16 μg/dl; both abnormalities responded to administration of vitamin A. Reversible night blindness was reported by Brown et al (27) occurring 3.5 years after surgery; a serum carotene level

of 6 μg/dl was found, indicating either severe impairment of absorption or a carotene-free diet.

Vitamin E levels less than 5.0 μg/dl in 18 of 40 patients (45%) were observed by Rogers et al (164); a level of 1.6 μg/dl was reported by Wechsler (208) in a patient who also had low serum β-carotene. The serum vitamin A, β-carotene, and vitamin E levels were not changed by 11 weeks of tetracycline therapy, suggesting that bacterial overgrowth was not the major factor in the deficiency. Prothrombin times were normal in the series of Rogers et al (164), which is consistent with normal bacterial production and colonic absorption of vitamin K.

THIAMINE A case of "atrophic beriberi" that presented four months following jejunoileal bypass was reported by Glad et al (82). This patient had eaten a low-residue, high-carbohydrate diet to reduce diarrhea and developed symptoms and sign of peripheral motor and sensory neuropathy. Serum thiamine was undetectable and folate was low; B_{12}, vitamin A, riboflavin, and ascorbic acid were normal. Sensory changes essentially remitted with dietary therapy and supplementation with thiamine and other vitamins. After discharge from the hospital the patient failed to comply with instructions concerning dietary supplementation and relapsed, eventually requiring reanastomosis. The authors emphasized the importance of her poor dietary intake in the development of the thiamine deficiency.

CARNITINE Frohlich et al (75) reported significant decreases in total and free plasma carnitine levels observed six weeks after jejunoileal bypass and persisting after six months. Preoperative values had been in the normal range. The authors suggest that the reduction in plasma carnitine resulted either from dietary inadequacy or secondarily from reduced synthesis from lysine, a deficiency of which can occur immediately after surgery (140).

PYRIDOXINE Howard et al (100) reported pyridoxine deficiency occurring after jejunoileal bypass. The patient became pregnant 18 months following surgery; despite routine vitamin and iron therapy she developed microcytic, hypochromic anemia and symtoms including insomnia, irritabilty, dizziness, and fatigue after the 32nd month. Plasma pyridoxine was 8.0 ng/ml (normal 30–80), with elevated serum iron and iron binding capacity. The symptoms and anemia responded to oral pyridoxine. The authors suggest that malabsorption, impaired storage, impaired hepatic conversion to pyridoxal phosphate, or increased vitamin demand associated with pregnancy may have been etiologic factors.

TRACE METALS Atkinson et al (8) demonstrated low plasma zinc and copper levels in patients 1–36 months after bypass surgery. Their patients

were apparently asymptomatic, except for one case with immunologic impairment and scrofula; neutropenia exhibited by one patient responded to supplementary copper. Weissman et al (209) described a case of clinically manifest zinc deficiency which occurred one year after bypass; the symptoms included anorexia, vomiting, dermatitis, and apathy. These deficiencies may reflect intestinal malabsorption or increased loss due to malabsorption of bile. It is interesting that morbidly obese subjects of Atkinson et al (8) had significantly low zinc levels preoperatively, which were further lowered postoperatively. Observed preoperative copper levels were significantly higher than normal. Anorexia and disturbed taste sensation from low zinc levels may compound postoperative problems (130).

MAGNESIUM Magnesium is absorbed along the small intestine, and hypomagnesemia has been reported following small bowel resection (71, 138, 141) as well as after bypass procedures (46, 113, 189). Swenson et al (189) considered magnesium deficiency to be an uncommon complication of bypass, reporting an incidence of less than 2.5% at about three years postoperatively; Compston (46), however, found hypomagnesemia in 6 of 21 patients 3–6 years after surgery. In Nielson & Thaysen's case (138), the patient became symptomatic within days after surgery, showing confusion, apathy, and muscle twitching followed by weakness. Tissue depletion preoperatively may account in part for postoperative deficit, as magnesium deficiency can be a concomitant of both inflammatory bowel disease and thiazide diuretic therapy for obesity. Postsurgical decrease in absorption is said to be proportional to length of small bowel resected or bypassed (195). Oral or parenteral replacement is effective (143, 195).

POTASSIUM LOSS A common complication of small bowel resection or bypass is hypokalemia, specifically because of diarrhea (59, 83, 102, 120, 151). Oral potassium supplementation should be prescribed routinely following such surgery.

FAT MALABSORPTION Increased fecal fat loss is routine following bypass or resection (120, 178). It results from decreased transit time, altered metabolism of bile salt, or decreased absorptive surface. Huseman (102) demonstrated a decrease in fatty acid absorption immediately after surgery, followed by some later "adaptive" increases. He also documented a persistent reduction in serum cholesterol attributable to increased bile salt loss and greater synthetic demand for cholesterol.

CALCIUM Hypocalcemia following small intestinal resection or bypass (120, 177) can lead to tetany (177).

CARBOHYDRATE ABSORPTION Decreased glucose absorption as reflected by flattened glucose tolerance curves follows small bowel resection (179, 151). The fasting glucose has been reported as normal; the clinical significance of the observed decreased absorption is not evident.

Ureteral Diversion

Anastomosis of the ureters to the bowel can result in metabolic alterations that change nutritional requirements. For instance, it may induce hypochloremic acidosis that alters calcium requirements and leads to bone disease (156). Hyperchloremic acidosis has been described following ureteroileostomy (53, 92, 105) and ureterosigmoidostomy (25, 189). It has been ascribed to bowel uptake of chloride and ammonia and to bicarbonate loss into the gut, compounded by renal damage from hydronephrosis or pyelonephritis. Ferris & Odel (71) observed hyperchloremia in 79% and acidosis in 80% of 141 patients at varying intervals (usually within one year) after ureterosigmoidostomy. Hypocalcemia and hypophosphatemia in conjunction with acidosis have been described following ureterosigmoidostomy (84). These were attributed to utilization of calcium to combine with excess acid, with secondary lowering of serum phosphorus induced by parathyroid hormone. Impaired gut absorption of vitamin D in acidosis has also been reported (115).

Rickets and osteomalacia may follow ureterosigmoidostomy in children (84, 115, 188) and in adults (99, 114, 180), bone changes becoming apparent 2–10 years following surgery. Both renal damage and acidosis may contribute. While some case reports indicate that correction of acidosis alone is sufficient (99, 184), other workers have demonstrated an additional requirement for vitamin D, or the occurrence of vitamin D "resistance" (92). Perry et al (153) described a case of vitamin D "resistant" osteomalacia after ureterosigmoidostomy. Deficiency of renal vitamin D-1 hydroxylase was indirectly demonstrated and attributed to hydronephrosis—effective vitamin D deficiency resulting from the kidney's failure to synthesize the active metabolite.

Stamey (189) stressed the dangers of chronic potassium loss in conjunction with acidosis after ureterosigmoidostomy and the therapeutic difficulties it presents. He attributed the loss of combined osmotic diuresis and colonic secretion of potassium.

Prosthetic Cardiac Valves

In a single report, 18 of 90 patients with prosthetic heart valves were reported to have anemia and low serum iron values, which responded to oral iron supplements (96).

HEMODIALYSIS

Bone Disease

Osteomalacia is a recognized complication of the treatment of chronic renal failure with hemodialysis (67, 152), but its etiology has been uncertain. Hypophosphatemia has been considered as a mechanism, via loss of phosphates through the dialyzer membrane (4, 19, 155). However, the osteomalacia was not prevented or cured by use of a phosphate-enriched dialysate in nonhypophosphatemic patients (70). The condition has not responded consistently to vitamin D_2, 1-OHD, or 1-25-OHD (67, 155, 183), and serum 25-OHD levels are reportedly normal (49). The Newcastle group has suggested that aluminum in dialysate may be responsible for osteomalacia by an unknown mechanism (52, 63, 207). Dialysis dementia, which has also been postulated to reflect aluminum toxicity, appears related epidemiologically to the osteomalacia.

Carnitine Deficiency

Reduction in plasma and muscle carnitine concentrations can accompany hemodialysis (17, 22) and may contribute to the cardiomyopathy sometimes seen with this treatment. Reduction in plasma carnitine concentration may be transient or persistent (15). In some patients a deficit in cellular carnitine concentrating capacity seemed to be present. Reduced synthesis of carnitine was apparent and was probably not part of a general synthetic deficit, since plasma protein concentration was normal. Bohmer et al (22) suggested that a lack of cofactors such as ascorbic acid or ferrous iron, or of a specific protein required for carnitine synthesis (113) might be involved.

Choline Deficiency

Reduced nerve conduction in hemodialysis patients has been related to choline loss (161). Therapy with choline or lecithin has not been systematically investigated.

Potassium Depletion

Chronic potassium depletion has been observed in patients receiving hemodialysis (123, 187). The mechanism has not been elucidated.

Hypovitaminosis

Reduced serum levels of folate have been described in patients undergoing repeated hemodialysis (see 163), as have reduced vitamin B_{12} (173) and megaloblastic hematologic changes. Reduced serum ascorbic acid levels have also been reported (94).

IRRADIATION

Therapeutically administered ionizing radiation frequently results in nausea, vomiting, anorexia, and weight loss. A malabsorption syndrome may result from radiation damage to the small bowel. Villous atrophy, lymphangectasia, steatorrhea, dissacharidase deficiency, and protein-losing enteropathy have been described (197, 198). The effects of radiation enteritis may be exacerbated through inhibition of protein synthesis by chemotherapeutic agents. Recovery is promoted by nutrient repletion and by avoiding resultant food intolerances, for example, to gluten and lactose (61).

DRUGS

The growing literature on effects of a variety of drugs on nutrient status has been summarized elsewhere (40). This review updates current thinking resulting from most recently reported studies. The monographs by Hathcock & Cook (95) and Roe (163), and the review by Ovesen (147) provide extensive background and bibliographies.

In general, acute drug use may have little effect on nutriture, but chronic use of some drugs may have more significant impact on nutrient status. In some instances, chronic use may exacerbate preexisting dietary or conditioned nutrient deficiencies.

Drugs may alter intake, synthesis, absorption, transport, storage, metabolism, or excretion of nutrients. Susceptibility to drug-induced nutrient deficiency may be greater during periods of increased requirements—i.e. during growth, pregnancy, and lactation.

The effect of a given dose of a drug varies among individuals; one may expect similar variation in the effect on nutritional status. Drugs such as diphenylhydantoin, tricyclic antidepressants, and procaine amide are classic examples of drugs the effective concentration of which following a given dosage varies among individuals. Concomitant ingestion of other drugs may also increase or decrease the effective concentrations of medication. From experimental animal data arises the suggestion that nutritional status per se may likewise alter drug metabolism. Genetic heterogeneity in drug metabolizing enzymes seems to be an important basis for interindividual differences; intercurrent diseases also alter drug metabolism. In hepatic and renal diseases there are notable examples of effective drug overdosage.

Primary Folate Antagonists

Dihydrofolate reductase is inhibited by a group of drugs including methotrexate, pyrimethamine, trimethoprim, pentamidine, and triamterene. As a result, administration of these drugs can deplete tissues of tetrahydrofolic

Table 3 Drug nutrient interactions

Nutrient	Drug	References[a]
Vitamin A	mineral oil	
	neomycin	
Vitamin B_6	hydralazine	
	isoniazid	80
	L-dopa	
	oral contraceptives	1, 28, 111, 196
	penicillamine	
Vitamin B_{12}	biguanides	33
	cholestyramine	
	colchicine	
	neomycin	
	nitrous oxide	3, 56, 116, 127
	oral contraceptives	
	potassium chloride	
Vitamin C	oral contraceptives	
	salicylates	
	tetracycline	
Vitamin D	anticonvulsants	6, 16, 87, 88, 118, 125, 138, 191, 212
	cholestyramine	
	irritant cathartics	74
	mineral oil	
Folate	anticonvulsants	36, 186, 203
	cholestyramine	
	methotrexate	5
	oral contraceptives	14
	pyrimethamine	
	sulfasalizine	
	triamterene	
	salicylates	
	trimethoprim	
Vitamin K	anticonvulsants	109
	cholestyramine	
	coumarin	109, 192
	mineral oil	
	salicylates	
Magnesium	gentamycin	110, 149
	diuretics	64, 66
Niacin	isoniazid	41, 42, 86, 91
Riboflavin	oral contraceptives	142, 202
	chlorpromazine	157, 158
Thiamin	oral contraceptives	142, 202

[a] In addition to the text and the reviews by Roe (163), Ovesen (147), Clark (40) and Hatchcock & Coon (95).

acid and lead to megaloblastic anemias (5), particularly in individuals already low in folate. The potency of these drugs in producing folate antagonism parallels their degree of binding to the enzyme. Methotrexate is the most powerful. Treatment of toxicity with folinic acid (citrovoram factor) has been at least partially effective (24, 194).

Anticonvulsants

Chronic treatment with anticonvulsants such as phenobarbitone, phenytoin, and primadone, singly or in combination, often result in folate deficiency (36, 186), megaloblastic anemia occurring in 0.15–0.75% of patients. Vogel (203) has proposed that drug-induced gingival hyperplasia may be mediated by folate deficiency. The mechanisms involved are unknown. There have been conflicting reports as to whether or not supplementing anticonvulsants with large doses of folate increases seizure frequency in epileptics. Folic acid supplementation has been reported to decrease serum and cerebrospinal fluid concentrations of phenytoin and phenobarbitone (126).

The anticonvulsant drugs disturb metabolism of vitamin D (6, 16, 87, 88, 191). Between 10 and 30% of epileptics on long-term therapy show biochemical or radiologic evidence of impaired vitamin D status; asymptomatic hypocalcemia or hypomagnesemia, increased alkaline phosphatase, as well as osteomalacia on bone biopsy or X-ray have been reported. Such evidences of osteomalacia may occur within several months after initiation of anticonvulsant therapy. Generally, the derangements are mild, clinically manifest bone disease being uncommon. The relationship between small biochemical or radiologic abnormalities and clinical disease is not defined.

Anticonvulsant drugs may induce liver enzymes that metabolize vitamin D or its active metabolites (125). Indirect data consistent with that mechanism are the reduction of serum 25-hydroxycholecalciferol (25-OHD) levels in treated epileptics compared to controls (138, 212), and findings of decreased plasma half-life of vitamin D_3 (125) and increased excretion of polar metabolites in treated epileptics. Multiple anticonvulsants seem to be additive in their effects on liver enzymes. Acetazolamide may accelerate bone changes (122) by inducing metabolic acidosis which favors calcium mobilization. Dietary intake and degree of exposure to sunlight are probably important modifying factors (118).

These radiologic and biochemical changes have been reported to respond to vitamin D (38, 154, 145). Stoffer et al (193) suggest that simply changing anticonvulsants may result in resolution of the abnormalities. Monitoring of epileptics for biochemical or radiologic evidence of early changes of bone disease remains a controversial issue (37, 180).

Klein et al (112) reported a case of cardiomegaly and congestive heart

failure responsive to thiamine in a young child receiving long-term anticonvulsants. It is possible that the primary disorder in this child related to thiamine metabolism.

Hemorrhagic disease attributed to drug-induced vitamin K deficiency has been reported in the offspring of mothers treated chronically with phenytoin (109). This has been attributed to increased vitamin K catabolism due to enzyme induction. Oral and intravenous supplementation prior to labor has been suggested. A discussion of drug effects on fetal nutrition and development is beyond the scope of this review; the reader is referred to Roe (163).

Antitubercular Drugs

Isoniazid therapy has long been recognized as inducing peripheral neuropathy due to pyridoxine deficiency, the reported prevalences being as high as 40%. The effect occurs within months after the initiation of therapy. Prophylaxis through co-administration of vitamin B_6 has been demonstrated (but see 31). Pyridoxine-responsive anemia during isoniazid therapy has also been reported. Cycloserine, another pyridoxine antagonist, has also been associated with anemias responsive to the vitamin. Neonatal convulsions responsive to pyridoxine have occurred following maternal isoniazid treatment (128). The mechanism for such pyridoxine deficiency has been variously attributed to increased urinary excretion of pyridoxine complexed with drug or competitive inhibition of pyridoxal phosphate. Direct neural toxicity by the drug-vitamin complex has been reported (80).

Pellagra is a rare complication of isoniazid therapy in well-nourished populations, but has been recorded in malnourished tuberculous patients (41, 42, 86, 91). Proposed mechanisms include impaired niacin synthesis secondary to pyridoxine deficiency and competitive inhibition by isoniazid of the coenzyme function of the vitamin. Malabsorption, particularly of vitamin B_{12}, with resultant megaloblastic anemia has been observed in users of p-aminosalicylic acid (97).

Oral Contraceptives

The effects of estrogen-containing oral contraceptives (ECOC) on folate metabolism seem of less clinical import than earlier indicated. The megaloblastic anemia recorded in association with their use (14) is usually attributed to preexisting depletion of folate stores or to other contributing factors.

Reduction in serum vitamin B_{12} levels has been described during ECOC use, possibly through redistribution among tissues. The clinical significance, if any, of this effect is unknown.

Pyridoxine lowering has been reported in 20% of women using ECOC (28, 111, 196). An association between such reduction and depressive symp-

toms has been suggested (see Roe), as has a relationship with glucose intolerance (1); but definitive evidence is not at hand.

It has been indicated that oral contraceptives may increase requirements of thiamine and riboflavin (142, 202), but clinical significance of the changes observed has not been established. Similarly, decreased plasma and tissue concentrations of ascorbic acid have been recorded in conjuntion with ECOC use without establishing clinical significance; no cases of clinical scurvy have been reported.

Anticoagulants

Coumarins act as vitamin K antagonists. The mechanism of action in the prophylaxis of thrombosis is not established but may involve accumulation of abnormal forms of vitamin K-dependent coagulation factors that are unable to bind calcium (192). A variety of other drugs may potentiate the actions of coumarin through decreased microbial synthesis of vitamin K, decreased absorption, decreased coumarin binding to albumin, inhibition of coumarin metabolism, and decreased synthesis or increased catabolism of vitamin K-dependent clotting factors (see 163).

Oral Hypoglycemic Agents

Metformin, a biguanide drug used for treatment of diabetes, may infrequently cause a selective, reversible deficiency of vitamin B_{12} (33). The mechanism may be a competitive inhibition of absorption or drug inactivation of the vitamin.

Laxatives and Antacids

It long has been established that chronic use of laxatives and antacids may impair absorption. For example, mineral oil impairs absorption of fat-soluble carotene and vitamins A, D, and K. Abuse of phenolphthalein and other laxatives has been associated with factitious diarrhea, protein-losing enteropathy, and malabsorption, including that of vitamin D and calcium (74). Loss of integrity of intestinal epithelial cells or increased peristaltic rate have been put forward as mechanisms for such effects of phenolphthalein (76). Prolonged use of magnesium and aluminum hydroxide antacids has resulted in phosphate depletion and osteomalacia through binding of phosphate in the intestinal lumen (50, 103).

Diuretics

Oral diuretics, including furosemide, ethacrynic acid, and triameterene, induce hypercalcuria; in contrast, the thiazides cause calcium retention. Magnesium deficiency has been associated with administration of thiazides, ethacrynic acid, and furosemide (66). Dyckner & Wester (64) demonstrated

that magnesium infusion reduced ventricular ectopy in cardiac patients receiving diuretics. Digitalis may augment diuretic-induced excretion of calcium or magnesium. Diuretics may deplete tissue and serum zinc through increased urinary excretion. Evidence concerning induction of tissue depletion of potassium by diuretics has been critically reviewed by Morgan et al (133), who conclude that most studies suffered from improper matching by age of controls and failure to take account of muscle wasting.

Anesthesia

Prolonged ventilation with nitrous oxide can produce megaloblastic changes in blood and has been associated with neurologic changes resembling the myelopathy and peripheral neuropathy of vitamin B_{12} deficiency (3). Recent animal studies (56, 127) and tissue culture experiments (116) indicate that nitrous oxide interferes with vitamin B_{12} metabolism, inhibiting methylcobalamin synthesis and thus reducing methionine synthetase activity.

Antibiotics

There are recent case reports of renal magnesium wasting and associated hypomagnesemia, hypocalcemia, and hypokalemia in patients treated for months with high doses of gentamycin (110, 149). The biochemical changes seem to occur after a latent period of weeks, and may lead to frank clinical symptoms.

Psychotropic Drugs

Pinto et al (157, 158) have documented an interaction between chlorpromazine and the metabolism of riboflavin, the structure of which resembles that of the drug. Chlorpromazine inhibits incorporation of riboflavin into flavin adenine dinucleotide (FAD) in rat liver, brain, and heart, in part through the inhibition of hepatic flavokinase. Chronic administration of clinically relevant doses increased riboflavin excretion, significantly lowered tissue FAD and flavin mononucleotide (FMN) concentrations, and altered the activity coefficient of the FAD-containing enzyme erythrocyte glutathione reductase. Psychoactive drugs structurally unrelated to riboflavin were ineffective. The tricyclic antidepressants, imipramine and amitriptyline, also alter riboflavin metabolism in rats, but only at very high doses.

Drug Effects on Food Intake

The potential effects of drugs on nutriture through alteration of the amount or character of food intake have received little attention except for those drugs designed as appetite depressants. Widely used drugs such as digitalis may reduce appetite, even at therapeutic levels (91, 160). Drugs may also

effect food selection; for example, a reported side effect of amitriptyline, a tricyclic antidepressant, is the induction of carbohydrate craving (150). Several drugs, including allopurinol, affect taste and smell (165). Much wider studies of these phenomena associated with commonly used drugs would be useful.

CONCLUSIONS AND RECOMMENDATIONS

The above discussion catalogs nutritional abnormalities accompanying a number of therapeutic regimens and documents that physicians may impair their patients' nutriture while treating their illnesses. The data suggest several generalizations and recommendations.

Many surgical therapies regularly result in important nutritional complications, the recognition and management of which are an essential part of good surgical care. Nutritional problems are particularly frequent consequences of surgery on the gastrointestinal tract.

Nutritional complications of small bowel bypass are potentially so severe that they limit the benefits of this procedure. Regular laboratory evaluation of the nutritional status of these patients is a necessary part of good care following bypass surgery. Weight loss, neuropathy, cardiac arrhythmias, loss of stamina, or changes in mental status are clinical findings that should alert the physician to potential nutritional problems. Minimum laboratory tests should include hematologic evaluation (complete blood count, smear, packed cell volume, etc), B_{12}, folate, and iron levels, albumin, calcium, phosphorus, alkaline phosphatase, transaminases, and sodium, potassium, chloride, and CO_2. Roentgenologic examination of the bone should be obtained. In patients who develop cardiac disease or neuropathy after bypass, it is prudent to obtain a measure of thiamine nutriture—either blood pyruvate or blood transketolase dependence on thiamine pyrophosphate (29). Other more specialized nutritional evaluations are necessary in patients with persistent problems, but will usually need the resources of a specialized nutrition center laboratory. Gastric bypass may be an attractive alternative to small bowel bypass (90, 124), with potentially less severe sequelae (2, 30, 85).

Gastrectomy, whether partial or complete, places patients at risk for a characteristic series of nutritional problems (32, 121). It is important to remember that vitamin B_{12} deficiency can first present as depression, dementia, or other changes in mental status. Postgastrectomy patients should be followed at least yearly, with careful history and examination, including accurate weight, hematologic evaluation, and studies of iron, B_{12}, and folate.

Loss of bone substance is a major complication of many types of therapy, since it can result from simple immobility (60), as well as more specific

mechanisms, notably after surgery on the gastrointestinal tract. Osteoporosis is a major problem of older populations, and its proper management is controversial (68). In particular, the proper role of dietary supplements of calcium and vitamin D is unsettled. Bone films at regular intervals appear indicated in patients after gastrectomy or gut bypass, and dietary supplementation with calcium is warranted (78, 176, 210).

Patients vary markedly in the metabolic effects of drugs, and recommendations for nutrition must be interpreted in light of age, sex, reproductive status, and genetic endownment. Altered nutritional needs directly due to genetic effects have only rarely been documented (21, 172). More extensive data demonstrate the genetic variations in drug metabolism, and consequently in the potential effects of medicines on nutrition. These effects are part of the field of pharmacogenetics (201). Finally, the underlying illness being treated can itself alter nutritional requirements and the effect of the treatment on nutrient status—e.g. a morbidly obese person who undergoes intestinal bypass is in a disadvantaged nutritional state initially.

The clinical significance of many of the demonstrable changes in nutritional levels listed above are obscure, particularly some of those that relate to drug (e.g. contraceptive) use and other medical therapies. Reported abnormalities are often limited to low blood levels of nutrients, the relationships of which to clinical syndromes may not have been established. Drugs prescribed for chronic medication are often for use by people who are chronically ill and therefore already at risk of nutritional deficiency. For instance, psychotropic drugs are appropriately given to people whose behavior, including their feeding behavior, is chronically or recurrently disordered. Schizophrenics may eat bizarre diets, and depressed people characteristically suffer anorexia. Even in a schizophrenic who appears relatively intact on phenothiazines, it is hard confidently to attribute a nutritional disorder to the effects of the phenothiazines. In general, physicians should determine and monitor the nutritional status (by dietary history and applicable biochemical and clinical observations) of chronically ill patients receiving multiple or chronic medications. Bone changes and calcium metabolism should be watched particularly closely. It is reasonable to give pyridoxine to patients on isoniazid, and to give folate to patients who develop laboratory or clinical evidence of complications of anticonvulsant therapy. Routine nutrient supplementation on the basis of drug therapy alone, however, is not generally justified.

Further research to assess the biochemically detectable changes in nutriture induced by drugs is to be encouraged, including especially the appraisal of the clinical significance of laboratory changes. In those instances where the clinical significances and predictibility are established, biochemical assessment of the nutriture at intervals during therapy is beneficial both in the management of the patient and in diagnosis of those signs and symptoms

that occur during therapy. Appropriately selected biochemical and physiologic measures of nutriture are useful initially in guiding therapy in patients known to be nutritionally at risk, such as alcoholics, schizophrenics, and individuals with malabsorption or other syndromes that are recognized as diseases that may condition nutritional deficiencies. Although not specifically discussed in this review, these measures likewise are of particular usefulness in identifying instances of hypervitaminoses, such as hypervitaminosis A, carotenemia, hypervitaminosis D, and the like.

In many of the situations discussed in this chapter, nutritional complications are a price for effective therapy. If the therapy is necessary, then the price seems justified. Therapeutic interventions that effect treatment of severe illnesses have inherent potential to cause side effects. The ability to alter physiology for the patient's benefit implies the ability to alter it to the patient's harm. Powerful new therapies enable physicians successfully to treat patients for whom previously nothing effective could be done. The side effects that accompany new regimens, however, complicate their use. Nutritional side effects that can be identified by proper assessment procedures and managed by oral or parenteral supplementation are among the more satisfying of these to manage.

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