METABOLISM IN IDIOPATHIC STEATORRHEA. I. THE INFLUENCE OF DIETARY AND OTHER FACTORS ON LIPID AND MINERAL BALANCE

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(Received for publication August 24, 1938)

When idiopathic steatorrhea of temperate climates and tropical sprue are compared, certain clinical and biochemical similarities are noted. Both are chronic diseases during which remissions not infrequently occur; both exhibit a peculiar, fatty and fermentative type of diarrhea with bulky, foul stools; anemia, sometimes resulting from a deficiency of iron, more often of the macrocytic type is common in each (1, 2, 3, 4, 5). The tongue is often sore and the papillae atrophic; when the diseases are well advanced oral ingestion of glucose causes only a slight elevation of blood sugar (3, 6, 7, 8). Reliable anatomical studies are few and diagnostic lesions have not been described in either disease (3, 8). Owing to defective absorption from the gastro-intestinal tract there is gradually progressing emaciation. Almost every sort of recognized deficiency has been described in connection with these syndromes (9). Insufficient production or absorption of the anti-anemia principal found in liver (10) seems to lead to the most characteristic deficiency of sprue (2), while hypovitaminosis D and its consequences are rather more frequent in idiopathic steatorrhea (1).

Review of the histories of patients with steatorrhea points in some cases to the origin of symptoms as celiac disease in childhood (1, 11, 8), in others the disease seems to have developed after maturity (9, 12). Apparently the relationship between celiac disease and idiopathic steatorrhea has not been questioned recently. Thaysen (8) regarded the latter as the non-tropical equivalent of sprue. English investigators, on the other hand (1, 3), have not accepted Thaysen's arguments as proof of the identity of steatorrhea and sprue. Hypotheses with respect to etiology differ somewhat (1, 2, 13), but as a general proposition it may be stated that breakdown in the absorptive mechanism of the gastro-intestinal tract produces the clinical syndrome in each condition. Whether this malabsorption is the result of hormonal or dietary deficiencies is unknown.

Failure to recognize a specific etiology has led to diverse forms of treatment, particularly in idiopathic steatorrhea. Those who believe that a disturbance in digestion and absorption of starches may be of primary importance give special attention to correcting that defect (14, 15); those who believe that all deficiencies stem from defective absorption of fats (4, 16) find low fat diets palliative; those who focus attention primarily on deficiencies, such as avitaminosis B or D or lack of some principle occurring in liver (2, 17, 18, 19, 20) assign their favorable results to adequate replacement therapy; still others (11, 13) are convinced that success is achieved only by the judicious combination of all methods of treatment.

In studying four patients whose clinical histories, physical status, and metabolic abnormalities characterized them as cases of idiopathic steatorrhea, evidence for or against the value of any particular therapeutic régime has been gathered while the subject was on a rigidly controlled diet. Although the individual's subjective impressions of his condition have had to be discounted in some instances, they have usually coincided with more objective data, such as the weight of the body, the weight of the stools, the amount of lipid in the stools, the degree of anemia, the vitamin A absorption and glucose tolerance curves, the concentration of protein, calcium, and inorganic phosphorus in the serum, and the calcium, phosphorus, and nitrogen balances. These data have also served to demonstrate the interrelation between several of the metabolic defects.

GENERAL PROCEDURE

The patients were admitted to the metabolism unit after a preliminary period of observation, during which the diagnosis was established. The diets employed were carefully weighed and fed to the subjects by a nurse, especially trained in this procedure. Once a given dietary régime was begun it was continued without variation of the menu until it was thought that the desired information had been obtained. In a few instances experimental periods were discontinued when the patient rebelled at the monotony of the routine.

Care was taken to collect the urine and feces quantitatively. The stools were weighed when passed and then pooled in periods of three, four, or six days before being analyzed. Carmine was used to mark the stools in metabolic periods of the desired length. Urine collected in twenty-four-hour periods was analyzed daily for nitrogen; aliquot portions were saved and analyzed for calcium and phosphorus.

Types of diet. Eight different diets were used during the course of the investigation. Their composition is shown in Table I.[1] It will be noted that the menus in several instances were closely similar. For example, Diet I differed from Diet II only in the substitution of banana and monosaccharide to replace other forms of carbohydrate; likewise Diets VI and VII differed chiefly in the omission of skimmed milk from VII, a change necessitated by a desire to obtain a much lower intake of calcium. Supplements of butter fat and soybean phospholipid were used at times to increase the amount of lipid in the low fat diets. Repeated analyses of sample diets were made for nitrogen, fatty acids, calcium, phosphorus, and magnesium. When supplementary feedings of lipid or other relatively simple foodstuffs constituted the sole departure from the basic formula, the

[1] Casec (calcium caseinate) used in the diets was contributed by Mead Johnson and Company.

TABLE I

Composition of diets

(grams per day)

Articles of food	Diet numbers							
	I	II	III	IV	V	VI	VII	VIII
Orange juice	50		1200	200	200	100	40	400
Grape juice							200	
Prunes	25							
Strawberries					100			
Apple	120			120		100	100	
Banana		750	800	100	200	650	550	600
Tomato	120					100	100	
Peas	75							
Spinach					80			
Cauliflower						70		
Onion								40
Potato				100	100	100	100	
Rice							20	
Shredded wheat	20			20		20	20	
Bread, white	62	12		122	60	120	120	
Sugar, cane	25		50	25	35	30	35	
Dextrose		15						30
Casec powder			64		16			32
Steak, tenderloin					200			100
Steak, round					150	200	300	
Liver, calves								100
Milk, skimmed			1000			700		400
Milk, whole	750	750		930	440			
Cheese, cream				40				
Cheese, American	36	36		36				
Egg	206	206		36		50		
Cream 40 per cent	80	80		80	30	170	100	
Butter	25	23		30	15	40	55	10
Mayonnaise containing egg and Wesson oil							25	
Calories (approximately)	2100	2200	2100	2300	1900	2900	2900	1500
Analyses for								
Calcium	1.35	1.33	2.38	1.46	1.04	1.092	0.235	1.090
Magnesium	0.22	0.40	0.60	0.256	0.37	0.521	0.442	0.415
Phosphorus	1.67	1.69	1.93	1.53	1.55	1.808	1.127	1.561
Nitrogen	11.46	10.74	15.59	9.85	18.50	15.74	14.12	14.16
Fatty acids	104	100	2.8	113.4	67	103.8	103.1	15.5

latter was corrected by making a separate analysis of the supplement.

METHODS

References to the methods employed in the chemical analysis of the blood and of solutions of ash of urine, feces, and food have been given elsewhere (21). The absorption of vitamin A was determined for us by Dr. A. B. McCoord of the Department of Pediatrics (22).

Preliminary preparation of sample diets and collection of feces differed from methods we have used previously and requires mention.

Feces. The stools for a metabolic period were collected in a large glass jar and if not frankly diarrheal were covered with water and weighed. They were converted next into a homogenous suspension by means of a mechanical stirring device and sampled while being stirred. All sampling was done by weight. The samples removed were for the determination of nitrogen, lipids, dry weight, and for ashing.

Diets. A series of sample diets was prepared and divided into two sets. Those analyzed for nitrogen and minerals were liquefied by adding concentrated sulphuric acid to about one-third of the original weight and heating to the boiling point in a large pyrex beaker. The liquefied material was cooled, weighed, and sampled while being stirred rapidly. Analyses for lipids were made on diets digested in glass vessels on the steam bath after addition of 50 to 100 grams of solid potassium hydroxide. Sampling was performed as in the case of the acid digests.

Determination of lipid. The wet extraction procedure described by Fowweather (23) was used with certain modifications suggested to us by Dr. R. G. Sinclair of the Department of Biochemistry.

Food. Diet samples were treated with solid potassium hydroxide to approximately 20 per cent of the weight of the sample. They were digested on a steam bath in a covered flask for forty-eight hours and extracted, after acidification, three or four times with ethyl ether (24). If an emulsion formed, this was broken down by centrifuging before attempting to draw off the ether layer. The ether extracts were concentrated in a separatory funnel by drawing air through it. When the ether had been removed, the residue was taken up in 40 per cent alcohol alkalized with 1 per cent potassium hydroxide and then reacidified with hydrochloric acid. The lipids were extracted with petroleum ether and transferred to a saponification flask, where after evaporation of the ether they were saponified for 30 minutes using boiling 95 per cent ethyl alcohol containing 10 per cent potassium hydroxide. This second saponification appeared necessary to ensure the complete hydrolysis of all the neutral fat. Water was added to bring the concentration of the alcohol to 40 per cent, and non-saponifiable matter was removed by extraction with petroleum ether. The soap solution was then acidified and extracted with petroleum ether. The amount of non-saponifiable matter and fatty acid was determined by evaporation of the respective fractions of petroleum ether and weighing the residues.

Feces. The technique devised by Fowweather (23) for removal of total lipid from an acidified suspension of feces was followed to the point of removal of the first ether extraction. The formation of stubborn emulsions at this juncture was obviated by centrifuging. After removing the lipids and blowing off the ether, the residue was alkalized and taken up in 40 per cent ethyl alcohol. The neutral fat and non-saponifiable matter were extracted with petroleum ether. The split fat remained behind as soap and the fatty acids were extracted from these with petroleum ether after acidification. Neutral fat and non-saponifiable matter were separated by an alcoholic saponification and subsequent extraction, as in the case of food. In using this procedure, certain precautions were found necessary. These will be reported elsewhere.

CASE REPORTS

Case S. B.

This case illustrates the gradual evolution of the syndrome of idiopathic steatorrhea during a period of observation lasting ten years.

A male furniture salesman, aged 36 years, born in Wisconsin but living the remainder of his life in the vicinity of Rochester, New York, entered the Rochester Municipal Hospital because of respiratory infections on August 3, 1927, and again on April 5, 1932. At the time of the second admission complaints of poor appetite, pyrosis, and gaseous distention of the abdomen were mentioned but were not investigated. He had had attacks of asthma between the ages of 24 and 34, coming on in August and September but none for two years. He described his bowels as regular; the stools as normal in consistency and formed. He had always been thin, weight varying between 54 kgm. (120 lbs.) and 59 kgm. (130 lbs.). Physical examination revealed a small, pale, undernourished, chronically ill man. Height 164 cm. Weight 50.6 kgm. Blood pressure 115/70. The subcutaneous fat was sparse, buttocks flattened, with marked folding of the skin along the natal cleft. Several of the teeth were carious. Hemoglobin 80 per cent; leukocytes 8,200; urine normal; stool formed; Wasserman and Kahn reactions were negative. An x-ray of the chest was normal except for a few calcified hilar lymph nodes.

In October 1933 the patient entered another hospital with an attack of diarrhea lasting ten days and in August 1934 returned to the Municipal Hospital with the same complaint. He appeared wasted and dehydrated. Weight 42 kgm. The tongue was clean and smooth; the abdomen was distended, tympanitic, and tender to pressure. Bacteriological examination of the feces and search for amebae revealed nothing of importance. There was definite macrocytic, hyperchromic anemia (significant laboratory examinations for this and subsequent admissions have been tabulated in Table II). Free hydrochloric acid (49 ml. N/10 acid per 100 ml.) was present in the fasting gastric contents. There was

TABLE II

Case S. B. Tabulation of laboratory data

Date	Red blood cells	Hemoglobin	Leukocytes	Mean corpuscular volume	Serum calcium	Serum inorganic phosphorus	Total serum protein	A : G ratio	Fasting blood sugar	Nonprotein nitrogen	Fecal lipid, dry feces	Blood pressure	Weight	
	millions	*grams per cent*		*cu. micra*	*mgm. per cent*	*mgm. per cent*	*grams per cent*		*mgm. per cent*	*mgm. per cent*	*per cent*	*mm. Hg*	*kgm.*	
Aug. 3, 1927		11.6	8,200									115/70	50.6	
Apr. 5, 1932	3.5	10.9	6,800									80/55	50.8	
Aug. 15, 1934	3.3	12.0	13,300	108	8.0	3.0	4.5	1.64				95/60	42.2	
Sept. 11, 1934	3.2	11.3	9,600						69				45.8	After 30 ml. liver extract (Lederle) i.m. 34 grams iron and ammonium citrate p.o.
Dec. 8, 1934	3.6	12.3	16,400		7.2	3.7			75			75/60	37.2	Loose stools
Jan. 23, 1935	2.9	10.4	10,000				4.9	1.33		21		90/60	43.6	Liver extract (Lilly) p.o. equal to 600 grams liver daily for 21 days
May 16, 1935	3.26	11.7	12,500	110	6.3	2.1	4.5	1.81		33		95/65	43	Active tetany. Diarrhea
June 8, 1935					5.8	2.5				25			37.2	Active tetany after parathormone. 20 units s.c. daily for 8 days
July 3, 1935					7.7	3.2					50		39.8	No more tetany. Received viosterol (Squibb) 250 D, 40 drops daily 12 days. Liver extract p.o. equal to 600 grams liver daily 21 days
July 29, 1935	2.9	10.0	6,500	108	8.70	3.4	5.7	2.0	73				42.8	No liver 15 days. Viosterol continued. Special diet 15 days
Aug. 21, 1935	3.0	10.0			8.7	4.7	5.5	1.9					51.8	Viosterol and special diet continued
Sept. 17, 1935	2.8	11.0		125	9.5	4.0	6.3	1.86				90/65	54.0	Liver extract (Lilly) 24 ml. i.m. and liver extract (Lederle) 72 ml. i. m. 21 days
Aug. 6, 1936	4.1	14			9.0	3.7	6.6				47		51.0	Special diet—viosterol. Ferrous sulphate 11 months
July 2, 1937					6.8	2.4	4.7						43.9	Viosterol stopped Aug. 6, 1936. Diet as desired—3 months. Loose stools—3 months

no icterus. Stools were soft and unformed; they were not examined for fat on this admission.

Because of the anemia 30 ml. of liver extract (Lederle) was given intramuscularly during seven days. The reticulocytes increased from 1 per cent to 5 per cent but the red cells and hemoglobin did not increase. Subsequent administration of 34 grams of iron and ammonium citrate did not affect the anemia. A biopsy of the sternal bone marrow showed hypoplastic erythroid elements.

The diarrhea subsided within 48 hours and the patient gained strength slowly. He was discharged after one month weighing 45.8 kgm. The etiology of the anemia and diarrhea was not determined.

Ten days later the patient returned complaining of painful gaseous distention of the abdomen. A barium enema showed the colon greatly distended and redundant; it required four to five times the usual quantity of barium suspension to fill it.

In November 1934 there was another sudden recurrence of diarrhea which led to hospitalization on December 8th.

Again there was flatulence, distention, and dull shifting abdominal pain accompanied by anorexia, nausea, and vomiting. The patient was profoundly emaciated; the weight was 37.6 kgm. Trousseau's sign was positive; Chvostek's negative. There was hypocalcemia and hypoproteinemia (Table II). Stools at first were fluid, brown-green, and had a very foul odor. The condition remained extremely grave for three weeks. Active diarrhea was controlled during the first few days by the administration of camphorated tincture of opium but the stools remained unformed, were grayish in color, and sometimes contained traces of occult blood. Fluids were given parenterally. On January 6, 1935, he had recovered sufficiently to be able to take a more liberal diet. Liver extract (Lilly) equivalent to 600 grams of whole liver was taken daily by mouth for 21 days. There was little improvement, and he was discharged to the County hospital for continued care. Weight 43 kgm. The nature of his disease was still unrecognized. He left the County Hospital after 10 weeks and reentered the Municipal Hospital during a severe relapse on May 16, 1935. Besides diarrhea there was now active tetany. An x-ray of the right knee joint showed marked atrophy of the bony structures. Fine opacities on the cortex of each lens were noted on examination of the eyes with the slit lamp. The weight declined from 43 to 37 kgm. during a period of 30 days. Intramuscular parathormone, intravenous calcium gluconate, calcium lactate by mouth and 45 drops daily of a solution of viosterol in oil (Squibb 250 D) were given with some relief of tetany. The stools decreased to 3 or 4 daily after a few days of rest in bed, but nausea and abdominal distention and discomfort persisted. Oral liver extract (Lilly) equivalent to 600 grams fresh liver daily was administered for 31 days. There was no improvement.

In July 1935 the diagnosis of idiopathic steatorrhea was made and the diet was altered radically. The patient was given a diet of 1,500 calories, low in fat, relatively high in protein, and with all starchy foods replaced by monosaccharides and banana. Viosterol was continued. Within ten days crampy abdominal pain and gaseous distention, almost constant features of the illness for 18 months had disappeared. The appetite returned, and the stools gradually became formed. The caloric intake was increased slowly by the addition of more ripe banana, orange juice, cream, and butter to the diet until ap-

proximately 4,000 calories were taken daily. When return of appetite, formed stools, increase in strength, and a gain in weight of 8 kgm. indicated that convalescence was well established, it was decided to test the effect of liver extract on the anemia, until now unchanged. Accordingly, during a period of 40 days the patient was given 24 ml. of concentrated liver extract (Lilly) intramuscularly followed by 72 ml. of intramuscular liver extract (Lederle). As on previous occasions the anemia was not affected.

Recovery continued and at discharge in September 1935 the weight had increased to 54.6 kgm.

The diet prescribed in the hospital was followed at home for eleven months. Ten grams of calcium lactate, 4 ml. of syrup of ferrous sulphate and 10 drops of viosterol (250 D) were taken daily. The red cells increased slowly to 4 million, and the hemoglobin to 14 grams per 100 ml.; serum calcium and inorganic phosphorus remained within normal limits; stools were partially formed but more than 40 per cent of the dry weight was lipid.

In August 1936 he stopped taking medication and began to experiment with his diet. Aside from the fact that he ate liver once or twice weekly his personal preference was permitted to dictate his choice of foods. He began to lose weight and strength on this régime and in March 1937 complained of stiffness of the hands. The stools were more frequent and were loose. The serum calcium decreased to 6.1 mgm. per cent, the inorganic phosphorus to 2.7 mgm. per cent but there was no frank tetany. He continued to become gradually worse until his admission to the metabolism unit July 1, 1937.

Data obtained on this admission have been referred to in the text of this report. He left the hospital against advice on July 25, 1937. Three days later the right knee became tender and swollen, followed in another day or two by a painful swelling of the right ankle. He was readmitted to the hospital on August 3, 1937.

Joint involvement was present as noted above; in addition, several moderate sized ecchymotic spots were found on the lower legs which, according to the patient's statement, were unrelated to trauma. The urine was found to be grossly bloody; the stools gave a positive guaiac test for blood; and blood withdrawn on venipuncture clotted only after 40 minutes. Clot retraction was poor and the clot was friable. Bleeding time was 11 minutes. Platelets were present in abundance in a smear of blood from the finger. Rumpel-Leede test for capillary fragility was negative. When as little as 0.05 ml. of normal serum was added to 2 ml. of the patient's blood a firm clot was obtained in 6 minutes. Without normal serum clotting occurred in 35 to 55 minutes. Fibrin could not be obtained from oxalated plasma by recalcification until a small amount of normal serum was added. Fibrin thus determined was 270 mgm. per 100 ml. plasma.

The picture seemed to fit Fanconi's description of purpura fulminans (hypothrombinemia) (25) more closely than that of scurvy.

He was given a diet low in fat, high in protein, and large amounts of orange juice. Ascorbic acid was given intravenously in doses of 0.2 gram daily on two successive days and on the third day 0.11 gram. Bleeding continued, although the clotting time had fallen to 18 minutes. Transfusions of compatible blood in amounts of 500 ml. were given on August 8th, 21st, and 27th. Following the third transfusion, bleeding from the urinary tract and from the bowel gradually diminished, but did not cease altogether until September 25. Subsequent to each transfusion there was a decrease in clotting time and in the loss of blood from urine and stool. Ultimate recovery, however, seemed to depend upon the gradual replacement of some factor essential to the normal clotting of blood which probably was obtained from the diet.

The condition of the patient since discharge on September 27, 1937 has remained unsatisfactory. Diarrhea has been infrequent as long as the low fat, low starch diet has been rigidly followed.

In February 1938 he contracted an upper respiratory infection and began to have diarrhea again. On February 24, 1938, he was readmitted because of a questionable hemorrhage in the left groin and hematuria.

August 29, 1935

Typical glucose tolerance after ingestion of 50 grams of glucose

Time, *minutes*	Fasting	30	60	90	120
Blood glucose, *mgm. per cent*	80	83	93	95	93

September 17, 1935

Vitamin A absorption after ingestion of 10 ml. of haliver oil[2]

Time, *hours*	Fasting	2	4	6	9	12	24
Vitamin A, *units per 100 ml. plasma*	13	15	21	53	44	64	30

August 30, 1935

Plasma lipids

Total lipid 559 mgm. per 100 ml.
Neutral fat 159 mgm. per 100 ml.
Total fatty acid 333 mgm. per 100 ml.
Total cholesterol 159 mgm. per 100 ml.
Ester cholesterol 97 mgm. per 100 ml.
Phospholipid 176 mgm. per 100 ml.

Case J. B.

A woman 48 years old entered the Medical Clinic on December 2, 1932, complaining of (*1*) pain in the back and legs made worse by walking, straining, coughing, or sneezing, (*2*) a sore tongue, (*3*) urgency and frequency of urination, (*4*) swelling of the legs,

[2] The dose of haliver oil which was used in the vitamin A absorption test was estimated on the basis of body weight and vitamin A potency of the particular sample of oil available at the time. Each subject received approximately 7,000 I.U. of vitamin A per kilogram of body weight.

(*5*) recurrent episodes of diarrhea in which the stools were white and frothy, (*6*) loss of weight of 20 pounds. She was born in South Dakota and had never lived in the tropics or in the Southern United States.

Past history revealed many years of chronic invalidism. At the age of 3 a febrile illness was followed by abdominal distention. During the subsequent 8 to 9 years abdominal paracentesis for removal of fluid was performed on a number of occasions. Tuberculous peritonitis was suspected at the time. During adolescence health was fair but at 20 years bouts of diarrhea began with large, pasty, and sometimes foamy stools. The general course has been one of exacerbation and remission since. In 1926 she was admitted to another hospital where a macrocytic type of anemia was discovered.

Physical examination. Weight 50 kgm., height 161 cm., blood pressure 90/50. A small rather poorly developed thin woman with marked dorsal kyphos. Skin was dry, inelastic, and scaly over the lower trunk, with diffuse brownish pigmentation of the face and about the neck. The muscles were flabby and of poor tone. The spine was moderately tender to percussion and the ribs to pressure. The eyes, ears, and nose were not remarkable. The jaws were edentulous, and the tongue was smooth and red. The heart and lungs were normal. The abdomen showed marked gaseous distention but no fluid. The liver was palpable at the costal margin. Positive neurological findings were: hyperesthesia below the level of the fifth dorsal vertebra, vibratory and position sense intact.

Urine was infected with colon bacilli but no tubercle bacilli were found in it either by direct examination or after injection into a guinea pig.

Stool was soft and unformed, 57 per cent of the dry weight was lipid.

Blood. Red cells 3.4 million; hemoglobin 11 grams per 100 ml.; leukocytes 5,500. A smear revealed many macrocytes.

Gastric analysis revealed free hydrochloric acid equivalent to 30 ml. N/10 acid per 100 ml. gastric juice after injection of histamine.

Glucose tolerance after ingestion of 50 grams of glucose

Time, *minutes*	Fasting	30	60	90	120
Glucose in blood, *mgm. per cent*	76	92	87	83	78

Roentgenograms. (*1*) Chest, slight prominence of left ventricle and aortic knuckle but otherwise normal; (*2*) barium enema, moderately dilated colon; (*3*) anteroposterior abdominal film, marked diffuse decalcification of the lumbar vertebral bodies and the pelvic bones; (*4*) gastro-intestinal series: Spastic pyloric sphincter, greatly increased peristaltic activity of the duodenum with delayed emptying, suggesting obstruction.

In view of the apparent duodenal obstruction and persistent complaint of burning sensations in the center of the abdomen an exploratory laparotomy was performed. The duodenum was markedly dilated. The mesentery of the small bowel was unusually fatty and no blood vessels could be seen through it. The paraduodenal fossa was quite deep and the operator considered the possibility that prolapse of the bowel into it might have caused obstruction. No lesion, adhesion, or congenital band that could have caused obstruction was found. A mesenteric lymph node was removed for microscopic examination. The pathologist reported a mild chronic non-tuberculous lymphadenitis.

Recovery from the operation was uneventful, and the patient was discharged on March 2, 1933, somewhat improved.

She was readmitted on January 3, 1936, because of a recent fracture of the right greater trochanter, and fractured ribs following a slight fall. Other x-rays taken on this admission disclosed old infractions of the right femoral shaft and pubic bone probably the result of decalcification with pathological fractures. The dorsal spine was affected by diffuse atrophy and collapse of many of the vertebral bodies producing a profound kyphos. The picture was one of advanced osteomalacia.

The serum calcium was 8.0 mgm. per cent; inorganic phosphorus 2.3 mgm. per cent and total protein 5.8 grams per cent. Glucose tolerance was the same as previously reported.

Vitamin A absorption after 5 ml. of haliver oil

Time, *hours*	Fasting	2	4	6	9	12	24
Vitamin A, *units per 100 ml. plasma*	9	11	15	31	25	32	19

Free hydrochloric acid which had been present in the gastric contents on the 1932 admission was now absent after injection of 0.5 mgm. of histamine. The red blood cells numbered 3.8 million, and the hemoglobin 11.4 grams per 100 ml. The administration of 46 ml. of liver extract concentrated (Lilly) by intramuscular injection during an interval of two weeks has been referred to elsewhere. It seemed to be accompanied by subjective improvement, but in the absence of a reticulocyte response, relief of anemia, change in the chemical analysis of the feces or gain in weight, we were unable to evaluate its effect. The subsequent course of the patient has been unsatisfactory. She has remained a chronic invalid and has cooperated poorly, returning only at rare intervals for advice with respect to diet and medication.

Case R. G.

A clergyman, aged 43 years, had had periodic attacks of diarrhea for 20 years. Except for a few months spent in the Southwestern United States he had always lived in the Northern States or in Canada. Six months prior to admission he became incapacitated because of loose, voluminous stools, loss of weight and strength, anorexia, nausea, flatulence, and burning sensations in the epigastrium. He described a recent attack of tetany.

Physical examination. Weight 53 kgm., height 168 cm., blood pressure 98/80.

Appearance was that of moderate undernourishment. Tongue was clean, red with atrophic marginal papillae.

Abdomen was moderately distended with gas. Examination of the heart, lungs, abdominal organs, genitalia and rectum were normal. Neurological examination revealed no signs of tetany. Tendon reflexes were sluggish and elicited in the lower extremities only after reinforcement. There was no less of vibration or position sense.

Urine was normal. Stools were very large, one passed shortly after admission weighed 900 grams, was of pale grey color, soft in consistency, unformed, with a foul and sour odor. Fifty-eight per cent of the dry weight was lipid. The guaiac test for blood was negative.

Blood count. December 31, 1936. Red cells 3.7 million, hemoglobin 12.1 grams per 100 ml., leukocytes 5,400, mean corpuscular volume (Wintrobe) 100 cu. mi.

Blood chemistry. Serum calcium 6.7 mgm. per cent; inorganic phosphorus 1.36 mgm. per cent; total protein 5.7 grams per cent; nonprotein nitrogen, 32 mgm. per cent.

Gastric analysis. No free HCl in fasting specimen. After 50 ml. of 7 per cent alcohol, free HCl was present equivalent to 23 ml. N/10 acid per 100 ml. of gastric content.

Glucose tolerance after ingestion of 60 grams of glucose

Time, *minutes*	Fasting	30	60	90	120	180
Glucose in blood, *mgm. per cent*	77	82	101	99	101	90

Vitamin A absorption after ingestion of 10 ml. of haliver oil

Time, *hours*	Fasting	2	4	6	9	12	24
Vitamin A, *units per 100 ml. plasma*	4.4	7.4	5.9	14.4	8.4	15.9	9.4

X-ray of the dorsal spine showed marked osteoporosis.

Response to therapy. Administration of intramuscular liver extract (Lilly) in connection with a high fat diet as described in the following paper (27) failed to cause improvement in the steatorrhea; there was no reticulocyte response and after a month of treatment the red blood cell count was still 3.7 million and the hemoglobin 12.4 grams per 100 ml. With ingestion of a low fat diet, containing carbohydrate mostly in the form of monosaccharide, the stools became normal in appearance and nearly normal in their content of lipid. There was some gain in weight (about 2 kgm.) on this régime but no change of note in the blood. A vitamin D concentrate was now given without change in the diet. The weight remained the same but strength improved as did the anemia and the calcium and inorganic phosphorus content of the serum. At time of discharge on June 24, 1937 the red blood cell count was 4.68 million, and hemoglobin 14 grams per 100 ml.

Glucose tolerance after ingestion of 60 grams of glucose

Time, *minutes*	Fasting	30	60	90	120	180
Glucose in blood, *mgm. per cent*	81	116	108	99	86	69

Vitamin A absorption after ingestion of 10 ml. of haliver oil

Time, *hours*	Fasting	2	4	6	9	21
Vitamin A, *units per 100 ml. plasma*	10.5	13	27	27	38	21

Since leaving the hospital the patient has taken a diet containing about 80 grams of fat, relatively high in protein, and has practically excluded starchy foods from the menu. He has gained 10 kgm. in weight and has had no recurrence of the symptoms of steatorrhea.

Case P. A.

This patient entered the clinic on February 8, 1935 at the age of 14 years. His complaints at that time were weakness, poor appetite, and failure to grow normally during a period of five years.

Physical examination. Weight 31.4 kgm., height 136 cm., blood pressure 94/58.

The principal findings were poor development, pallor, carious teeth, and a large protuberant abdomen.

Urine was normal. *Stools* were soft, unformed, and of foul odor; 57 per cent of the dry weight was lipid. A guaiac test for blood was negative.

Blood count. Red cells 4.5 million, hemoglobin 10.5 grams per 100 ml., leukocytes 8,600. A smear showed rather small red cells poorly filled with hemoglobin.

Blood chemistry. Serum calcium 9.2 mgm. per cent; inorganic phosphorus 5.1 mgm. per cent; total protein 6.2 grams per cent; nonprotein nitrogen 29 mgm. per cent; plasma fatty acids 215 mgm. per 100 ml.; phospholipid 50 mgm. per 100 ml.; cholesterol 103 mgm. per 100 ml.

Glucose tolerance after ingestion of 44 grams of glucose

Time, *minutes*	Fasting	30	60	120	180
Glucose in blood *mgm. per cent*	74	77	74	78	85

Vitamin A absorption after ingestion 3 ml. of haliver oil

Time, *hours*	Fasting	2	4	6	9	12	24
Vitamin A, *units per 100 ml. plasma*	12	10	10	19	20	20	16

Intracutaneous tuberculin test negative.

Course. After a year on a diet low in fat, high in protein and containing carbohydrate largely in the form of fruit juices and banana, the weight had increased to 45.8 kgm. and the height to 151 cm. Many of the stools were quite normal in appearance, others were soft and grey. The fecal lipid had decreased to about 35 per cent of the dry weight of the stool.

November 3, 1936 he was admitted to the metabolism unit for study as described in the text. Some of the laboratory data not listed elsewhere follow.

Blood count. November 3, 1936, red cells 5.1 million, hemoglobin 12.7 grams per 100 ml., red cell hematocrit 38.5 per cent, mean corpuscular volume 75.3 cu. mi.; mean corpuscular hemoglobin 25 mi.mi.

Glucose tolerance after ingestion of 46 grams of glucose

Time, *minutes*	Fasting	30	60	120	180
Glucose in blood, *mgm. per cent*	97	105	102	96	95

Vitamin A absorption after ingestion of 10 cc. of haliver oil

Time, *hours*	Fasting	2	4	6	12	24
Vitamin A, *units per 100 ml. plasma*	11	12	42	42	13	11

The blood serum was also analyzed for calcium and inorganic phosphorus on a number of occasions, both before and after administration of liver extract and the vitamin D concentrate. Representative values were calcium 10 mgm. per cent; inorganic phosphorus 4.8 mgm. per cent. Neither form of medication appeared to influence these values, nor was the blood count changed from that of November 3, 1936.

The patient has continued the dietary régime instituted prior to the metabolic study and when last seen on October 14, 1937 he weighed 52 kgm. and his height had increased to 162 cm.

Effect of constant diet on fecal lipids. The ingestion of a constant diet by subjects with either severe or mild steatorrhea led after an interval of several days to a fairly constant average elimination of lipid in the feces. Since the severity of the steatorrhea was apparently a measure of the disturbed absorption of fat, the effect on fat absorption of different procedures could readily be tested after the average loss of fat on a given dietary régime had been established. The fecal lipids of the juvenile patient were but little above the normal level when the intake of fat was high (Table III). In the two more severe cases the fecal loss was in excess of 50 per cent of the intake. A considerable variability in the amount of lipid excreted was noted in short metabolic periods and seems to have resulted from unavoidable errors in the demarcation of feces, which were usually soft and sometimes diarrheal in character.

In general the amount of fecal fat rose and fell paralleling the dietary fat. Appreciable changes in quantity of fecal fat could, however, be brought about by alterations in diet and medication which did not involve an increase or decrease in dietary fats. These will be discussed in their proper sequence.

Little tendency toward spontaneous exacerbations or remissions was noted during intervals of a month or more. In one case steatorrhea was increased during an acute respiratory infection.

Dietary carbohydrate and steatorrhea. While one gains the impression from the literature that intolerance of starch may be as much a fault in steatorrhea as intolerance of fat, the effect of starch on fat tolerance does not appear to have been studied quantitatively. An effort in this direction was made in Case J. B. who was given a diet containing both fat and starch for 15 days

TABLE III

Lipid excretion in severe and mild steatorrhea

(Daily average in grams)

Diet		Period number	Number of days	Fecal weight	Total lipid	Fatty acids
Number	Fatty acids					
CASE R. G.						
VI.....	104	2–4	10	380	48.8	46.5
	104	5–9	15	459	56.0	53.7
	104	10–12	9	469	54.9	52.3
CASE P. A.						
VI.....	104	1–3	12	185	13.6	
	104	4–7	21	168	14.1	12.5
	104	8–10	18	175	13.8	12.4
CASE S. B.						
VIII	23	2	4	210	21.2	17.3
+50 per cent	86*	3	2	340	45.7	41.7
	23	4	4	173	21.0	18.3
	23	5	4	142	23.1	20.1
	23	6	3	152	17.9	14.8

* Includes butter fat supplement.

(Diet I, Table IV). During the succeeding 18 days most of the carbohydrate of the diet was replaced by ripe banana (Diet II). There was a slight, but probably not significant, decrease in the fatty acid content of the feces; nitrogen, calcium, and phosphorus balances were not materially affected.

Some improvement might have been expected if the carbohydrate of the banana was more suited to the needs of the patient than starches (14, 15, 26). For example, less destruction of carbohydrate by intestinal fermentation might have led to better absorption and so to a higher caloric intake. A higher caloric intake from carbohydrate because of its protein sparing action might then have been reflected in increased nitrogen retention. A slightly negative nitrogen balance during the banana periods, however, did not point to a protein sparing action of this diet.

The weight increased approximately 0.7 kgm. but the well known hydrolability (25) in this disease is such that no significance can be attached to small changes in weight.

Since no correlation between steatorrhea and the quality of the carbohydrate was noticed in

TABLE IV

Summary of metabolism studies, Case J. B.

Period	Number of days	Diet per day							Daily medication	Daily feces						Daily balances			Body weight
		Number	Protein	CHO	Fatty acids	Ca	P	Calories (approx.)		Weight		Ca	P	N	Fatty acids	Ca	P	N	
										Moist	Dry								
			grams	*grams*	*grams*	*grams*	*grams*			*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*kgm.*
1–5	15	I	72	171	104	1.35	1.67	2100	None	123.8	34.3	1.26	0.45	1.27	17.5	+0.016	+0.15	+0.51	45.05 46.53
7–11	15	II	67	226	100	1.33	1.69	2200	None	197.2	40.1	1.33	0.73	1.59	15.0	−0.08	+0.06	−0.14	47.25
12–13	6	I	72	171	104	1.35	1.67	2100	None	158.2	32	1.23	0.57	1.32	14.8	+0.04	+0.04	+0.18	46.83
16–19	12	III	97	407	2.8	2.38	1.93	2100	None	116.2	26.4	2.47	1.36	1.48	1.1	−0.20	−0.02	−0.70	46.80
20	3	IV	62	233	113.4	1.46	1.53	2300	None	123.4	29.3	2.20	1.26	1.28	8.8	−0.80	−0.40	−0.71	47.10
21	3	IV	62	233	113.4	1.46	1.53	2300	None	86.6	22.2	1.09	0.60	0.68	11.2	+0.33	+0.26	+1.06	46.90
22	3	IV	62	233	113.4	1.46	2.81*	2300	Na glycerophosphate 12 grams	265	48.7	2.32	1.67	1.49	24.5	−0.90	−0.15	+0.68	47.47
23	3	IV	62	233	113.4	2.32†	1.53	2300	HCl 233 ml. N/10. $CaCl_2$ 2.39 grams	256	42.6	2.13	1.11	1.43	21.9	+0.14	−0.51	+0.53	47.30
26–29	12	IV	62	233	113.4	3.40†	2.49*	2300	Na glycerophosphate 9 grams. $CaCl_2$ 5.38 grams‡	241	51.8	3.46	1.71	1.31	29.5	−0.12	−0.004	+0.22	47.37
30	3	III	97	407	2.8	2.38	1.93	2100	None	213.7	41.4	2.91	1.57	1.76	9.5	−0.59	−0.04	+1.68	47.66
31	3	III	97	407	2.8	2.38	1.93	2100	None	172	29	2.12	1.25	1.63	1.2	+0.19	+0.05	−0.23	47.60
32	3	III	97	407	2.8	2.38	1.93	2100	Beef bile 3.3 grams	282	33.8	2.39	1.35	1.80	1.3	−0.11	−0.12	−0.95	47.86
33	3	IV	62	233	113.4	1.46	1.53	2300	Beef bile 1.5 grams	498.8	56.7	2.45	1.30	2.74	22.9	−1.05	−0.55	−2.83	47.00
34	3	IV	62	233	113.4	1.46	1.53	2300	Beef bile 1.25 grams	433.9	37	1.27	0.68	1.66	14.4	+0.12	+0.06	−0.72	47.24
Observation discontinued for 5 days																			
35	3	V	115	183	67	1.04	1.55	1900	Liver extract 5 ml.	167.3	32.6	1.37	0.58	1.85	11.3	−0.44	−0.12	+0.74	47.73
36	3	V	115	183	67	1.04	1.55	1900	Liver extract 5 ml.	85	21.2	0.86	0.38	1.11	6.4	+0.08	+0.01	+0.91	48.69

* Includes phosphate given as medication.
† Includes calcium chloride given as medication.
‡ 10,000 Vitamin D units daily intramuscularly.

J. B., no further specific attempt was made to change the carbohydrate fraction of the diets without altering either the amount or source of fat, and consequently less attention was given to this phase of metabolism than it apparently deserved. Later, while studying Case R. G., it became evident that some factor in addition to malabsorption of fat took part in the production of his steatorrhea. While observing his response to a low intake of fat and to vitamin D (Table V), it was found that supplements of butter fat were well tolerated. The diet to which these supplements were added (Diet VIII) contained very little starch, while the control diet (Diet VI) contained bread, rice, and potatoes as well as large amounts of cream. Butter supplements eventually raising the intake of fatty acids of Diet VIII to 91 grams daily were given in Periods 38 to 41 (Table V) without increasing the steatorrhea. As the intake of fat now approached that of the control diet, the latter was substituted for Diet VIII (Period 42). The patient promptly developed abdominal distention and bulky gaseous fatty stools. Whether this response was caused entirely by the combination of fat and starch in the diet or whether it was in part a result of the psychic upset caused by his repugnance for the particular menu in question, or to some other factor could not be established with certainty. After three days he refused further cooperation until the low fat diet was resumed. Since leaving the hospital there have been several occasions on which he has attempted to include bread, cereals, and potatoes in the diet, always with the result that he became worse. This is perhaps further evidence incriminating starchy foods in his case.

Effect of low fat diets. Two very low fat diets containing most of the carbohydrate in the form of fruit juices and banana were given. Case J. B. received Diet III containing no meat, while Cases R. G. and S. B. were given Diet VIII containing lean meat and liver. The former diet was lower in fat, furnishing by actual analysis less than 3 grams of fatty acid daily. The energy value of Diet VIII as originally planned was too low, and after a preliminary trial it was increased by 50 per cent bringing the intake of fatty acids up to approximately 23 grams daily and calories to 2200.

Diet III was well tolerated by J. B., and there

was almost immediate improvement in the stools, which changed from soft, pale, greasy, and unformed to normal color and consistency (Table IV, Periods 16 to 19). Complaints of bloating and anorexia were no longer mentioned. Nitrogen balances were slightly positive during this time. There was a slight loss of calcium and phosphorus from the body in spite of a higher intake of these elements. The concentration of serum calcium increased and the inorganic phosphorus decreased. The changes in the blood have been discussed in more detail in another paper (*27*).

Fecal analysis showed a marked decrease in

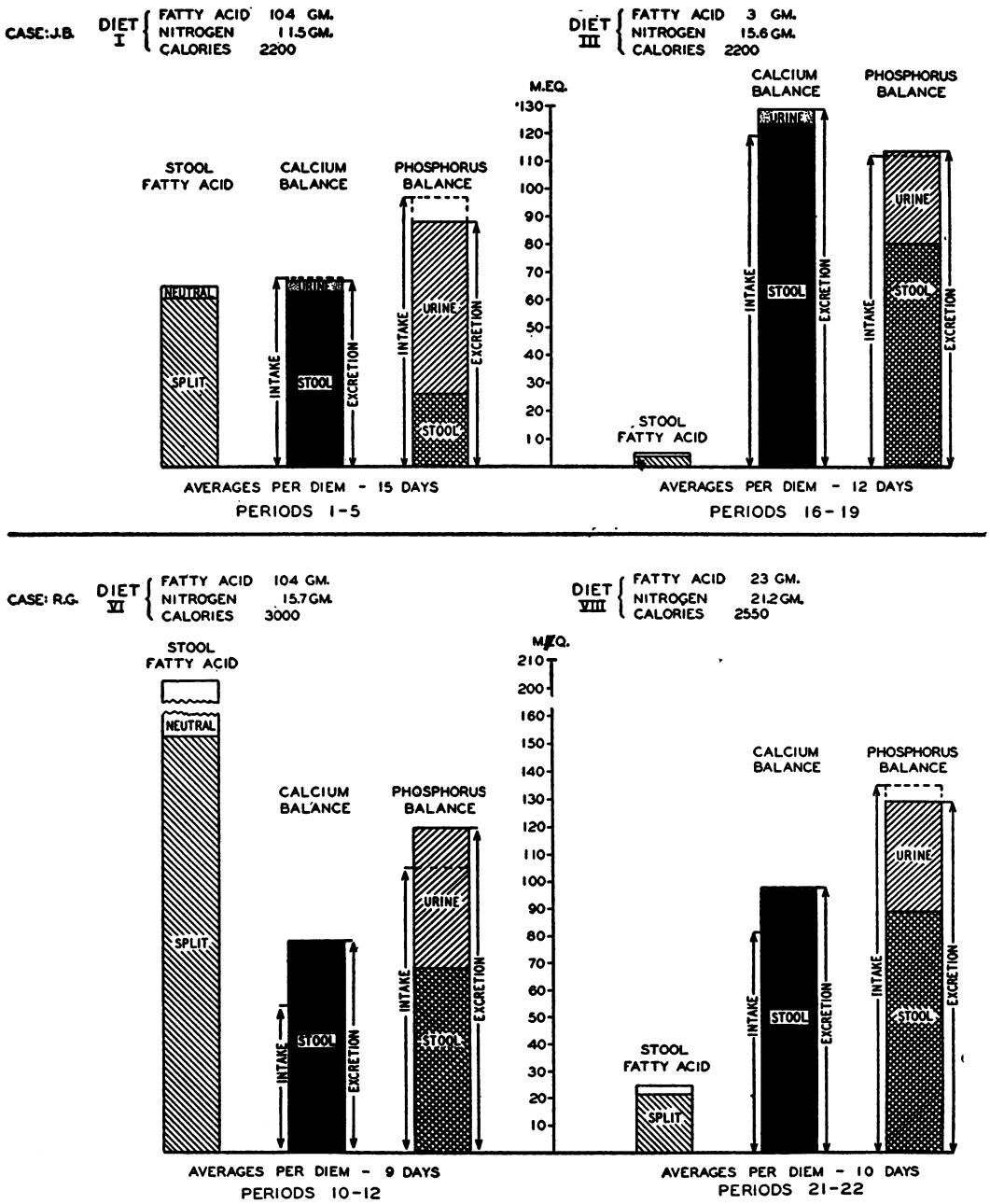

FIG. 1. CALCIUM-PHOSPHORUS BALANCES OF CASES J. B. AND R. G. ON HIGH AND LOW FAT DIET

the amount of lipid and the moist and dry weights also decreased. This form of diet abolished the steatorrhea and with it many of the more unpleasant symptoms. The comparatively short time allotted to this study did not permit deduction with regard to ultimate effects. One may safely conclude, on the basis of calcium and phosphorus balances, that steatorrhea was not the only factor leading to loss of these elements from the body (Figure 1).

The effect of the second type of low fat diet on R. G. was equally satisfactory. Within 48 hours the stools became formed; abdominal discomfort largely disappeared, and the fecal lipids decreased from about 49 to 12 grams a day (Table V). As previously stated, R. G. was quite tolerant of supplementary fats added to this diet after he had received vitamin D. Case S. B., on the other hand, exhibited less initial tolerance for Diet VIII and reacted unfavorably when butter supplements were added to it (Table VI). While ingesting 23 grams of fatty acids he excreted 17 grams and after increasing the intake to 86 grams by addition of butter he excreted 42 grams. Obviously, a greater amount of fat was retained at the higher level of intake, but the patient was subjectively worse; the stools increased in weight and became soft. In summary, it may be stated that low intakes of fatty acid caused a prompt decrease in the fecal lipid and subjective improvement in three patients, but did not prevent loss of calcium from the body. When fat was practically excluded from the diet (Case J. B.) fecal lipid was still less than the amount ingested. The evidence

TABLE V

Case R. G.

Period	Number of days	Diet per day				Daily medication	Fecal weight daily		Fecal lipid daily		
		Number	Fatty acids	Calories (approx.)	Supplements		Moist	Dry	Total	Split fatty acids	Neutral fat
			grams				*grams*	*grams*	*grams*	*grams*	*grams*
2–4	10	VI	104	2900	None	None	380	83	48.8	35.3	11.2
20	3	VIII*	23.2	2200	None	None	169	46	11.7	8.7	1.1
37	6	VIII*	23.2	2200	None	Vitamin D 225,000 I.U.	80.5	20.6	5.8	3.9	0.5
38	4	VIII*	68.2†	2700	Butter 50 grams	Vitamin D 225,000 I.U.	138	37	13.5	10.1	1.2
39	4	VIII*	68.2†	2700	Butter 50 grams	Vitamin D 225,000 I.U.	97	25	8.2	5.6	0.9
40	4	VIII*	68.2†	2700	Butter 50 grams	Vitamin D 225,000 I.U.	123.5	25	9.6	6.7	0.8
41	4	VIII*	90.7	2900	Butter 75 grams	Vitamin D 225,000 I.U.	88	17.4	8.0	5.8	0.6
42	3	VI	104	2900	None	Vitamin D 225,000 I.U.	391	65.2	26.8	21.8	2.4

* Diet VIII increased by 50 per cent.
† Includes fatty acids of the butter supplement.

TABLE VI

Effect of increased intake of fat on calcium and phosphorus balance in Case S. B.

Period	Number of days	Diet per day			Daily feces							Daily balances	
		Number	Fatty acids	Supplement	Moist	Dry	Total fatty acids	Split fatty acids	Mg	Ca	P	Ca	P
			grams		*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*
2	4	VIII*	23.2	None	210	58.3	17.3	12.7	0.423	2.26	1.70	−0.64	+0.13
3	2	VIII*	86.2†	Butter 70 grams	340	91.1	41.6	33.8	0.514	2.56	1.51	−0.93	+0.20

* Diet increased 50 per cent.
† Includes fatty acids of butter supplement.

is, therefore, against excretion of lipid into the bowel as an important factor in the mechanism of production of idiopathic steatorrhea.

Effect of oral administration of sodium glycerophosphate. Verzár and Laszt (28) have suggested that formation of glycerophosphate in the intestine may be necessary for phosphorylation and absorption of fatty acids. Macrae and Morris (29), on the other hand, thought that the increased acidity of the small intestine after administration of sodium acid phosphate was responsible for better absorption of fats and minerals. A careful study of Verzár's experimental results shows that the effects he obtained may well have been caused by changes in the reaction within the intestinal loop. At pH's of 7 or greater there was little absorption of fatty acid, while at a lower pH the absorption improved. In this respect at least they confirm the results obtained by Macrae and Morris.

The administration of sodium glycerophosphate failed to improve Case J. B.'s steatorrhea, on the contrary it was made worse (Period 22, Table IV). The diet in this instance did not conform to the original control, since the patient refused it. A similar diet (IV) was substituted in its place. In periods (20 and 21) serving as controls, the fecal lipids were surprisingly low, even though the intake of fatty acids was slightly higher than before. This moderate decrease of fecal fatty acids may have been owing to failure to develop immediately the characteristic rapid passage of intestinal contents or to somewhat better absorption of the mixture of fatty acids included in this diet.

Administration of 12 grams of sodium glycerophosphate daily for the next three days (Period 22) was followed by a sharp fall in the serum calcium, active tetany, soft stools, a great increase in fecal lipid, and markedly negative calcium and phosphorus balances. Glycerophosphate was stopped until the tetany could be brought under control. This required about four days. A single intravenous injection of 1 gram of calcium gluconate relieved the more acute symptoms. One liter of N/10 hydrochloric acid was given by mouth over a period of 3 days with the intention of counteracting the effect of the extra base given with the alkaline phosphate. Calcium chloride solution by mouth was started on the last day of Period 23. In Period 24 the signs of tetany had disappeared and glycerophosphate was again given in amounts of 9 grams daily, together with calcium chloride as indicated in Table IV. The extra calcium was sufficient to have combined with all the extra phosphorus as tricalcium phosphate. The phosphate solution was given with meals, the calcium chloride about two hours after each meal. On this régime the serum calcium remained about one milligram per cent higher than the level at which the patient had tetany. The feces continued to be soft and unformed. Fecal weight increased as did the quantity of fecal lipid. The latter reached its maximum value in these periods. Even at the much higher levels of calcium and phosphorus intake, consistently positive balances of these elements were not obtained.

Ox bile. The conflicting opinions on the value of bile salts in steatorrhea have been discussed by Macrae and Morris (29). A purified preparation of dried ox bile [8] was given to Case J. B. in an attempt to determine whether it would have any effect on intestinal absorption. The administration was begun in Period 32 (Table IV) while the low fat diet was being ingested. Four grams were given on the first and second days of the period. Abdominal distress was noted after the first few doses and the stools became liquid. The dose of bile for the third and last day of this period was reduced to 2 grams. Complaints of nausea and of "burning like a fever in the stomach" persisted. In Period 33, the dose of bile was further reduced to 1.5 grams a day and the diet was changed to one high in fat (Diet IV). During this and the subsequent period on the same régime, the patient was quite ill and complained bitterly of the diet and of the medication. The stools continued to be loose and the fecal fatty acids were well above the previous control periods on Diet IV. Average nitrogen, calcium, and phosphorus balances were negative (Table IV). There was no loss of weight.

All metabolic observations were omitted for the five days immediately following Period 34, and the patient was allowed to make her own selection of foods. Diet V was evolved as a result. It

[8] Purified ox bile was contributed by Burroughs Wellcome and Company.

was higher in protein and contained considerably less fat than the control diets. Much of the protein was derived from meat. Unfortunately, no control observations were made on this diet. Its effect has been taken up in connection with the discussion of the use of liver extract (27).

An apparent interrelation between the amount of fecal alkaline earth and fatty acid. Certain procedures causing an increase in Case J. B.'s fecal calcium were associated with an increase in the amount of split fatty acids eliminated in the feces (see Table IV). The calcium content of the feces was considerably increased by (*1*) administration of a solution of sodium glycerophosphate in Period 22, (*2*) administration of hydrochloric acid and calcium chloride in Period 23 and (*3*) administration of both calcium chloride and sodium glycerophosphate in Periods 24 to 29.

Undesirable side effects consisting of tetany and loose stools were encountered in Periods 22 and 23. Loose stools continued to occur in Periods 24 to 29 but there was no tetany. There was a marked increase in the amount of fatty acid eliminated in the stools of all these periods. The exclusion of tetany as a cause of the increase in steatorrhea seems justifiable on the ground that the syndrome occurred only in Periods 22 and 23. Although the laxative effect of the salts continued, this never amounted to a true diarrhea, such as occurred in the bile periods 32 to 34. Frequent watery stools in the latter, as well as the passage of carmine in six and one-half hours, indicated an acceleration in the rate of passage of the contents of the intestine which considerably exceeded that of other periods. Small, frequent, watery stools persisted until bile was discontinued at the end of the second day of Period 34. Then diarrhea stopped. The calcium content of the feces of Period 33 was much higher than in Period 34 and probably represented a lag from the higher intake and fecal excretion produced by Diet III. That the lag was not an exclusively diarrheal effect is evident from the fact that it occurred in other transition periods in which there was no diarrhea. The much higher fatty acid content of the feces of Period 33 over that of 34 becomes explicable if one postulates a decrease in the length of the absorptive period plus an increase in the concentration of calcium ions in the gut which hindered absorption through formation of insoluble soaps. The effect of diarrhea alone on the absorption of fats of Diet IV seems better exemplified by Period 34. The irritative effects of bile in this period when combined with a lower calcium intake and a smaller excretion of fecal calcium, did not lead to such marked steatorrhea. Moreover, the irritation produced by bile seems, both on clinical grounds and from the weight of the feces, to have been much greater than that of the salt solutions given in Periods 22 to 29. This is likewise against the supposition that salt effects were entirely a matter of acceleration of the rate of passage of the ingesta through the small intestine.

From the experiments cited it is evident that administration of an alkaline phosphate, a calcium salt, or a diet having a high calcium and phosphorus content, increased the amounts of these elements found in the feces. The combination of a high output of fecal calcium and phosphorus with a high intake of fatty acid accentuated the steatorrhea. Both calcium chloride, and sodium glycerophosphate might be expected to make the content of the intestine more alkaline; the former because chloride is rapidly and almost completely absorbed leaving calcium behind (30), the latter because of its alkaline buffer effect.[4] Conditions favorable to the formation of insoluble soaps and phosphates would thus be produced. Period 22, which was the least complicated of the group, may be taken as an example. Sodium glycerophosphate by increasing the alkalinity of the small bowel could have caused precipitation of the calcium of the food and from the intestinal secretions as phosphate and quite possibly as carbonate. A further reaction between fatty acids and calcium ions or salts tended to place additional restraints on the already defective absorption of fatty acids. Four factors seem to have acted together to increase steatorrhea:

(1) A supply of fatty acids from a dietary source undergoing abnormally slow absorption.

(2) An abnormally alkaline reaction of the contents of the intestine.

[4] The pH of a M/10 solution of sodium glycerophosphate was found to be 8.8.

(3) An unusually high concentration of calcium ions or salts.

(4) Some degree of acceleration of the rate at which the chyme passed through the small bowel.

Effect of a low intake of calcium on steatorrhea. Case P. A. showed a rather striking interrelationship between fecal calcium, magnesium, phosphorus, and split fatty acids. In his case a decrease in the sum of milliequivalents of calcium plus magnesium was associated with a comparable decrease in the amount of fatty acids in the stool. On the other hand, there appeared to be an inverse relationship between fecal phosphorus and fatty acid.

Table VII shows that when the intake of fatty acids was constant and when the amount of calcium, magnesium, and phosphorus was known, the amounts of split fecal fatty acids could be predicted quite accurately.[5] This held true not only in the high fat-normal calcium and high fat-low calcium diets but also in the periods when the calcium and phosphorus content of the feces was diminished by the administration of a vitamin D concentrate. While vitamin D caused more complete absorption of both calcium and phosphorus, the effect on fecal phosphorus was if anything greater than the effect on fecal calcium, and there remained in the feces as much calcium and magnesium as before which was free to combine with fatty acids. There was, therefore, no decrease in fecal split fat.

In estimating fatty acids in milliequivalents, the average molecular weight of the fatty acids was taken as 270. The base combining power of phosphorus was assumed to have been 1.8 times

TABLE VII

Case P. A. Relationship between fecal calcium, magnesium, phosphorus, and split fatty acids

		Control periods 17 to 19 (15 days)	Low calcium periods 15 to 16 (9 days)	Vitamin D periods 22 to 25 (16 days)
		grams per day	*grams per day*	*grams per day*
Intake	Fatty acid	104.0	105.0	104.0
	Calcium	1.092	0.235	1.092
	Phosphorus	1.808	1.127	1.808
		m.eq. per day	*m.eq. per day*	*m.eq. per day*
Feces	Split fatty acid	41.3	18.0	38.0
	Phosphorus	35.7	21.4	15.1
	Total	77.0	39.4	53.1
	Calcium	52.1	18.4	35.0
	Magnesium	19.3	16.5	15.5
	Total	71.4	34.9	50.5

the number of millimols of phosphorus, as it would have been at the pH of the blood. These values have been used arbitrarily in Table VII and in graphs in which fatty acids and phosphorus have been expressed in milliequivalents. No data were obtained on the nature of the fecal phosphates, and there is no justification for the choice of a base combining power for phosphorus of 1.8, other than the fact that the sum of milliequivalents of fatty plus phosphoric acids so calculated approximately balanced the sum of milliequivalents of calcium plus magnesium in the feces of Case P. A. over a long period of time and under quite different experimental conditions. Nearly the same results would have been obtained had all of the fecal phosphorus been considered to be present as dicalcium phosphate.

The stools of R. G. showed changes qualitatively similar to those of P. A. (Figure 2), but there was usually no very close agreement between the sum of alkaline earths on the one hand and phosphorus plus fatty acids on the other. With the change from normal to low calcium diet there was a greater reduction in the amount of split fatty acids excreted in the feces than was predictable from the decrease in alkaline earths. Lack of a good correlation is not surprising when the severity of disturbance of fat absorption and the different rates at which the intestinal contents traversed the bowel are considered. Diarrhea introduced a particularly erratic variable when this

[5] For example: using the data recorded in Table VII the predicted decrease of fatty acids in feces during low calcium periods was equivalent to:

(Ca+Mg of control) − (Ca+Mg of low calcium period)
71.4 − 34.9
− Decrease in phosphorus
− 14.3 = 22.2 m.eq.
Observed decrease = 23.3 m.eq.

The predicted decrease of fatty acids in feces during vitamin D periods was equivalent to:

(Ca+Mg of control) − (Ca+Mg vitamin of D periods)
71.4 − 50.5
− Decrease in phosphorus
− 20.7 = 0.2 m.eq.
Observed decrease = 3.3 m.eq.

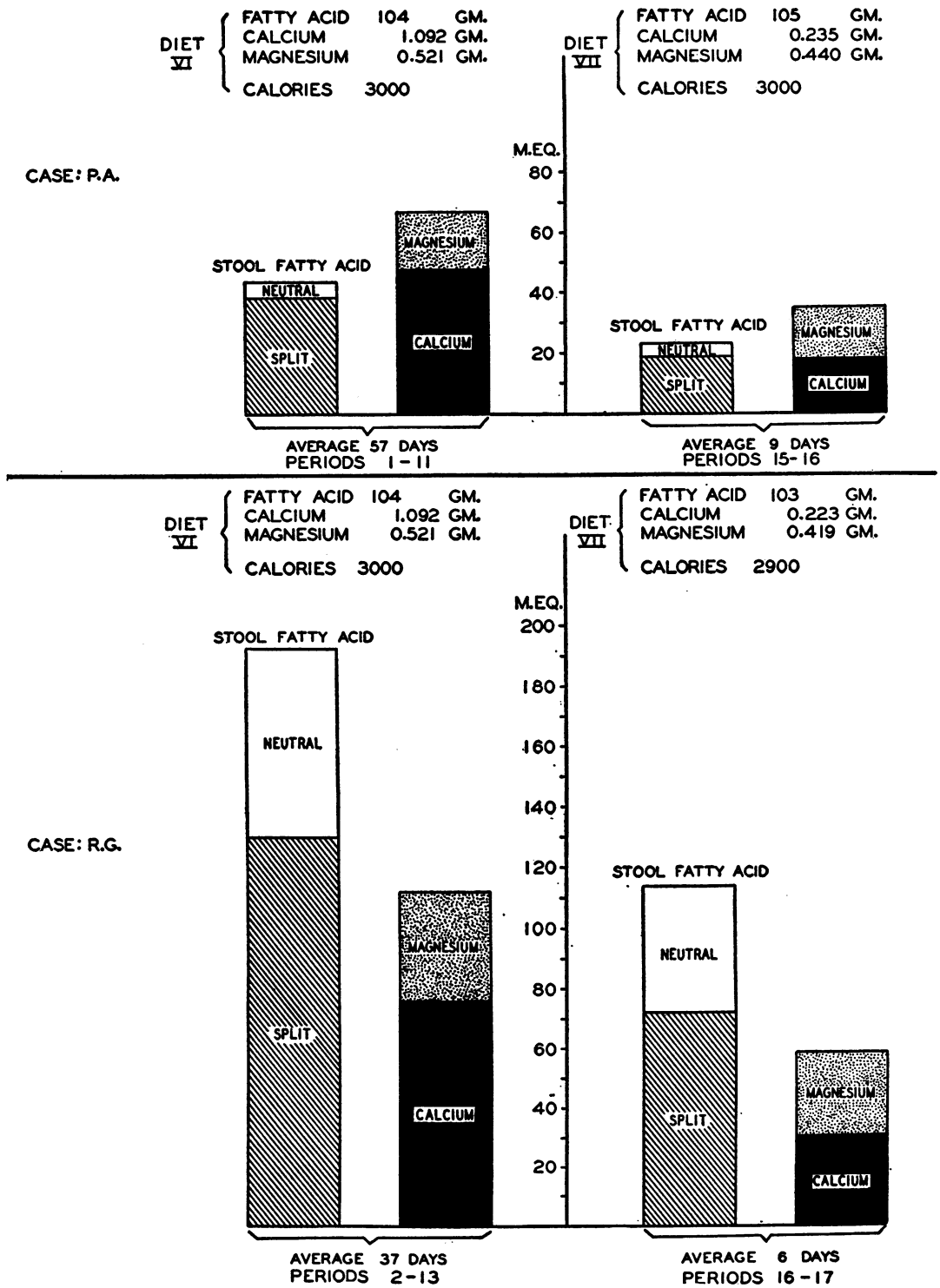

FIG. 2. DECREASE IN STEATORRHEA ACCOMPANYING THE INGESTION OF A LOW CALCIUM DIET BY P. A. AND R. G.

patient was on the high fat régime and probably prevented the attainment of a state of equilibrium in the intestine. It was usually necessary to collect the stools for from six to ten days to obtain a reliable estimate of the daily excretion of fatty acids.

The time required for passage of carmine markers was followed with considerable care. While taking Diet VII, the average rate of passage of carmine was 16 hours, the same average time as in Periods 2 to 13 which have been chosen for comparison (Figure 2). This is evidence against the assumption that the fats of Diet VII were more completely absorbed because the absorptive period was longer. If lengthening of the absorptive period is not to be offered as one of the reasons for the better absorption of fats of the low calcium diet, the most probable alternative assumption would be that at a normal level of dietary calcium, fat absorption was impeded by formation of insoluble soaps.

Low calcium-high fat diets and calcium balance. Both of the subjects ingesting the high fat-low calcium diet (VII) were in negative calcium balance. The fecal lipids of the mild juvenile case of steatorrhea (P. A.) were brought within the normal range by this diet, but the change from positive to negative calcium and phosphorus balances was highly undesirable. In the long run, injury to the skeletal system might be expected on such a régime, which would more than offset any improvement derived from more complete absorption of fatty acids.

Interestingly enough the loss of calcium by the severe adult steatorrhea, R. G., was almost the same on both normal and low calcium intakes. Representative effects of two diets containing the same amount of fat but providing normal and low levels of calcium respectively are given in Table VIII. Total failure of calcium absorption may be offered as an explanation for R. G.'s loss of equally large amounts of calcium at the two levels of intake. As the urine was nearly devoid of calcium, the only important avenue of excretion was the intestine. In order to have a nearly constant negative balance, one need only assume that the feces contained all of the calcium of the food plus a fairly constant daily increment derived from secretions entering the intestine.

High fat intake and calcium balance. A survey of the data obtained from Subject R. G. shows that calcium loss was more pronounced when he ingested the high fat diet (VI). (Figure 1 and Table VIII.) The inference is that a high intake of fat increased the excretion of calcium in the feces. The evidence must be accepted with reservation, for at the low level of dietary fat he had a higher intake of both calcium and phosphorus and no diarrhea. More direct evidence of a relation between higher intakes of fat and increased excretion of fecal calcium was obtained from another subject (S. B.). It was possible to supplement his low fat diet (VIII) with butter without producing diarrhea (Table VI). Under the conditions of the experiment, calcium, split fatty acids, and neutral fat in the feces increased, the first two appearing in practically equivalent amounts. The fecal excretion of phosphorus decreased slightly. The net effect was a definite increase in the loss of calcium from the body and a small retention of phosphorus. While diarrhea does not seem to have been a cause of the greater loss of calcium, the results are still open to question since the experimental period was very short.

Supplementary feeding of phospholipid. Phos-

TABLE VIII

Effect of high and low calcium diets on calcium balance in Cases P. A. and R. G.

Diet number	Diet per day			Case P. A.				Case R. G.			
	Fatty acids	Ca	P	Periods	Number of days	Daily balances		Periods	Number of days	Daily balances	
						Ca	P			Ca	P
	grams	*grams*	*grams*			*grams*	*grams*			*grams*	*grams*
VI.....	104	1.092	1.808	8–10	18	+0.140	+0.092	10–12	9	−0.477	−0.248
VII.....	105	0.235	1.127	12–13	6	−0.283	−0.133	15–17	9	−0.449	−0.341
VIII.....	23.2	1.635	2.342					32–33	8	−0.020	+0.119

pholipid was given to one subject (R. G.) and was well tolerated. The supplements were superimposed on a low fat-low starch diet (Diet VIII, Table IX). As this individual was apparently made worse by starchy food, the low starch intake may have been the major factor in his tolerance of this form of lipid. Another possibility is that the patient with steatorrhea may be able to absorb phospholipid more readily than fatty acid derived from neutral fat. In order to test this assumption he was given a commercial preparation made from soybean, which was stated to be pure lecithin but was found to be a mixture of lecithin, cephalin, and perhaps phosphatide.[6]

The supplementary lipid was given at first mixed with shredded cocoanut and chocolate syrup to disguise a rather unpleasant flavor. Later the cocoanut was omitted. During the ingestion of these supplements some difficulty was experienced in fractionating the fecal lipids, and only the total lipid appears to have been determined with sufficient accuracy to be of significance. The total amount of lipid excreted in the feces was about doubled, while the total intake of fatty acids increased about threefold. Nitrogen retention was greater. There was consistent retention of considerable amounts of phosphorus, in spite of a negative calcium balance. The patient gained in weight. The net gain of nitrogen was 85 grams, of phosphorus 11.1 grams while calcium was lost to the extent of 4.26 grams. Phosphorus available for metabolism was thus the 11.1 grams retained from the food plus about 1.9 grams derived from bone or 13 grams in all. This gave an N : P ratio of 6.5; therefore, more phosphorus was retained than could have been deposited with protein. We believe this is evidence that phospholipid was retained in the body.

Fecal nitrogen. The excretion of nitrogen in the feces of patients with celiac disease and idiopathic steatorrhea has often been observed to be higher than normal (8, 25, 29, 31, 32, 33, 34), but never attains the high levels observed in pancreatic steatorrhea. This has been considered by Thaysen (8) to be caused by factors other than defective digestion and absorption of proteins. Some data from three of our cases is given in Table X.

The fecal nitrogen of J. B. was consistently normal when the protein intake varied between 62 and 115 grams daily. There was no correlation demonstrable between fecal nitrogen and fecal lipid. The nitrogen of the stools was found to be slightly higher than normal only in those periods of diarrhea which were induced by administration of ox bile. In the case of R. G., there was rather good correlation between fecal nitrogen, lipid, and water. The physical effects of his failure to absorb fatty acids and his constant tendency toward diarrhea when taking Diets VI and VII seem sufficient explanation for the high fecal nitrogen. His response to administration of vitamin D while taking Diet VIII was quite definite (Period 36 to 40). Fecal nitrogen and water both decreased, the latter to an entirely normal value. Nevertheless his reaction to an unfavorable diet was not altered materially. When he was shifted back to the irritative type

[6] Personal communication from W. R. Bloor.

TABLE IX

Metabolism of phospholipid supplements by Case R. G.

Period	Number of days	Diet per day						Sources and amounts of supplementary fatty acids daily			Daily feces		Daily balances			Body weight
		Number	F.A.	Ca	P	N	Calories (approx.)	Phospholipid	Cocoanut	Chocolate	Weight	Total lipid	Ca	P	N	
			grams	*grams*	*grams*	*grams*		*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*kgm.*
21–22	10	VIII	23.2	1.64	2.34	21.24	2200	None	None	None	155	8.8	−0.323	+0.107	+1.64	50.85 51.08
23	6	VIII	67.4	1.79	3.89	21.74	2800	30.7	12.1	1.4	164	14.8	−0.072	+0.807	+3.03	52.55
24–25	10	VIII	67.4	1.79	3.89	21.74	2800	30.7	12.1	1.4	213	16.1	−0.191	+0.241	+2.55	53.17
26	4	VIII	67.4	1.79	3.89	21.74	2800	30.7	12.1	1.4	199	15.0	−0.211	+0.035	+2.02	53.47
27	4	VIII	67.6	1.82	4.55	22.25	2800	43.0		1.4	220	13.5	−0.181	+0.142	+2.28	53.87
28	4	VIII	67.6	1.82	4.55	22.25	2800	43.0		1.4	194	11.7	+0.181	+0.314	+2.27	54.24
29	6	VIII	67.6	1.82	4.55	22.25	2800	43.0		1.4	192	12.2	−0.069	+0.318	+2.54	54.37

TABLE X

Fecal nitrogen, total lipid, and water

Case J. B.						Case R. G.						Case P. A.					
Period	Number of days	Diet number	Daily feces			Period	Number of days	Diet number	Daily feces			Period	Number of days	Diet number	Daily feces		
			N	Lipid	Water				N	Lipid	Water				N	Lipid	Water
			grams	*grams*	*grams*				*grams*	*grams*	*grams*				*grams*	*grams*	*grams*
2–5	12	I	1.30	19.9	95.4	2–4	10	VI	3.05	48.8	297	4–7	21	VI	2.34	14.1	131
7–11	15	II	1.59	17.2	157	5–9	15	VI	3.68	56	355	8–10	18	VI	2.34	13.8	135
16–19	12	III	1.48	2.1	89.8	14–15	6	VII	4.40	52.4	472	14–16	12	VII	1.97	8.9	82
26–29*	12	IV	1.31	30.9	188.8	16–17	6	VII	3.57	32.7	395	22–25†	16	VI	2.26	14.9	98
31	3	III	1.63	2.1	142.5	21–22	10	VIII	2.25	8.8	112	26–27¶	8	VI	2.07	14.8	93
33–34†	6	IV	2.21	20.2	415	36–37‡	10	VIII	1.62	7.6	93						
						39–40‡	8	VIII	1.37	9.2	86						
						42‡	3	VI	2.95	26.8	325						

* Sodium glycerophosphate 9 grams; calcium chloride 5.38 grams daily
† Ox bile (See text).
‡ Vitamin D concentrate 225,000 I.U. daily
¶ Vitamin D concentrate 100,000 I.U. daily.

of diet (VI, Period 42) the excretion of nitrogen, lipid, and water immediately increased.

Case P. A.'s excretion of fecal nitrogen was consistently rather high, but neither diet nor medication as employed in his case produced any radical change in the composition of the feces.

From the data at hand, it may be surmised that the quantity of fecal nitrogen is related to the physical properties of the feces and to diarrhea. Irritative diets produce diarrhea and, perhaps, as suggested by McCrudden and Fales (33), increase secretion of nitrogenous material (secretions from intestinal glands, diapedesis of leukocytes, *etc.*) into the lumen of the bowel. When these effects were not prominent, as in Cases J. B. and P. A., there was little alteration of the fecal nitrogen from the normal; when irritative effects were prominent definite increases in fecal nitrogen were found.

COMMENT

Features common to all of the cases studied were mild anemia, flat glucose tolerance and vitamin A absorption curves, an excess of split fatty acids in the feces when a diet high in fat was ingested, and vitamin D deficiency. One subject developed a hemorrhagic disease associated with defective coagulation of the blood. In general the metabolic abnormalities correspond to those described by Fanconi (25), Lehndorff and Mautner (32), Macrae and Morris (29), and Parsons (11) in celiac disease and by Linder and Harris (35), Bennett *et al.* (1), Bauer and Marble (17), Thaysen (8), and Brull (36) in idiopathic steatorrhea of adults.

Response to dietary fat. There were marked individual differences in the behavior of the four patients, but the average daily amount of fecal lipid was remarkably uniform for a given subject on a constant régime. The two more severe cases lost upwards of 50 per cent of the ingested fatty acids in the feces during periods of high fat intake. In the mildest case the loss amounted to only about 11 per cent of the intake. When the dietary fat was increased, there was a higher percentage of absorption, but a high intake frequently led to episodes of diarrhea, anorexia, and loss of weight. The advantage gained by greater absorption of fat was more than offset by loss of inorganic salts, water, and probably carbohydrate in the feces.

Low intake of fat. Steatorrhea was always controlled when sufficiently stringent limitations were imposed on the intake of fat. There was no evidence to suggest that idiopathic steatorrhea resulted from an abnormally high excretion of lipid into the bowel.

Dietary carbohydrate. The nature of the dietary carbohydrate did not affect the steatorrhea of one of the subjects. No improvement resulted from substituting monosaccharide for starch. In another individual the evidence suggested that an increase in fatty diarrhea accompanied the ingestion of starches. This effect was presumably

one of greater irritability of the bowel caused by fermentation. Miller (16) has suggested that granules of starch become coated with fatty acids and are thus protected from the action of amylase. Bacteria within the masses then ferment the starch and produce gas and irritating split products.

Alkaline earths and fecal lipid. It has been pointed out that the quantity of fecal split fat was increased when the amount of alkaline earths provided by the diet was increased or when they were precipitated in the intestine by rendering the contents of the gut more alkaline. Reduction of the intake of alkaline earths while the intake of fatty acids was maintained at a constant level diminished the loss of split fat in the feces. When a higher intake of fat was given while the alkaline earths and phosphorus were kept at a constant level the loss of calcium in the feces increased. It is obvious then that there is a certain degree of interdependence between the presence of alkaline earths and fat in the feces. Such a relationship may well provide the elements of a vicious circle and accelerate the decalcification of the bones of an adult, whose diet is deficient in vitamin D.

Avitaminosis D as a cause of decalcification and tetany. When dietary fat was reduced to the point at which the feces were freed from an excess of fatty acids, the faulty absorption of calcium was not materially improved although it seemed to cause some diminution in the negative calcium balance. The loss of lime from the bones was unquestionably a manifestation of D avitaminosis for it could be corrected by ingestion of adequate doses of a vitamin D concentrate (*27*). Low levels of serum calcium and inorganic phosphorus were likewise restored to normal by this treatment and the symptoms of tetany disappeared.

SUMMARY

1. Case histories and metabolic studies on four patients with idiopathic steatorrhea are presented.

2. The subjects exhibited great individual variation in their tolerance of fat, but the fecal excretion of fat in each subject was nearly constant for a given régime.

3. A very low dietary intake of fat prevented steatorrhea. There was no evidence that steatorrhea was caused by an exceedingly high excretion of fat into the intestine.

4. The tolerance of fat was not improved in one instance by replacing dietary starch with monosaccharide; in another patient a low starch diet seemed to prevent diarrhea and markedly increase the ability to absorb fat.

5. Administration of sodium glycerophosphate and ox bile made the steatorrhea of one patient worse.

6. Ingestion of an alkaline phosphate, a calcium salt, or both caused an increase in the total amount of split fat in the feces.

7. Reduction in the intake of calcium facilitated the absorption of fatty acids. This procedure resulted in the loss of calcium and phosphorus from the body in a subject with mild steatorrhea.

8. Increase in dietary fat, when accompanied by steatorrhea, increased the loss of calcium in the feces at the expense of calcium stored in the body.

9. Moderately high levels of calcium and phosphorus intake, in the absence of vitamin D, failed to produce consistently positive balances of these elements.

10. The ingestion of a phospholipid by one subject was accompanied by a considerable retention of phosphorus, an increase in retention of nitrogen, and a loss of calcium. Reasons for the belief that part of the phosphorus was retained as phospholipid have been cited.

11. Rather high values for fecal nitrogen were encountered in one case. These appeared to parallel the fecal lipid and water. In periods free from fatty diarrhea there was no increase in fecal nitrogen.

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