Response of Blood Serum Constituents to Production of and Recovery from a Kwashiorkor-Like Syndrome in the Young Pig (43470)

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Abstract. **Twenty-six 3-week-old genetically obese pigs were fed in two experiments to determine the serum chemistry profile during severe protein malnutrition and repletion. Severe protein deficiency was produced in pigs fed the high-fat, low-protein diet (growth failure, rough hair, low serum total protein and albumin). In Experiment 1, blood was sampled from the anterior vena cava of each pig five times during depletion and three times during repletion to determine serum total cholesterol, high density lipoprotein (HDL)-cholesterol, triglycerides, total protein, albumin, glucose, Ca, inorganic P, Mg, Na, K, Cl, total bilirubin, urea N, creatinine, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, and γ-glutamyltransferase. In Experiment 2, blood was sampled weekly for 8 weeks for serum total cholesterol, HDL-cholesterol, triglycerides, albumin, glucose, Ca, P, Mg and alkaline phosphatase. HDL-cholesterol was increased ($P < 0.01$) and albumin was decreased ($P < 0.01$) in protein-deficient pigs in both experiments. Creatinine, total bilirubin, γ-glutamyltransferase, alanine aminotransferase, and aspartate aminotransferase were elevated in protein-deficient pigs compared with controls after 7 weeks of depletion. Inorganic P ($P < 0.01$), Ca ($P < 0.01$), and Mg ($P < 0.05$) concentrations were depressed in protein-depleted pigs compared with controls in both experiments. After 8 weeks of repletion in Experiment 1, all elements except inorganic P were similar in the two groups. Short-term, severe, protein malnutrition affected lipid, electrolyte, and structural mineral metabolism and indices of liver function in the absence of parasites, diarrhea, and infection. The effects were reversed after 8 weeks of repletion. We conclude that the elevated serum cholesterol in protein deficiency is related primarily to an increase in the HDL fraction.** [P.S.E.B.M. 1992, Vol 200]

Protein malnutrition in infants and children remains a major health problem worldwide (1–3). Clinical manifestations of protein malnutrition include growth failure, hypoproteinemia, hypoalbuminemia, edema, and fatty infiltration of the liver (4–9). Nutritional rehabilitation of infants suffering from protein-calorie malnutrition is often confounded by concomitant infections and parasitism; such factors complicate quantification and interpretation of the metabolic changes associated solely with dietary protein depletion and repletion. The young pig has been used as a model in which signs and symptoms that mimic the kwashiorkor syndrome have been induced (10, 11, unpublished results). Genetically lean or obese pigs have been used in such studies and have been available since the cross-mating of purebred Duroc and Yorkshire pigs began in 1974 within high- and low-fat lines (12) and propagated at Clay Center, NE. Lean and obese pigs were originally selected (12) for backfat thickness over approximately 16 generations. We report changes in the serum chemistry profile of protein-malnourished, genetically obese pigs during the course of protein depletion and repletion. Body fat content of the genetically obese pig at 3 weeks of age resembles that of human infants more closely than that of genetically lean pigs. It was considered important to determine the responses of obese pigs to protein malnutrition in that context.

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Materials and Methods

Experiment 1. Eighteen 3-week-old genetically obese (50% Duroc, 50% Yorkshire) pigs were studied. Nine pigs were fed *ad libitum* a high-fat (23%), low-protein (5%) diet and nine pigs were fed a high-protein (21%), low-fat (3%) control diet for 7 weeks (Table I). Four pigs from each group were sacrificed at the end of the 7-week protein-depletion period for body composition determinations and gross and microscopic anatomical measurements (unpublished data). The remaining five animals in both groups were fed the adequate control diet *ad libitum* for an additional 8 weeks. Blood was sampled from the anterior vena cava of each pig at Weeks 0, 2, 3.5, and 7 during the protein-depletion period and at Weeks 10, 12.5, and 15 during the repletion period for determinations of total cholesterol, high density lipoprotein (HDL)-cholesterol, triglycerides, total protein, albumin, glucose, urea N, creatinine, total bilirubin, γ-glutamyltransferase (GGT), alkaline phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase, inorganic P, Ca, Mg, Na, K, and Cl by automated analysis (CIBA-Corning 550 Express chemistry analyzer and FAST-4, a 4-channel system for electrolyte analysis; Ciba-Corning Diagnostic Corp., Oberlin, OH). Body weights were recorded at each blood sampling period.

Data were analyzed by analysis of variance with repeated measures using BMDP2V (13). Diet, time, and diet × time interaction were tested for each serum trait during the 7-week depletion period (five times) and during the 8-week repletion period (three times).

Experiment 2. Eight genetically obese pigs were selected from the same obese strain used in Experiment 1. At age 3 weeks, four pigs were assigned to the same protein-deficient diet used in Experiment 1, and four were assigned to an adequate control diet that differed from the control diet of Experiment 1 only in that it contained 20% added corn oil to make this diet isocaloric (Table I) with the protein-deficient diet. The pigs were fed their respective diets *ad libitum* for 8 weeks. Blood was sampled weekly from the anterior vena cava of each pig for determinations of serum total cholesterol, HDL-cholesterol, triglycerides, albumin, glucose, Ca, inorganic P, Mg, and alkaline phosphatase (CIBA-Corning 550 Express chemistry analyzer). Body weights were recorded weekly. Blood serum and body weight data were analyzed as in Experiment 1 (13).

Table I. Composition of Experimental Diets

Ingredient	Protein deficient (%)	Control	
		Expt 1 (%)	Expt 2 (%)
Corn (ground)	60.65	60.80	35.65
Soybean	—	35.00	40.00
Corn starch	15.00	—	
Corn oil	20.00	—	20.00
Vitamin premix[a]	0.25	0.20	0.25
Trace mineral premix[b]	0.25	0.20	0.25
Choline chloride	0.25	0.20	0.25
Dicalcium phosphate	2.40	2.40	2.40
Ground limestone ($CaCO_3$)	0.80	0.80	0.80
Iodized salt	0.40	0.40	0.40
Total	100.00	100.00	100.00

[a] Supplies the following (units/kg diet when added at 0.20% and 0.25%, respectively): vitamin A, 5280 IU; vitamin D_3, 704 and 880 IU; vitamin E, 70.4 and 88.0 IU; vitamin K, 3.52 and 4.40 mg; vitamin B_{12}, 26.4 and 33.0 μg; riboflavin, 5.28 and 6.60 mg; niacin, 28.16 and 35.20 mg; D-pantothenic acid, 21.12 and 26.40 mg; biotin, 88 and 110 μg; and thiamin, 2.2 and 2.7 mg.

[b] Supplies the following (ppm when added at 0.20% and 0.25%, respectively): Cu (as cupric oxide), 10 and 12.5; Fe (as ferrous sulfate heptahydrate), 160 and 200; Mn (as manganese oxide), 20 and 25; Zn (as zinc oxide), 100 and 125; $CaCO_3$ used as carrier (0.30% of diet).

Results

Experiment 1. Mean values for body weight and all serum traits measured during the 7-week protein depletion period are shown in Table II; mean values for the 8-week repletion period are shown in Table III. Time trends for albumin, total cholesterol, HDL-cholesterol, total bilirubin, GGT, ALT, and inorganic phosphorus are shown in Figures 1A through 1G, respectively. Body weight curves are shown in Figure 2. Plasma total protein and albumin concentrations decreased, as expected, throughout the 7-week depletion period in pigs fed the protein-deficient diet. Normal values were restored after 8 weeks on the adequate control diet. Serum total cholesterol declined from initial values in both groups from the first to the second sampling period, probably caused by a change from sow milk to a corn-soybean meal-based diet at weaning 2 days before the experiment began. Overall, during protein restriction, serum total cholesterol was higher ($P < 0.01$) in protein-deficient pigs than in control pigs (Table II and Fig. 1B). The increase in total cholesterol concentration appeared to be associated primarily with an increase in the HDL fraction (Table II and Fig. 1C). The HDL-cholesterol concentration dropped immediately in protein-depleted pigs when protein repletion began (Table III and Fig. 1C). At Week 7 of protein depletion, mean HDL-cholesterol was 1.608 mmol/liter in protein-deficient pigs compared with 0.832 mmol/liter in controls; corresponding values at the first sampling period during repletion were 0.563 and 0.905 mmol/liter. Serum triglyceride concentration increased in pigs on the protein-depleted diet compared with those on the adequate control diet ($P < 0.01$), but the difference disappeared at the end of the 8-week repletion period. Glucose concentrations were above normal fasting levels in both groups throughout depletion and repletion, as was expected in the absence of fasting before blood sampling. There was no evidence for a

Table II. Body Weight and Serum Chemistry of Protein-Deficient versus Control Pigs[a]

	Diet group		SD	*P*		
	Control ($n = 9$)	Deficient ($n = 9$)		Diet	Time	Diet × time
Initial body wt (kg)	3.23 ± 0.73	2.98 ± 1.01				
Final body wt (kg)	19.37 ± 4.13	3.93 ± 1.12				
Mean wt (kg)	10.34	3.55	1.00	0.001	0.001	0.001
Total cholesterol (mmol/liter)	2.312	3.747	0.450	0.007	0.001	0.001
HDL-cholesterol (mmol/liter)	0.861	1.590	0.220	0.001	0.109	0.001
Triglycerides (mmol/liter)	0.466	0.659	0.211	0.006	0.002	0.001
Total protein (g/liter)	54.6	43.7	3.1	0.001	0.001	0.001
Albumin (g/liter)	37.9	26.2	2.5	0.001	0.001	0.001
Glucose (mmol/liter)	8.98	8.62	1.95	0.459	0.001	0.385
Urea N (mmol/liter)	5.68	2.71	1.1	0.001	0.001	0.001
Creatinine (μmol/liter)	80.4	92.8	8.8	0.001	0.001	0.001
Total bilirubin (μmol/liter)	3.5	8.3	3.1	0.001	0.001	0.001
GGT (μkat/liter)	0.68	1.00	0.165	0.001	0.001	0.001
ALT (μkat/liter)	0.67	1.10	0.136	0.001	0.001	0.001
Aspartate aminotransferase (μkat/liter)	1.08	1.00	0.520	0.450	0.103	0.043
Alkaline phosphatase (μkat/liter)	6.2	6.8	1.3	0.104	0.001	0.116
Inorganic P (mmol/liter)	2.13	1.80	0.24	0.003	0.001	0.001
Ca (mmol/liter)	2.65	2.51	0.10	0.001	0.001	0.001
Mg (mmol/liter)	0.78	0.72	0.09	0.047	0.001	0.005
Na (mmol/liter)	163	162	8	0.345	0.001	0.001
K (mmol/liter)	7.9	6.9	1.0	0.007	0.001	0.010
Cl (mmol/liter)	117	121	6	0.014	0.001	0.001

[a] Study Weeks 0 to 7, Experiment 1.

Table III. Body Weight and Serum Chemistry of Protein-Repleted versus Control Pigs[a]

Trait	Diet group		SD	*P*		
	Control ($n = 5$)	Deficient ($n = 5$)		Diet	Time	Diet × time
Initial body wt (kg)	19.37 ± 4.13	3.93 ± 1.12				
Final body wt (kg)	49.94 ± 6.88	28.39 ± 0.46				
Mean wt (kg)	37.67	17.67	1.32	0.001	0.001	0.076
Total cholesterol (mmol/liter)	2.563	2.455	0.296	0.479	0.058	0.006
HDL-cholesterol (mmol/liter)	0.918	0.710	0.172	0.011	0.001	0.003
Triglycerides (mmol/liter)	0.319	0.395	0.130	0.079	0.165	0.001
Total protein (g/liter)	59.9	53.2	14.9	0.001	0.002	0.001
Albumin (g/liter)	37.9	33.7	2.9	0.002	0.024	0.001
Glucose (mmol/liter)	6.82	7.17	0.95	0.430	0.481	0.926
Urea N (mmol/liter)	8.57	5.69	1.00	0.002	0.001	0.001
Creatinine (μmol/liter)	78.4	65.4	7.7	0.002	0.001	0.739
Total bilirubin (μmol/liter)	1.6	1.5	0.5	0.555	0.051	0.677
GGT (μkat/liter)	0.69	0.64	0.22	0.583	0.272	0.680
ALT (μkat/liter)	0.74	0.66	0.11	0.164	0.001	0.101
Aspartate aminotransferase (μkat/liter)	1.04	1.30	0.57	0.264	0.027	0.131
Alkaline phosphatase (μkat/liter)	2.4	4.2	0.3	0.003	0.001	0.001
Inorganic P (mmol/liter)	1.99	2.28	0.31	0.036	0.075	0.068
Ca (mmol/liter)	2.71	2.67	0.17	0.471	0.590	0.755
Mg (mmol/liter)	0.73	0.74	0.05	0.668	0.001	0.006
Na (mmol/liter)	151	148	3	0.046	0.566	0.139
K (mmol/liter)	6.2	5.9	1.0	0.479	0.017	0.025
Cl (mmol/liter)	106	105	2	0.201	0.001	0.836

[a] Study Weeks 7 to 15, Experiment 1.

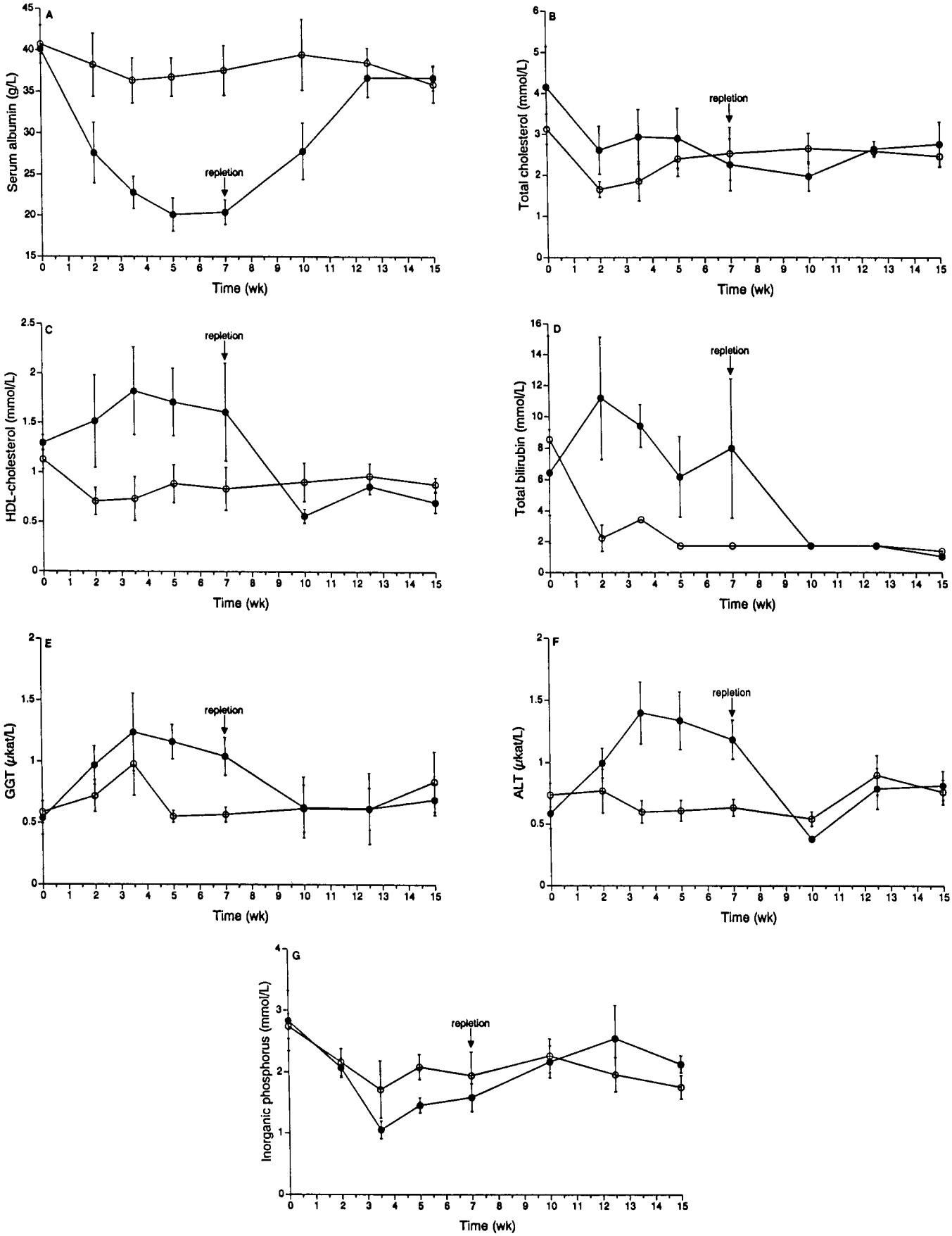

Figure 1. Concentrations of serum constituents of adequately fed versus protein-deficient pigs during depletion and repletion. ●—●, deficient ○—○, adequate. Each point is the mean of four observations ± SD. (A) Albumin. (B) Total cholesterol. (C) HDL-cholesterol. (D) Total bilirubin. (E) GGT. (F) ALT. (G) Inorganic P.

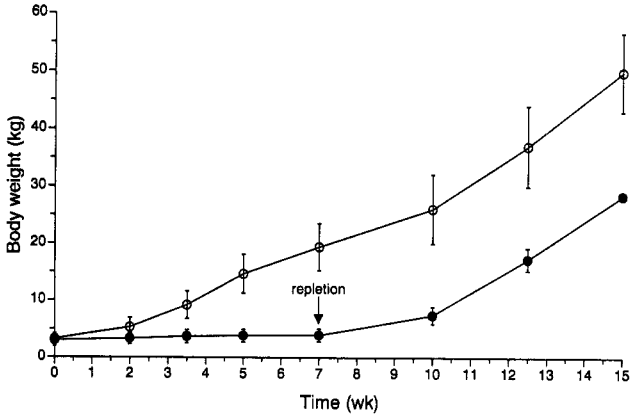

Figure 2. Body weight curves of adequately fed pigs (○—○) and protein-deficient pigs (●—●) during protein depletion and repletion.

diabetic response to protein deficiency, despite the severe atrophy of the pancreas observed in the protein-deficient pigs after 7 weeks of protein restriction (unpublished results). Urea N concentration was decreased as expected in protein-depleted animals; the lower concentration persisted during repletion, presumably because of high efficiency and rate of protein accretion after 7 weeks of growth failure during protein deprivation. Serum creatinine concentration, an index of tissue protein catabolism, was higher in protein-deficient than in control pigs during depletion (Table II). The reverse was true during repletion (Table III), which indicated prompt recovery of lean tissue growth after 7 weeks of growth failure caused by severe protein deficiency. Total bilirubin (Fig. 1D), GGT (Fig. 1E), and ALT (Fig. 1F) were increased in pigs on the protein-deficient diet compared with controls after 7 weeks of depletion. Values for all of these metabolites were similar in the two groups after 8 weeks of repletion. Aspartate aminotransferase activity was unaffected by protein deficiency.

Indices of bone metabolism were affected by protein deficiency; inorganic P, Ca, and Mg were reduced in protein-depleted pigs (Table II); Ca and Mg concentrations returned to normal after 8 weeks of repletion, but that of inorganic P (Fig. 1G) and serum alkaline phosphatase activity were higher in repleted pigs than in controls after 8 weeks of repletion. Serum Cl was increased and serum K was decreased in protein-deficient pigs (Table II), but serum concentrations of these electrolytes were similar in both groups at the end of the 8-week repletion period.

Experiment 2. Protein deficiency signs, including growth failure and low serum albumin, were produced in the pigs, as in Experiment 1 (Table IV). The HDL-cholesterol concentration was increased ($P < 0.01$) as a result of protein deficiency, and the ratio of HDL-cholesterol to total cholesterol was greater in protein-deficient pigs; total cholesterol concentration was similar in the two groups. Triglyceride values ($P < 0.01$) were lower in protein-deficient pigs, although glucose was unaffected. Concentrations of Ca, inorganic P, and Mg were reduced ($P < 0.01$) by protein deficiency as in Experiment 1, but alkaline phosphatase activity was increased sharply as depletion progressed ($P < 0.01$) compared with control values.

Discussion

The increase in total serum cholesterol described in Experiment 1 confirmed earlier observations in young pigs fed protein-deficient diets (14–16). Pond *et al.* (16) reported a greater rise in plasma cholesterol values, which resulted from low levels of protein in the diet rather than from high fat-cholesterol levels. The increase in serum total cholesterol in the severely protein-depleted pigs appeared to be linked primarily with an increase in the HDL-cholesterol fraction. In Experiment 2, in which protein-deficient and adequate diets were isocaloric, there was no difference between groups in total cholesterol; HDL-cholesterol, however, was elevated as in Experiment 1.

Numerous reports indicate that protein-malnourished infants often have reduced plasma total cholesterol and triglyceride concentrations (17–21). Dhansay *et al.* (17) concluded that reduced plasma lecithin-cholesterol acyltransferase activity is an important factor related to abnormalities in lipoprotein composition and concentrations. The elevated HDL-cholesterol level in protein-depleted pigs in the present experiments agrees with the observation of Taylor *et al.* (22) that at least some malnourished children have a high proportion of HDL-cholesterol to total cholesterol. The suggestion by Taylor *et al.* (22) that the observed changes in HDL-cholesterol in plasma of protein-malnourished children could result from combined effects of inadequate nutrition and infections raises the question of interrelationships between malnutrition and infection when clinical and biochemical changes in malnourished infants are interpreted. Triglyceride concentration was less in protein-deficient pigs in Experiment 2, in agreement with observations in human infants (17). The low concentration suggests that the high triglyceride values in protein-deficient pigs in Experiment 1 may have resulted from the higher fat content of the low-protein diet rather than from protein deficiency per se.

The changes we have observed in serum lipids and other serum constituents in protein-deficient pigs were not confounded by the presence of infections, diarrhea, or parasites. Our data support reports of aberrations in lipid metabolism in protein-malnourished human infants, as summarized by Dhansay *et al.* (17). In the present study, the changes in concentrations of serum total cholesterol, HDL-cholesterol, and triglycerides in the protein-deficient pigs were corrected within 3 weeks after the pigs were fed the adequate control diet. It is important to note that the protein-deficient diet in Experiment 1 was increased in caloric density (20%

Table IV. Body Weight and Serum Chemistry of Protein-Deficient versus Control Pigs[a]

Trait	Diet group		SD	*P*		
	Control ($n = 4$)	Deficient ($n = 4$)		Diet	Time	Diet × time
Initial body wt (kg)	3.06 ± 1.03	3.60 ± 0.51				
Final body wt (kg)	25.65 ± 6.08	6.26 ± 1.09				
Mean body wt (kg)	12.24	4.90	1.25	0.004	0.001	0.001
Total cholesterol (mmol/liter)	2.48	2.46	0.48	0.946	0.006	0.908
HDL-cholesterol (mmol/liter)	0.93	1.31	0.18	0.009	0.001	0.001
Triglycerides (mmol/liter)	1.82	0.91	0.45	0.001	0.002	0.487
Albumin (g/liter)	37	23	1	0.001	0.001	0.001
Glucose (mmol/liter)	8.0	7.5	0.8	0.046	0.041	0.390
Alkaline phosphatase (μkat/liter)	4.135	5.754	0.714	0.028	0.001	0.001
Inorganic P (mmol/liter)	2.40	2.00	0.89	0.001	0.001	0.001
Ca (mmol/liter)	2.86	2.61	0.09	0.001	0.001	0.001
Mg (mmol/liter)	0.70	0.66	0.03	0.008	0.001	0.535

[a] Study Weeks 0 to 8, Experiment 2.

added corn oil) to hasten the onset of kwashiorkor symptoms. Therefore, the fat content of the protein-deficient and control diets differed markedly, although neither diet contained cholesterol. In view of the induced hypercholesterolemic response to low dietary protein in the absence of added fat in pigs fed low-protein diets (15, 16), the higher concentration of serum HDL-cholesterol observed in Experiment 1 in the present work was interpreted as a response to low dietary protein, rather than to high dietary fat. Our interpretation is supported by the results of Experiment 2, in which the protein deficiency syndrome was induced in pigs by feeding the same protein-deficient diet as used in Experiment 1. The only difference between Experiments 1 and 2 was that the adequate diet with which the deficient diet was compared contained the same amount of total fat (20% added corn oil). The increased serum concentration of HDL-cholesterol observed in Experiment 1 was also obtained in Experiment 2, in which the protein-deficient and adequate diets were isocaloric.

The increases in serum ALT and GGT activity and in total bilirubin concentration in pigs fed a protein-deficient diet suggested altered liver function, although microscopic anatomy revealed no evidence of excessive fat accumulation or of pathologic changes. After 8 weeks of repletion on the adequate control diet, serum activities of these enzymes and concentration of total bilirubin were similar to those of control pigs, indicating no permanent effects of protein deficiency on these serum constituents.

The depressed serum concentrations of Ca, inorganic P, and Mg that we observed agreed with observations in protein malnourished infants. These effects of protein deficiency on serum Ca, inorganic P, and Mg concentrations occurred despite the adequate concentration of all of these mineral elements in both the low-protein and adequate control diets. Reduced bone ash and osteoporosis have been recorded previously (11) in young pigs fed a protein-deficient diet similar to that used here. Although serum Ca and Mg concentrations in repleted and control pigs were similar after rehabilitation in Experiment 1, serum inorganic P and alkaline phosphatase were higher in repleted than control pigs. The higher values indicate active bone growth during protein repletion, after a period of growth failure caused by protein depletion. The higher alkaline phosphatase activity in serum of protein-deficient pigs in Experiment 2 and the trend for higher alkaline phosphatase activity in Experiment 1 were probably related to bone loss associated with osteoporosis in severe protein deficiency (11).

The pattern of serum electrolyte concentrations in protein malnourished pigs was similar to that observed in human infants (23). That is, K was decreased and Cl was increased after 7 weeks of protein depletion, and both electrolytes were restored to normal concentrations when protein levels were restored.

The serum chemistry values of protein-deficient infant pigs monitored throughout the study provide evidence that changes recorded in cholesterol metabolism in protein deficiency are related to increased HDL-cholesterol concentration and a higher HDL-cholesterol to total cholesterol ratio. The reduced values for serum albumin, Ca, Mg, inorganic P, and K, and the increased values for total bilirubin, ALT, and GGT in the absence of diarrhea, infections, or parasites indicate that the kwashiorkor-like syndrome produced in the pigs was specific for protein malnutrition and not the result of multiple factors often present in clinical studies of malnourished human infants. Serum concentrations of metabolites measured in these experiments agreed generally with other reported values for pigs (24) and healthy children (25). This animal model system enabled us to isolate the metabolic events in dietary

protein deficiency from uncontrolled confounding variables in human infant malnutrition.

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