JCI The Journal of Clinical Investigation

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J Clin Invest. 1975;55(1):94-104. https://doi.org/10.1172/JCI107922.

Research Article

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Elemental Balances during Intravenous Hyperalimentation of Underweight Adult Subjects

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ABSTRACT Intravenous hyperalimentation was done in 11 underweight adults whose body weight (body wt) was less than 85% of ideal. For the first 6 days, "complete formula" was infused furnishing per kilogram ideal body wt per day: 15 g glucose, 0.40 g N, 0.018 g P, 2.4 meq K, 3.0 meq Na, 2.3 meq Cl, 0.5 meq Mg, 0.45 meq Ca, and 50 ml H_2O. Patients gained weight at an average rate of 9.0 g/kg ideal body wt/day and showed average balances/kilogram ideal body wt/day as follows: + 0.14 g N; + 0.012 g P; + 0.43 meq K; + 0.49 meq Na; + 0.37 meq Cl; and + 0.085 meq Ca. Application of standard equations to the elemental balances indicated weight gain consisted of 35–50% protoplasm, 35–50% extracellular fluid, 5–25% adipose tissue, and < 1% bone.

Withdrawal of N, P, Na, or K impaired or abolished retention of other elements. Removal of N halted retention of P, K, Na, and Cl; withdrawal of K stopped retention of N and P; and removal of Na or P interrupted retention of all other elements. Weight gain continued at a rate of 1.4–3.1 g/kg ideal body wt/day despite zero or negative elemental balances of N, K, P, and sometimes Na and Cl. Calculations showed that weight gain during infusion of fluids lacking N, P, K, or Na consisted largely of adipose tissue, with little or no contribution by protoplasm or extracellular fluid.

Data show that repletion of protoplasm and extracellular fluid of wasted adults by intravenous hyperalimentation is retarded or abolished if N, P, Na, or K is lacking. Repletion of bone mineral does not occur in absence of Na or P but proceeds in absence of N or K. Repletion of adipose tissue proceeds in absence of N, P, K, or Na. Thus, quality of weight gained by underfed adult patients during hyperalimentation depends on elemental composition of the infusate.

Received for publication 17 June 1974 and in revised form 28 August 1974.

INTRODUCTION

For emaciated patients who cannot satisfy their nutritional requirements by eating, the intravenous hyperalimentation technique of Dudrick, Long, Steiger, and Rhoads (1) provides a means of achieving rapid gain in body weight (body wt).

Increase in body wt is caused by enlargement of one or more of four body compartments: protoplasm, extracellular fluid, adipose tissue, and bone. Each compartment has a characteristic content of N, P, Na, K, Cl, and Ca (2). N and K are largely intracellular, Cl is almost exclusively extracellular, Na is two-thirds extracellular and one-third skeletal, and Ca is located almost entirely in bone. Therefore, retention of N and K indicate net formation of protoplasm, retention of Cl reflects net expansion of extracellular fluid, and retention of Ca shows net deposition of mineral in bone. Provided that elemental composition of body tissues remains normal during a period of weight gain, the change in mass of each compartment during the period can be estimated from amounts of N, P, Na, K, Ca, and Cl retained (3).

Hyperalimentation fluid provides glucose, amino acids (furnishing N), P, Na, K, Cl, Ca, and Mg. Concentrations of these elements in the fluid have varied from one clinic to another (1, 4–9). Do these differing elemental contents influence the quality of weight gained by emaciated patients during intravenous hyperalimentation? Are the ratios of increments in the four compartments influenced by the ratios of elements in the hyperalimentation fluid? Can repletion of a particular body compartment be selectively suppressed by omitting an element specific for that compartment?

TABLE I

Clinical Data of 11 Subjects at Beginning of Hyperalimentation

Case	Age	Sex	Wt	Ht	Body wt as percent of ideal body wt	Diagnosis	Duration	Plasma albumin	Hemato-crit
			kg	*cm*	%		*yr*	*g/100 ml*	%
1	36	F	32	157	64	Postexentration of pelvis for carcinoma of cervix	2	1.9	29
2	59	F	46	157	84	Regional enteritis	12	4.2	33
3	52	M	61	180	80	Postresection of pancreatic carcinoma	1	3.6	36
4	47	F	52	167	84	Regional enteritis	5	3.7	41
5	62	M	57	167	83	Postsubtotal gastrectomy	2	4.4	43
6	16	M	29	153	62	Regional enteritis (pre-op for intestinal resection)	3	2.2	34
7	76	F	42	157	84	Anorexia, wt loss (pre-op for total hip replacement)	1½	3.5	39
8	48	F	51	165	82	Postjejunoileal bypass	1½	2.7	36
	42	M	30	156	64	Regional enteritis	10	2.3	34
	53	F	34	155	68	Postsubtotal gastrectomy	8	2.7	36
11	60	M	53	170	79	Regional enteritis	20	2.5	35

During hyperalimentation of 11 undernourished adult subjects, we have investigated relationships between elemental composition of the infused fluid and the amount of each element retained by the patient. Subjects initially received a complete hyperalimentation formula furnishing all seven elements and glucose, and elemental balances were measured. Then N, P, Na, or K was withdrawn, other components remaining unchanged, and the effect on elemental balances was observed.

METHODS

Clinical summaries of the 11 subjects are given in Table I. These individuals were selected as follows: during 1970–1973, 20 patients were referred to this clinic for hyperalimentation because their body wt was < 85% of ideal and they were unable to satisfy nutritional requirements by mouth. All were enrolled in the protocol described below. In nine cases, hyperalimentation was complicated and sometimes discontinued because of fever with or without positive blood culture, pneumothorax, persistent glycosuria, or obstruction of catheter. The remaining 11 patients, who received hyperalimentation for 30 days or longer without complications, form the basis of this report.

Hyperalimentation was done for 30–60 days through a catheter placed in the superior vena cava through the subclavian vein, according to the technique of Dudrick et al. (1). The tubing contained a 0.22-μm filter that was changed every 8 h. A constant flow rate of 100–150 ml/h was maintained by a Sigmamotor infusion pump (Schaar Sci-

TABLE II

Design of Experiments

Experiment	Period	Composition of formula
N1	I	Complete
	II	Complete minus all N
	III	Complete minus 80% of N
	IV	Complete minus 60% of N
	V	Complete minus 40% of N
	VI	Complete minus 20% of N
	VII	Complete
N2	I	Complete
	II	Complete minus all N
	III	Complete
P	I	Complete
	II	Complete minus all P
	III	Complete
K	I	Complete
	II	Complete minus all K
	III	Complete
Na	I	Complete
	II	Complete minus all Na
	III	Complete

TABLE III
Results of Experiment N1

Period	Daily intake								Daily output											
									Urine						Stools					
	Glucose	N	P	K	Na	Cl	Mg	Ca	N	P	K	Na	Cl	Ca	N	P	K	Na	Cl	Ca
	g	*g*	*g*	*meq*	*meq*	*meq*	*meq*	*meq*	*g*	*g*	*meq*	*meq*	*meq*	*meq*	*g*	*g*	*meq*	*meq*	*meq*	*meq*
I	15	0.40	0.018	2.40	3.00	2.30	0.5	0.45	0.25 ±0.03	0.007 ±0.0008	1.84 ±0.16	2.44 ±0.36	1.91 ±0.17	0.21 ±0.03	0.02 ±0.001	0.001 ±0.0002	0.16 ±0.04	0.06 ±0.005	0.03 ±0.003	0.08 ±0.009
II	15	0	0.018	2.40	3.00	2.30	0.5	0.45	0.04 ±0.004	0.019 ±0.004	2.37 ±0.34	2.90 ±0.32	2.23 ±0.25	0.22 ±0.01	0.01 ±0.002	0.002 ±0.0004	0.12 ±0.03	0.05 ±0.007	0.05 ±0.007	0.08 ±0.012
III	15	0.08	0.018	2.40	3.00	2.30	0.5	0.45	0.04 ±0.005	0.013 ±0.003	2.15 ±0.20	2.87 ±0.29	2.21 ±0.20	0.28 ±0.02	0.01 ±0.001	0.003 ±0.0004	0.17 ±0.02	0.03 ±0.001	0.02 ±0.005	0.06 ±0.021
IV	15	0.16	0.108	2.40	3.00	2.30	0.5	0.45	0.10 ±0.02	0.012 ±0.002	2.12 ±0.33	2.84 ±0.30	2.15 ±0.30	0.25 ±0.03	0.01 ±0.001	0.002 ±0.0002	0.15 ±0.03	0.01 ±0.004	0.04 ±0.001	0.075 ±0.007
V	15	0.24	0.018	2.40	3.00	2.30	0.5	0.45	0.14 ±0.01	0.009 ±0.001	2.09 ±0.30	2.69 ±0.24	2.02 ±0.22	0.22 ±0.04	0.01 ±0.002	0.001 ±0.0001	0.07 ±0.02	0.03 ±0.002	0.04 ±0.002	0.08 ±0.009
VI	15	0.32	0.018	2.40	3.00	2.30	0.5	0.45	0.19 ±0.02	0.007 ±0.0007	1.94 ±0.18	2.60 ±0.29	1.91 ±0.15	0.26 ±0.02	0.02 ±0.001	0.002 ±0.0003	0.13 ±0.03	0.04 ±0.003	0.05 ±0.004	0.06 ±0.010
VII	15	0.40	0.018	2.40	3.00	2.30	0.5	0.45	0.23 ±0.03	0.004 ±0.0006	1.82 ±0.29	2.42 ±0.31	1.87 ±0.24	0.20 ±0.02	0.01 ±0.001	0.001 ±0.0001	0.10 ±0.02	0.04 ±0.002	0.03 ±0.003	0.12 ±0.011

Values, expressed/kilogram ideal body wt, represent mean ±SEM, $n = 18$ (6 days of observation in each period for each of three patients). Δ values during periods II–VI which differ significantly from corresponding Δ values during period I by analysis of variance (24) are identified thus: * $P < 0.005$; ‡ $P < 0.01$; § $P < 0.05$.
‖ Sum of (Δ each compartment as percent Δbody wt) may deviate from 100% by as much as ±5% because of calculated change in degree of intracellular hydration (3).

TABLE III—(*Continued*)

Period	Daily balance						Ratios of positive balances (relative to ΔN = 1)						Daily change in mass					Analysis of body wt‖ (Δ each compartment as percent Δbody wt)			
	ΔN	ΔP	ΔK	ΔNa	ΔCl	ΔCa	ΔN	ΔP	ΔK	ΔNa	ΔCl	ΔCa	ΔBody wt	ΔProto-plasm	ΔExtra-cellular fluid	ΔBone	ΔAdi-pose tissue	Proto-plasm	Extra-cellular fluid	Bone	Adi-pose tissue
	g	*g*	*meq*	*meq*	*meq*	*meq*	*g*	*g*	*meq*	*meq*	*meq*	*meq*	*g*	*g*	*g*	*g*	*g*	%	%	%	%
I	0.13 ±0.01	0.010 ±0.0008	0.40 ±0.16	0.50 ±0.36	0.36 ±0.17	0.06 ±0.031	1	0.08 ±0.004	3.0 ±0.21	3.9 ±0.20	2.5 ±0.20	0.46 ±0.12	9.6 ±0.98	+3.51 ±0.80	+3.46 ±1.6	+0.006 ±0.003	+2.29 ±0.41	37	36	0	24
II	−0.05§ ±0.005	−0.003‡ ±0.004	−0.10§ ±0.34	0.03‡ ±0.32	0.02* ±0.25	0.15‡ ±0.016							4.1* ±0.63	−1.35‡ ±0.12	+0.19§ ±1.1	+0.010 ±0.002	+5.0* ±0.72	−33	5	0	122
III	0.00§ ±0.005	0.002* ±0.003	0.02§ ±0.20	0.04* ±0.29	0.03* ±0.20	0.11 ±0.029							5.5‡ ±0.78	0.00* ±0.14	+0.29§ ±1.0	+0.011 ±0.003	+5.06‡ ±0.91	0	5	0	92
IV	0.05‡ ±0.02	0.004§ ±0.002	0.13* ±0.33	0.15‡ ±0.30	0.11‡ ±0.20	0.13§ ±0.031	1	0.08 ±0.005	2.6 ±0.13	3.0 ±0.14	2.2 ±0.13	2.5 ±0.39	5.9§ ±0.72	+1.35§ ±0.54	+1.10 ±1.9	+0.013 ±0.003	+3.48 ±0.63	23	19	0	59
V	0.09* ±0.01	0.008§ ±0.001	0.24‡ ±0.30	0.28§ ±0.24	0.24§ ±0.22	0.15‡ ±0.041	1	0.09 ±0.003	2.6 ±0.14	3.1 ±0.25	2.6 ±0.12	1.7 ±0.27	7.4§ ±0.94	+2.43 ±0.27	+2.30 ±2.11	+0.015 ±0.004	+2.68 ±0.55	33	31	0	36
VI	0.11‡ ±0.02	0.009 ±0.0007	0.33 ±0.18	0.36 ±0.29	0.34 ±0.15	0.13* ±0.022	1	0.08 ±0.005	3.0 ±0.11	3.3 ±0.30	3.1 ±0.16	1.1 ±0.17	8.0 ±1.1	+2.97 ±0.54	+3.26 ±1.44	+0.013 ±0.002	+1.54 ±0.32	37	41	0	19
VII	0.16 ±0.03	0.011 ±0.0006	0.48 ±0.29	0.54 ±0.31	0.40 ±0.24	0.13 ±0.023	1	0.07 ±0.003	3.0 ±0.16	4.0 ±0.20	2.5 ±0.19	0.81 ±0.14	10.6 ±1.8	+4.32 ±0.80	+3.84 ±2.30	+0.013 ±0.002	+2.11	41	36	0	20

entific Inc., Chicago, Ill.). During hyperalimentation, patients received nothing by mouth except one Theragran-M tablet (E. R. Squibb & Sons, Princeton, N. J.) [1] daily. 1-mg folic acid was injected daily and 1,000-μg vitamin B_{12} monthly. Every 18 days, 1 pint of fresh blood was transfused; elemental balances were not measured for 48 h after the transfusion.[2]

The "complete" hyperalimentation fluid (adapted from Dudrick et al. [1]) contained the following ingredients, expressed as the quantity infused/kilogram ideal body wt/day: glucose, 15 g; N, 0.4 g; P, 0.018 g; K, 2.4 meq; Na, 3.0 meq; Cl, 2.3 meq; Mg, 0.5 meq; Ca, 0.45 meq; and H_2O, 50 ml. N was supplied as Freamine (McGaw Laboratories, Glendale, Calif.), a mixture of 14 amino acids (8.5 g/100 ml) including the eight essential amino acids. This solution also furnished Cl. Na was introduced as the chloride, phosphate, and acetate salts; P as K and Na phosphate; K with phosphate, chloride, and gluconate as anions; Mg as $MgCl_2$; and Ca as Ca gluceptate. 10-ml of Multivitamin Infusion Solution[3] was added to the hyperalimentation fluid daily.

After insertion of the subclavian catheter, a 6-day adaptation period was conducted preceding the first experiment. During the first 3 days of adaptation, the daily ration of each component in the hyperalimentation fluid, with the exception of H_2O, was 33, 50, and 67%, respectively, of corresponding ration in the complete formula. During days 4–6 of equilibration, the complete formula was administered. Water was infused at 50 ml/kg ideal body wt from the beginning. During all 6 days of adaptation, regular insulin was injected as necessary to prevent glycosuria > 1 g/100 ml urine or hyperglycemia > 180 mg/100 ml blood; it was not required after day 6. During the 30–60 day course of hyperalimentation, plasma (blood) concentrations of urea (10), Na (10), K (10), CO_2 (11), Cl (12), Ca (13), P (14), and Mg (15), measured every 3–6 days, remained within normal limits except when a specified element was removed from the infusion fluid (see Results). Blood glucose concentrations (16), (measured at 3–6-day intervals) remained below 170 mg/100 ml and 24-h urine glucose (measured daily) was less than 5 g/24 h. Concentrations of Fe (17), Zn (18), and Cu (19) in serum, and of Mn (20) in blood, were measured at 10–14-day intervals and remained within the normal range.[4]

After adaptation, sequential 6-day[5] experimental periods ensued during which the composition of the formula was systematically varied (Table II). Experiment "N1" (cases 1–3) involved seven experimental periods and lasted 43 days. During period I, patients received the complete formula. During period II, N was withdrawn. During periods III–VII, N was given in progressive increments, each representing 20% of the complete ration. Experiments "N2", "P", "Na", and "K" (cases 1, 4–11)[6] each involved three experimental periods and lasted 18 days; two such experiments were done during a 36-day course of hyperalimentation. During periods I and III, patients received the complete formula. During period II, N, P, Na, or K was withdrawn. Thus each course of hyperalimentation lasted 44–53 days, including 6 days of adaptation and nonexperimental blood transfusion days.

In some instances, the catheter was changed to the contralateral subclavian vein after 20–30 days. Throughout hyperalimentation, urine was collected in 24-h pools and stools in 6-day pools to coincide with each 6-day period. The colon was emptied at the end of each period by enema. Daily fecal elemental content was considered one-sixth of the fecal content for the corresponding 6-day period. Urine and stools were analyzed for N (21), P (14), Na (10), K (10), Cl (12), and Ca (13, 22). Daily elemental balances (N and P in grams; Na, K, Cl, and Ca in milliequivalents) during each period were calculated as: daily intake minus daily urine content plus average daily fecal content/kilogram ideal body wt.

On day 5 or 6 of periods I and II during experiments N2 and K, muscle tissue was obtained from gastrocnemius muscle by percutaneous needle biopsy (23). The tissue was lyophilized and analyzed for N (21) and K (10).

RESULTS

Each of the five types of experiment (N1, N2, P, Na, and K) was performed in three or four patients. Results for each experiment were, in general, qualitatively similar in different individuals and are summarized in Tables III and IV as means±SEM for 15–24 observations (5 or 6 days of observation in each period for each of three or four patients).[5]

The data of each experiment were examined for statistically significant effects by analysis of variance (24). To illustrate this analysis, the daily N balances for each subject during periods I and II of experiment N1 are shown in Table V. Analysis of variance of these data, given in the same table, showed that daily N balance of the three subjects during period II was significantly less ($P < 0.01$) than during period I. N balance did not vary significantly ($P > 0.05$) with respect to day of observation, nor was there significant interaction between period and day of observation.

The same type of analysis was applied to all elemental balance data in each experiment of Tables III and IV. Balances generally did not vary significantly ($P > 0.05$ in 43 of 54 comparisons) in relation to the day of observation, and interaction between period and day was usually not significant at the 0.05 level (40 of 54 tests of variance). In 49 of 54 analyses, however, balances during periods of incomplete hyperalimentation

[1] Furnishing 30 mg $FeSO_4$, 4 mg $CuSO_4$, 1 mg $MnSO_4$ (H_2O), 2 mg $ZnSO_4$, and 1 mg KI.

[2] In preliminary experiments, three patients received 500-ml blood transfusion on day 10 during 17 or more days of hyperalimentation with complete formula. Daily elemental balances were monitored during the entire course of hyperalimentation. Elemental balances during days 12–17 did not differ significantly ($P > 0.05$) from those during days 4–9, when compared by Student's t test.

[3] Furnishing ascorbic acid, 500 mg; vitamin A, 10,000 USP U; vitamin D, 1,000 USP U; thiamine, 50 mg; riboflavin, 10 mg; niacinamide, 100 mg; pyridoxine, 15 mg; dexpanthenol, 25 mg; and vitamin E, 5 IU.

[4] Fe, 50–180 μg/100 ml; Zn, 55–150 μg/100 ml; Cu, 70–155 μg/100 ml; Mn, 0.08–0.26 μg/100 ml.

[5] In four experiments involving withdrawal of P or K, period II was shortened to 5 days because of symptomatic hypophosphatemia or hypokalemia.

[6] Case 1 was studied twice on two separate admissions.

formula differed with $P < 0.05$ from the balances during period I (complete formula) of the same experiment. P values for these comparisons, calculated by analysis of variance (24) as shown in Table V, are given in Tables II and IV.

Experiment N1 (Table III). (*a*) While patients were on complete formula (period I), they gained weight at an average rate of 9.6 g/day/kg ideal body wt. All elemental balances were positive, and showed average ratios ΔN/ΔP/ΔK/ΔNa/ΔCl/ΔCa = 1.0/0.08/3.0/3.9/2.5/1.2. (*b*) When N was withdrawn, weight gain declined to 4.1 g/kg ideal body wt/day. Balances of N, P, and K became negative; these of Na and Cl approached zero. Ca balance remained unchanged. (*c*) Reintroduction of N in increments caused progressive correction of the changes observed under (*b*). Each addition of N caused an increment in ΔN, which was associated with simultaneous increments of ΔP, ΔK, ΔNa, and ΔCl in approximately the same ratios as observed under (*a*).

Experiment N2 (Table IV). During control period I, weight gain averaged 8.0 g/kg ideal body wt/day. Elemental balances were positive in ratios ΔN/ΔP/ΔK/ΔNa/ΔCl/ΔCa = 1/0.09/2.9/3.2/2.8/0.71. Removal of N caused negative balances of N, P, and K. ΔNa and ΔCl declined close to 0. ΔBody wt fell to 1.4 g/kg ideal body wt/day. Return of N in complete daily ration to the hyperalimentation fluid restored positive elemental balances and weight gain to the values of period I.

The concentration of N in gastrocnemius muscle on day 6 of N withdrawal did not differ from that on day 6 of period I (Table VI).

Experiment P (Table IV). During complete formula feeding (period I), the rate of weight gain and positive elemental balances resembled corresponding values in experiments N1 and N2. Withdrawal of P caused negative balances of N, P, K, and Ca. Balances of Na and Cl fell to zero, and the rate of weight gain declined by 70%.

During this period serum P diminished from 4.2±0.9 mg/100 ml (mean±SEM, $n = 4$) to 2.4±0.5 on day 5–6 and patients complained of fatigue and restlessness. The return of P to the infusate corrected hypophosphatemia, restored positive balances for N, P, K, Ca, Na, and Cl, and accelerated weight gain.

Experiment K (Table IV). Elemental balances and rates of weight gain during period I were similar to those in the experiments described above. Withdrawal of K caused negative balances of N, P, and K. The rate of weight gain was halved. Balances of Na, Cl, and Ca remained unchanged. Serum K concentration fell from 4.6±0.3 meq/liter (mean±SEM, $n = 4$) to 2.5±0.2 on day 5–6 and patients complained of malaise. Positive balances of N, P, and K and a sense of well-being were restored within 24 h by returning K to the hyperalimentation fluid; weight gain accelerated to an average of 11.1 g/kg ideal body wt/day.

On day 5 or 6 of K withdrawal, K concentration in gastrocnemius muscle was 12% less than that on day 6 of period I (Table VI) ($P < 0.02$).

Experiment Na (Table IV). During period I, weight gain and positive elemental balances in the usual ratios prevailed. Withdrawal of Na virtually halted weight gain. Balances of N, P, and K remained positive, but at levels about one-third those during period I. Ca balance declined to zero; balances of Na and Cl became negative. Markedly positive balances for all six elements and restoration of weight gain followed within 24 h after Na was returned to the hyperalimentation fluid.

DISCUSSION

The data show that during hyperalimentation of underweight adults, elements are retained not independently of each other, but rather in certain groups and within these groups in characteristic ratios.

Undernourished adults receiving complete formula retained N, P, K, Na, and Cl in ratios 1/0.08/3.1/3.5/2.7. The patients retained between 30 and 40% (average 35%) of N provided by complete formula, in agreement with earlier observations by Filler, Eraklis, Rubin, and Das (25) and by Peden and Karpel (26). When N was withdrawn, retention of four other elements (P, K, Na, Cl) virtually halted. As N was reintroduced in increments, the five elements were retained in progressively increasing amounts, but at all levels of N intake the five balances adhered to a fixed ratio of 1/0.08/3.1/3.5/2.7. Only ΔCa remained essentially unchanged as ΔN was varied, averaging 0.11 meq/kg ideal body wt/day regardless of N intake.

The constancy of the observed ratios of ΔN, ΔP, ΔK, ΔNa, and ΔCl during infusion of complete formula can be explained as follows. Retained P is deposited either in bone, where the ratio P/Ca (grams/milliequivalents) is normally 0.009, or in protoplasm where the ratio P/N (grams/gram) is normally 0.07. Since ΔCa/ΔN (milliequivalents/gram) averaged 0.7, it can be calculated that approximately 90% of retained P was deposited in protoplasm and 10% in bone. Accordingly, the ratios of ΔN/ΔP/ΔK (1/0.08/3.1) observed during hyperalimentation are consistent with utilization of the retained amounts of these three elements largely to form protoplasm, where N/P/K ratio is normally about 1/0.07/3 (references 2 and 3). The observed ratios of ΔNa/ΔCl (3.5/2.7) approximate those in normal extracellular fluid. Constancy of ratios of balances of the two extracellular elements (Na, Cl) to those of the three protoplasmic elements (N, P, K) at all levels of N intake shows that during repletion of undernourished subjects, expansion of extracellular fluid took place in constant

TABLE IV
Results of Experiments

Expt	Cases	Period	Glucose	Daily intake N	P	K	Na	Cl	Mg	Ca	Daily balance ΔN	ΔP	ΔK	ΔNa	ΔCl	ΔCa
				g	*g*	*meq*	*meq*	*meq*	*meq*	*meq*	*g*	*g*	*meq*	*meq*	*meq*	*meq*
N2	4	I	15	0.40	0.018	2.40	3.00	2.30	0.5	0.45	0.14 ±0.01	0.012 ±0.002	0.40 ±0.06	0.45 ±0.03	0.39 ±0.03	0.10 ±0.02
		II	15	0	0.018	2.40	3.00	2.30	0.5	0.45	−0.07* ±0.009	−0.004‡ ±0.003	−0.18§ ±0.02	0.02‡ ±0.004	0.02* ±0.002	0.12‡ ±0.0
		III	15	0.40	0.018	2.40	3.00	2.30	0.5	0.45	0.16 ±0.02	0.013 ±0.002	0.42 ±0.03	0.46 ±0.03	0.40 ±0.006	0.10 ±0.02
P	3	I	15	0.40	0.018	2.40	3.00	2.30	0.5	0.45	0.12 ±0.02	0.014 ±0.003	0.41 ±0.04	0.38 ±0.05	0.34 ±0.02	0.115 ±0.01
		II	15	0.40	0	2.40	3.00	2.30	0.5	0.45	−0.03‡ ±0.002	−0.002* ±0.0004	−0.08‡ ±0.01	0.02* ±0.001	0.01§ ±0.003	−0.0005* ±0.01
		III	15	0.40	0.018	2.40	3.00	2.30	0.5	0.45	0.15 ±0.01	0.014 ±0.002	0.46 ±0.03	0.48 ±0.03	0.45 ±0.02	0.12 ±0.03
K	4	I	15	0.40	0.018	2.40	3.00	2.30	0.5	0.45	0.12 ±0.01	0.009 ±0.001	0.34 ±0.02	0.40 ±0.03	0.30 ±0.02	0.095 ±0.01
		II	15	0.40	0.018	0	3.00	2.30	0.5	0.45	−0.10* ±0.02	−0.08§ ±0.007	−0.40‡ ±0.02	0.40§ ±0.05	0.36§ ±0.02	0.0095* ±0.02
		III	15	0.40	0.018	2.40	3.00	2.30	0.5	0.45	0.16 ±0.03	0.014 ±0.002	0.70 ±0.09	0.51 ±0.05	0.47 ±0.05	0.12 ±0.02
Na	4	I	15	0.40	0.018	2.40	3.00	2.30	0.5	0.45	0.13 ±0.02	0.010 ±0.001	0.39 ±0.02	0.46 ±0.04	0.37 ±0.04	0.11 ±0.01
		II	15	0.40	0.018	2.40	0.2	2.30	0.5	0.45	0.04§ ±0.006	0.003§ ±0.0005	0.09‡ ±0.01	−0.60§ ±0.07	−0.40* ±0.03	0.001‡ ±0.01
		III	15	0.40	0.018	2.40	3.00	2.30	0.5	0.45	0.16 ±0.03	0.011 ±0.002	0.46 ±0.05	0.50 ±0.04	0.39 ±0.95	0.12 ±0.02

Values, expressed/kilogram ideal body wt, represent mean ±SEM, n = 15–24 (5–6 days of observation in each period for each of three or four patients). Δ values during period II which differ significantly from corresponding Δ values during period I by analysis of variance (24) are identified thus: * $P < 0.005$; ‡ $P < 0.01$; § $P < 0.05$.

‖ See footnote to "analysis of Δbody wt" in Table III.

proportion to formation of protoplasm, in an average ratio of 0.8 g extracellular fluid/1.0 g protoplasm.[7] In contrast, independence of ΔCa from ΔNa, ΔCl, ΔN, ΔP, and ΔK, as N intake varied from 0 to 0.4 g/kg ideal body wt/day, suggests that deposition of bone mineral is not coupled to repletion of extracellular fluid and protoplasm.

Withdrawal of P, K, or Na, like that of N, had wide-

[7] The ratios of N/P/Na/K/Cl in nonskeletal lean body mass of adult man average 1/0.06/1.2/3.0/0.72; in the newborn, these values average 1/0.07/2.9/2.8/2.1 (2). Similar differences apply to elemental contents of adult and infant muscle. These differences reflect the higher ratio of extracellular fluid/protoplasm in both the whole body and in the soft tissues of newborns, as compared to adults (2, 27–29). ΔN/ΔP/ΔNa/ΔK/ΔCl in our wasted adult patients receiving complete hyperalimentation fluid (Tables III and IV) closely resemble these ratios in the soft tissues of the human newborn. Thus, extracellular fluid and protoplasm were formed during repletion of these undernourished adults in the same proportion as they exist in the nonskeletal lean body mass at birth rather than in adulthood.

Ratios of positive balances (relative to ΔN = 1)						Daily change in mass					Analysis of Δbody wt‖ (Δ each component as %Δbody wt)			
ΔN	ΔP	ΔK	ΔNa	ΔCl	ΔCa	ΔBody wt	ΔProto-plasm	ΔExtra-cellular fluid	ΔBone	ΔAdi-pose tissue	Proto-plasm	Extra-cellular fluid	Bone	Adi-pose tissue
g	*g*	*meq*	*meq*	*meq*	*meq*	*g*	*g*	*g*	*g*	*g*	%	%	%	%
	0.09	2.9	3.2	2.8	0.71	8.0	±3.78	+3.74	+0.010	0.34				
1											47	47	0	4
	±0.004	±0.17	±0.16	±0.15	±0.10	±1.0	±0.27	±0.29	±0.002	±0.20				
						1.4‡	−1.89§	+0.19*	+0.012	3.02§				
											−135	14	1	216
						±0.2	±0.24	±0.02	±0.0	±0.79				
	0.08	2.6	2.9	2.5	0.65	10.1	+4.32	+3.84	+0.010	+2.04				
1											43	38	0	20
	±0.003	±0.14	±0.20	±0.13	±0.08	±1.6	±0.54	±0.06	±0.002	±0.47				
	0.12	3.4	3.2	2.8	0.96	8.5	+3.24	+3.26	+0.0115	1.41				
1											38	38	0	17
	±0.010	±0.20	±0.17	±0.13	±0.13	±0.7	±0.54	±0.19	±0.001	±0.42				
						3.0‡	−0.81*	+0.10‡	−0.00005*	3.70‡				
											−27	3	0	123
						±0.5	±0.05	±0.03	±0.001	±0.5				
	0.09	3.0	3.2	3.0	0.80	9.8	+4.05	+4.32	+0.012	1.06				
1											41	44	0	11
	±0.004	±0.15	±0.19	±0.20	±0.10	±1.1	±0.27	±0.19	±0.003	±0.35				
	0.075	2.9	3.3	2.5	0.79	7.9	+3.24	+2.88	+0.0095	1.68				
1											41	36	0	21
	±0.004	±0.20	±0.20	±0.14	±0.15	±1.4	±0.27	±0.19	±0.001	±0.33				
						3.1§	−2.70*	+3.46	+0.00095	+3.24‡				
1											−87	112	0	104
						±0.5	±0.54	±0.19	±0.002	±0.51				
	0.09	4.4	3.2	2.9	0.75	11.1	+4.32	+4.51	+0.012	0.41				
1											39	41	0	4
	±0.005	±0.22	±0.19	±0.15	±0.17	±1.5	±0.81	±0.48	±0.002	±0.30				
	0.08	3.0	5.0	2.8	0.84	8.2	+3.51	+3.55	+0.011	0.88				
1											43	43	0	11
	±0.007	±0.17	±0.27	±0.21	±0.12	±0.9	±0.54	±0.38	±0.001	±0.30				
	0.075	2.2			0.025	1.8*	+1.08‡	−3.84*	+0.0001‡	4.69§				
											60	−213	0	260
	±0.005	±0.13			±0.004	±0.2	±0.16	±0.29	±0.001	±0.63				
	0.07	2.8	3.1	2.4	0.75	8.1	+4.32	+3.74	+0.012	−0.14				
1											53	46	0	−2
	±0.007	±0.12	±0.21	±0.16	±0.09	±0.7	±0.81	±0.48	±0.002	±0.05				

spread effects. In the absence of P, the patient was unable to retain any of the other five elements. In the absence of K, balances of N and P reverted towards zero, while retention of Na, Cl, and Ca continued unabated. Withdrawal of Na reduced balances of N, P, and K by two-thirds, halted retention of Ca, and caused negative balances of Na and Cl.

In qualitative terms, the above observations on elemental balances can be interpreted as follows: Withdrawal of N interrupts repletion of protoplasm and extracellular fluid; withdrawal of P or Na interrupts repletion of protoplasm, extracellular fluid, and bone; and withdrawal of K interrupts repletion of protoplasm.

For quantitative analysis of the increments in mass of protoplasm, extracellular fluid, bone, and adipose tissue which occurred during each hyperalimentation period, the equations of Reifenstein, Albright, and Wells (3) can be used:

$$\Delta\text{protoplasm (g)} = 27\ \Delta N\text{(g)}$$
$$\Delta\text{extracellular fluid (g)} = 9.6\ \Delta Cl\ \text{(meq)}$$
$$\Delta\text{bone (g)} = 0.1\ \Delta Ca\ \text{(meq)}$$

TABLE V

Daily N Balance during Periods I and II in Experiment N1; Analysis of Variance in the Data

	N balance, *g/day/kg ideal body wt*					
Day.....	1	2	3	4	5	6
Period I						
Patient 1	0.17	0.14	0.13	0.15	0.16	0.14
Patient 2	0.16	0.15	0.13	0.18	0.14	0.15
Patient 3	0.08	0.11	0.10	0.08	0.10	0.14
Period II						
Patient 1	−0.07	−0.06	−0.05	−0.07	−0.04	−0.03
Patient 2	−0.05	−0.06	−0.03	−0.02	−0.01	−0.04
Patient 3	−0.08	−0.04	−0.07	−0.09	−0.05	−0.08

	Analysis of variance		
Source of variation	Amount of variation	Degrees of freedom	Estimated variance
Between periods	0.32	1	0.32
Between days	0.0012	5	0.00023
Period × days (interaction)	0.0016	5	0.00033
* Within subjects	0.011	2	0.0056
* Period × subjects	0.0015	2	0.00075
* Days × subjects	0.0039	10	0.00039
* Period × days × subjects	0.0034	10	0.00034
Total	0.33	35	

F ratios and P values: Periods/Periods × subjects = 0.32/0.00075 = 414, $P < 0.01$; Days/Days × subjects = 0.00023/0.00039 = 0.60, $P > 0.05$; Interaction/Period × days × subjects = 0.00033/0.00034 = 0.98, $P > 0.05$.
* Error term.

Δadipose tissue (gram) = Δbody wt (gram) − Δprotoplasm (gram) − Δextracellular fluid (gram) − Δbone (gram) − 0.7 ΔK (milliequivalents) − 19 ΔN (gram).

These equations assume normal concentrations of N and K in protoplasm, of Cl in extracellular fluid, and of Ca in bone. The concentration of extracellular Cl was monitored in each experiment and remained in normal range. The concentration of N in muscle during N withdrawal did not differ detectably from that during complete formula (Table VI). In four subjects during K withdrawal, muscle K averaged 12% below that during complete formula infusion; a change of this magnitude in protoplasmic K concentration, however, would cause < 10% change in the calculated value of daily increment in adipose tissue during period II of experiment K, and would not influence calculated values of increments in protoplasm, extracellular fluid, and bone. Accordingly, we have applied the Reifenstein equations to the balance data in Tables III and IV. These calculations (last eight columns of Tables III and IV) suggest that during infusion of complete formula, weight gain consisted of 35–50% protoplasm, 35–50% extracellular fluid, 5–25% adipose tissue, and < 1% bone. Contrastingly, when N, Na, or P was not provided by the infusate, only adipose tissue appeared to increase in mass. When K was withheld, masses of adipose tissue and extracellular fluid increased at similar rates but a daily loss in protoplasm occurred.

Calculations of changes in body composition from elemental balance data are only first approximations. Nevertheless, these estimates suggest the following conclusions about the repletion process.

(*a*) Chemical analyses of blood-free muscle, brain, and visceral organs (2, 27–30) have shown that each parenchymal cell in soft tissues is associated with a complement of extracellular fluid. Evidently repletion of the undernourished adult involves formation of tissue units containing protoplasm and extracellular fluid in fixed proportion and with fixed elemental compositions, as revealed by the characteristic ratios of ΔN, ΔP, ΔK, ΔNa, and ΔCl during hyperalimentation. If either a protoplasmic or extracellular element is not supplied, the unit of protoplasm and associated extracellular fluid apparently cannot be formed.

(*b*) In contrast, extracellular fluid can be formed independently of protoplasm during intravenous hyperalimentation (see experiment K).

(*c*) Positive Ca balance, presumably indicating repletion of bone mineral, can occur independently of repletion of extracellular fluid and protoplasm, since withdrawal of N or K does not interfere with retention of Ca. Withdrawal of either P or Na, however, abolishes Ca retention. Bone contains Ca, P, and Na in a ratio of 110/1/3 (meq/g/meq). About one-third of body Na is located in bone (2). Evidently repletion of bone mineral in underweight subjects requires simultaneous provision of Ca, P, and Na but not of N or K.

(*d*) Enlargement of adipose tissue can occur independently of enlargement of the other three compartments since it continues in the absence of N, Na, K, or P. An abundant supply of glucose seems the only requirement in the present experiments. The simple

TABLE VI

Effect of Withdrawing N and K upon Concentrations of these Elements in Gastrocnemius Muscle

		Period I	Period II	P value, period II vs. period I
Experiment N2	{N	135±9	132±11	>0.05
	{K	403±14	416±17	>0.05
Experiment K	{N	140±14	130±9	>0.05
	{K	450±10	396±16	<0.02

Biopsy was done on day 5 or 6 of each period listed. Values represent grams N or milliequivalents K/kilogram dry muscle (mean ±SEM, $n = 4$).

nutritional basis for expansion of adipose mass is consistent with the low contents of N, Na, K, or P in adipocytes (31) and the predominant role of triglyceride (containing only C, H, and O) in the enlargement of these cells (32). 85% of the fluid's calories (average, 4,500 calories/day for present subjects) are furnished as glucose. When N, K, or P is withdrawn, infused glucose continues to be utilized completely, as shown by the absence of glycosuria. Under these conditions, however, a larger proportion of glucose appears to be directed towards lipogenesis and storage of resulting triglyceride in fat cells than during infusion of the complete formula (Tables III and IV).

The balance data in Tables III and IV have these practical implications:

(*a*) Previous investigators have encountered depletion of plasma P or K during hyperalimentation (5, 33, 34). In view of the constancy of ratios of elemental balances during infusion of complete formula (Tables III and IV), the following guidelines can be suggested which will prevent depletion of these or other elements in plasma of undernourished adults receiving hyperalimentation, and will at the same time avoid infusion of solutes in needless excess: Set N at 0.4 g/kg ideal body wt/day. Retention of N will average 35%. Then retentions of P, K, Na, Cl, and Ca will average 0.012 g, 0.43, 0.49, 0.37, and 0.085 meq/kg ideal body wt/day, respectively. If we allow + 50% for a margin of safety, recommended daily rations/kilograms ideal body wt/day are: N, 0.4 g; P, 0.018 g; K, 0.65 meq; Na, 0.74 meq; Cl, 0.56 meq; and Ca, 0.128 meq. It must be emphasized, however, that these estimates will need to be revised upwards in patients with extrarenal losses of body fluid (diarrhea, vomiting, gastric suction, fistula) or with a hypermetabolic state (infection, trauma, fever).

(*b*) Certain types of incomplete formula lead to weight gain that consists largely of adipose tissue. Therefore weight gain may be a misleading measure of the effectiveness of hyperalimentation in some patients (35–37).

(*c*) Hyperalimentation of our starved adults with fluid lacking N or P failed to produce positive balance of K, Na, or Cl. Parenteral fluids in general clinical use contain glucose, Na, K, and Cl, but only rarely N and P. The present data suggest that the addition of N and P to conventional parenteral fluids may improve balances of Na, K, and Cl in patients unable to take nourishment by mouth.

ACKNOWLEDGMENTS

This work was supported by U. S. Public Health Service grant RR 39.

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