Refer to: Kerndt PR, Naughton JL, Driscoll CE, et al: Fasting: The history, pathophysiology and complications (Medical Progress). West J Med 1982 Nov; 137:379-399

Medical Progress

Fasting: The History, Pathophysiology and Complications

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An appreciation of the physiology of fasting is essential to the understanding of therapeutic dietary interventions and the effect of food deprivation in various diseases. The practice of prolonged fasting for political or religious purposes is increasing, and a physician is likely to encounter such circumstances. Early in fasting weight loss is rapid, averaging 0.9 kg per day during the first week and slowing to 0.3 kg per day by the third week; early rapid weight loss is primarily due to negative sodium balance. Metabolically, early fasting is characterized by a high rate of gluconeogenesis with amino acids as the primary substrates. As fasting continues, progressive ketosis develops due to the mobilization and oxidation of fatty acids. As ketone levels rise they replace glucose as the primary energy source in the central nervous system, thereby decreasing the need for gluconeogenesis and sparing protein catabolism. Several hormonal changes occur during fasting, including a fall in insulin and T_3 levels and a rise in glucagon and reverse T_3 levels. Most studies of fasting have used obese persons and results may not always apply to lean persons. Medical complications seen in fasting include gout and urate nephrolithiasis, postural hypotension and cardiac arrhythmias.

WE REVIEW IN THIS PAPER the current understanding of the pathophysiology of fasting and starvation. Although fasting implies an intentional abstention from food, the physiologic adaptive mechanisms (not necessarily psychologic) that come into play during this type of food deprivation are similar to starvation. These terms will be used synonymously, therefore, except when important differences are known to exist.

An appreciation of the physiology of fasting is essential for understanding many kinds of therapeutic dietary manipulations. Critical evaluation of protein-sparing diets, ketogenic diets or other hypocaloric mixed-diet regimens requires a knowledge of the response to acaloric fasting. Because many illnesses result in food deprivation, physicians should understand the usual physical and metabolic consequences of starvation; an illustra-

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This project was funded in part by a student assistantship of the predoctoral training grant in Family Medicine (#5D15 PE98002-01 STC) from the United States Department of Health, Education, and Welfare, Public Health Service, Health Resources Administration, Bureau of Health Manpower.

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ABBREVIATIONS USED IN TEXT

FSH = follicle-stimulating hormone
T_3 = triiodothyronine
T_4 = thyroxine
TSH = thyroid-stimulating hormone

tive case that was monitored according to a study protocol is presented. The effects of fasting are reviewed in association with the individual effects observed in the case.

A study protocol was designed to monitor a fasting person and was submitted to and approved by the Human Experimentation Committee of the University of Iowa College of Medicine, Iowa City, Iowa.

A Brief History of Fasting

Since early times, fasting has been advocated for spiritual development and promotion of health. Fasting as a religious practice developed independently among different people and religions worldwide.[1] In ancient Greece the belief that taking food risked entry of demonic forces contributed to the popularity of fasting. Fasting was required in preparation for many rituals that sought contact with supernatural forces.[2] Great importance was placed on fasting as a means of arousing ecstatic forces, dreams or visions. Pythagoras, Abaris and Epimenides in ancient Greece extolled the virtues of fasting, and in biblical times Moses, Elias and John the Baptist recognized its religious value.[1] During the holy month of Ramadan, Moslems abstain from all food and drink between dawn and dusk.[3]

In the Old Testament fasting was regarded as a powerful prayer that could prepare a prophet for divine revelations (Daniel 10:2-14). Although Christ fasted for 40 days in the desert (Luke 4: 1-2; Matthew 4:2-3), he left no definite law on the subject except to insist that it be done humbly and privately (Matthew 6:16-18). With time, customary observances of fasting developed in local Christian churches partly in an effort to replace early pagan and Jewish fasting customs. Fasting in the monastic tradition flourished in the fourth and fifth centuries, the dominant motive being asceticism guided by a spirit of penance and self-humiliation as a monk sought communion with his God.[1] The motive for the case reported in this paper was consistent with the monastic tradition and was a prayerful penitential response to modern-day social injustice.

Historically, fasting for health has been advocated by many.[4,5] In the mid-1800's, E. H. Dewey, MD, in his book *The True Science of Living,* wrote, "every disease that afflicts mankind [develops from] more or less habitual eating in excess of the supply of gastric juices." His "miraculously cured" patient and later publisher, Charles Haskell, did much to promote the fasting cure.[4] Upton Sinclair, better known for other literary works, wrote extensively on the health benefits of fasting.[5]

Notable nonobese persons who engaged in prolonged fasting and whose experiences were recorded in the early medical literature include Tanner who reportedly fasted for 40 days in 1880.[6,7] Alexander Jacques, a Frenchman, fasted for 30 days in 1887 and for 40 and again 30 days in 1888.[7] Signor Succi, an Italian professional faster, claimed to have completed at least 32 fasts of 20 days or more[8]; his longest recorded fasts were 40 and 45 days in 1890.[9] In 1905 a physician, F. Penny, MD, prompted by the claims of Dewey, fasted for 30 days and recorded simple observations on himself.[10] Observations during fasts in nonobese persons are less extensively recorded in the modern medical literature. Benedict's classic study in 1912 of Mr. L, who fasted for 31 days, included detailed physical and metabolic measurements.[9] In 1946 Bernard came under medical observations on the 40th day of a purported 45-day fast.[11] About the same time, Gamble's classic life-raft studies, wherein volunteers were subjected to food and water deprivation under conditions simulating being lost at sea, did much to elucidate the essential water requirements and protein-sparing effect of carbohydrate.[12] In the early 1950's Ancel Keys and co-workers[13] at the University of Minnesota compiled extensive data on 32 volunteers who underwent eight months of semistarvation.

Fasting as a therapy for obesity has long been advocated. Folin and Denis in 1915[14] recommended repeated short periods of starvation as a safe and effective method of weight reduction. In modern times Bloom,[15] Duncan and associates[16] and Drenick and colleagues[17] advocated prolonged fasts for weight reduction in morbid obesity. Drenick and colleagues[17] placed obese persons on fasting regimens of up to 117 days, whereas Thomson and co-workers[18] monitored fasts of 139, 236 and 249 days. The longest recorded fast was that of a 27-year-old obese man who fasted 382 days and lost 125 kg (276 lb).[19] Since the late 1950's many of the data on the metabolism of

fasting come from studies carried out on obese persons willing to fast for weight reduction.

Fasting for the treatment of convulsive disorders was used in France by Guelpa and Marie in 1910 (as cited by Keith[20]) and later investigated here by Geyelin in 1921.[21] Changes in the acid-base balance were originally thought to be responsible for the anticonvulsant effect until Wilder in 1921 (also cited by Keith[20]) suggested a role for starvation-induced ketone bodies. Since that time, ketogenic diets have been used successfully in the management of seizure disorders refractory to conventional drug regimens.[22]

Fasting has often been used as a means of political protest. Gandhi fasted for political reasons on at least 14 occasions, 3 times for as long as 21 days.[23] One of the longest recorded political fasts in a nonobese person was by Terence MacSwiney, a former mayor of Cork, who fasted for 74 days to his death after his arrest during English-Irish unrest in 1920.[24] Joseph Murphy, less well known but also a member of the Irish Volunteers, died on the same day as MacSwiney after 76 days of a hunger strike.[24] The hunger strike as a means of political persuasion is being used still in Ireland: To date ten members of the Irish Republican Army have fasted from 45 to 61 days to their death in the now-infamous H block of the Maze prison in Belfast, Northern Ireland.[25]

Study Protocol

A complete physical examination, including an electrocardiogram and a roentgenogram of the chest, was carried out before the fast. Laboratory determinations that were also done included serum potassium, chloride, calcium, phosphorus, uric acid, creatinine, total protein, albumin, globulin, triglycerides, total lipids, total bilirubin, direct bilirubin, aspartate aminotransferase (glutamic-oxaloacetic transaminase), alanine aminotransferase (glutamic-pyruvic transaminase), alkaline phosphatase, lactic dehydrogenase, thyroxine, iron, blood urea nitrogen, glucose and a complete blood count, including a differential cell count, using standard methods at METPATH, Teterboro, New Jersey.* Insulin, glucagon, growth hormone and plasma amino acid levels were measured using methods reported elsewhere.[26-29] Follicle-stimulating hormone and luteinizing hormone levels were measured using standard radioimmunoassay techniques. Zinc concentration was measured using a Perkin-Elmer atomic spectrometer. A urine specimen was collected for measurement of total volume and pH, qualitative determination of ketones, protein, blood, bilirubin and glucose, and quantitative determinations using standard methods for sodium, potassium, chloride, calcium, phosphorus, magnesium, urea, ammonia, creatinine, uric acid and total nitrogen.

Fluid intake (water only) was initially two liters a day for the first three weeks, then decreased to and maintained at a liter per day during the final week of the fast. A total intake of 60 calories from daily communion was recorded during the fast. The subject was ambulatory throughout the fasting period and was weighed daily on arising and after voiding. Pulse rate and blood pressure were determined twice a day. Electrocardiograms were obtained weekly. Complete physical examinations were done weekly for the first three weeks, followed by daily physician visits (provided by James Pearson, MD, Dubuque, Iowa) in the last ten days of the fast. Medical consultation was available by telephone at any time or by a physician visit within 20 minutes. All laboratory tests were repeated weekly except a dipstick urine analysis, which was done daily.

Case Report and Review of the Literature

A 41-year-old nonobese man, a member of a cloistered religious community, chose to undergo a 40-day acaloric fast. He requested that his fast be supervised medically to minimize any risk to his health. Monitoring was to be carried out within the confines of the monastic enclosure without undue distraction from the intent of the fast while maintaining strict anonymity for himself and his religious community. After all risks including the possibility of sudden death were discussed, a form releasing us from legal liability was signed. Furthermore, it was agreed that the fast could be terminated at any time either by him or upon medical recommendation. The past medical history was significant for occasional benign ventricular premature contractions and iron deficiency anemia. His usual diet had been ovolactovegetarian (that is, vegetables, eggs and milk products) for the preceding 24 years.

Control Data

On physical examination before commencement of the fast the man weighed 68.6 kg, was 172 cm tall and appeared in no acute distress. His skin

*Drs. L. J. Filer, L. D. Stegink, R. Thompson and D. E. Van Orden at the University of Iowa made available the use of their laboratory facilities and personnel for preparing many of the determinations for this study.

TABLE 1.—*Mean Blood Pressure and Pulse Changes in the Upright and Supine Positions at Weekly Intervals in the Fasting and Realimentation Periods*

Day of Study	Supine		Upright	
	Mean Blood Pressure (torr)	Mean Pulse Rate (beats/min)	Mean Blood Pressure (torr)	Mean Pulse Rate (beats/min)
Fasting Period				
1-7	110/66 (128-96)/(82-58)*	55 (60-48)	107/75 (124-92)/(92-64)	73 (90-64)
8-14 ...	108/64 (112-98)/(76-58)	54 (60-50)	90/65 (96-86)/(72-58)	88 (106-70)
15-21 ...	104/62 (110-98)/(66-60)	55 (60-50)	80/54 (92-72)/(58-46)	82 (96-68)
22-28 ...	100/61 (114-92)/(72-52)	57 (60-54)	72/54 (84-64)/(62-50)	86 (90-78)
29-36†...	92/53 (98-88)/(60-46)	56 (58-54)	70/51 (76-64)/(58-46)	83 (92-78)
Postfast Period				
1-7	100/59 (112-88)/(80-60)	60 (66-56)	70/53 (78-62)/(62-42)	96 (112-80)

*Range included in parentheses.
†Mean calculated on the basis of an 8-day period.

was clear and the head, eyes, ears, nose and throat showed no abnormalities. Examination of the chest showed a mild pectus excavatum and the lungs were clear to auscultation and percussion. On cardiac examination there were normally split first and second heart sounds with a grade 2/6 systolic ejection murmur present along the left sternal border without radiation or change with the Valsalva maneuver or position. The abdomen was soft, nontender and without evidence of hepatosplenomegaly. Prostatic enlargement was noted on examination of the rectum. Guaiac test of a stool specimen was negative for occult blood. No clubbing, cyanosis or edema was present in the extremities. Peripheral pulses were normal. There was no lymphadenopathy. On neurologic examination there were no abnormalities found.

An electrocardiogram showed sinus bradycardia with a rate of 45 to 50 beats per minute and an incomplete right bundle branch block. A treadmill exercise stress test done 16 months earlier showed no abnormalities at 100 percent of maximal predicted heart rate. An x-ray film of the chest showed only the small pectus excavatum deformity.

Physical Adaptations to Fasting

The subject fasted for 36 days until profound weakness and symptoms of postural hypotension interfered with his daily activities in the monastery.

Weight Loss

He lost 15.7 kg or 22.9 percent of his initial body weight after 36 days of acaloric fasting. Weight loss continued through the first two days of realimentation, resulting in a total weight loss of 16.6 kg or 24.2 percent of initial body weight. The rate of weight loss was initially 0.9 kg per day for the first five days, then it gradually decreased over the next two weeks and became stable at 0.3 kg per day after the third week.

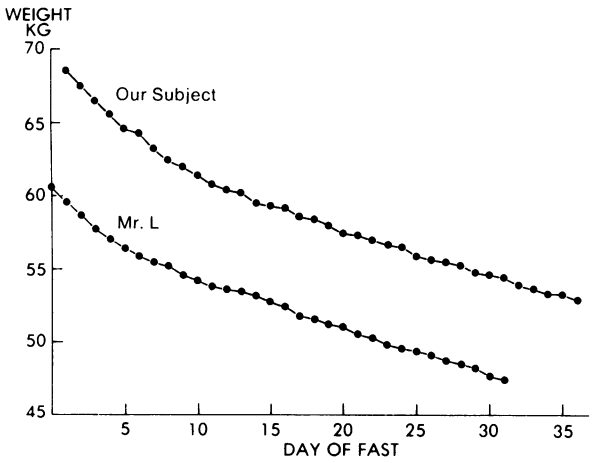

Figure 1.—Rate of weight loss during total fasting in our subject and Mr. L, studied by Benedict in 1912.[9]

The total weight loss and the rate of loss compare favorably with those reported elsewhere: In the initial fasting period (one to five days), weight loss occurs at the rate of 1 to 2 kg per day followed by a gradual decline through the third week, thereafter averaging 0.3 kg per day.[30] In Benedict's study,[9] Mr. L lost 13.25 kg or 21.9 percent of initial body weight after 31 days of fasting. This compares with a 14.2-kg loss or 20.7 percent of initial body weight after the same time in our subject (Figure 1).

Pulse Rate

Our subject's pulse rate did not decrease significantly during fasting (Table 1). This may reflect the presence of bradycardia in this well-conditioned man before onset of fasting. Slowing of pulse rate during prolonged periods of de-

creased caloric intake is otherwise well documented.[9,13,31,32] Benedict[9] reported that the pulse rate reached a minimum during the second to third week of total fasting and then increased in the fourth week. In another study[13] of 32 volunteers on semistarvation diets for 32 weeks who had an average weight loss of 16 percent, the pulse rates steadily declined, reaching a mean of 35.3 beats per minute at 13 weeks; however, after an additional ten weeks of caloric restriction and another 10 percent reduction in body weight, the pulse rates rose slightly but significantly to a mean of 37.3 beats per minute. In the studies by Jewish physicians during the siege of the Warsaw ghetto in World War II, bradycardia was seen in adults and children in all stages of starvation.[33]

Blood Pressure

In our study the mean blood pressure calculated for weekly intervals fell from 110/66 mm of mercury during the first week to 92/53 mm of mercury during the last eight days of the fasting period (Table 1). Blood pressure increased significantly toward prefast values in the realimentation period. Pronounced orthostatic hypotension occurred by the second week and persisted throughout the fasting period. The subject became symptomatic after several days and was nearly incapacitated by the postural hypotension after 33 days, requiring 20 to 30 minutes to go from the supine to the upright position on rising in the morning. Subjectively, the postural symptoms improved as the day progressed. There were no syncopal episodes during the fasting or realimentation periods.

A fall in blood pressure is a consistent observation during fasting and semistarvation states.[9,13,33,34] The development of symptomatic orthostatic hypotension during fasting is not predictable but seems to depend on the individual person, the duration and the type of fast. Drenick and colleagues[17] noted incapacitating postural hypotension in 3 of 11 obese persons after 25, 60 and 62 days of fasting. More recently, seven obese patients placed on a regimen of 400 kcal of protein per day and later 400 kcal of a mixed diet (50 percent protein, 50 percent carbohydrate) per day were followed for periods of 3 to 5½ weeks.[35] While on the protein diet, the systolic blood pressure fell 28 ± 3 mm of mercury versus 18 ± 3 mm of mercury on the mixed diet. Symptoms of orthostatic hypotension developed in all patients while on the protein diet and in only one while on the mixed diet. Along with raised serum ketone levels and increased salt excretion, plasma levels of norepinephrine were reduced in the basal state and after two minutes of standing in persons receiving the pure protein diet but not with the mixed diet regimen. The mechanism of the different effects of pure protein versus mixed diets on the sympathetic nervous system is not yet fully understood.

In another study using animals, an association between fasting and overfeeding with sucrose and rates of norepinephrine turnover was found.[36] A significant reduction in norepinephrine turnover was seen in food-deprived rats versus an increased turnover in rats overfed with sucrose. Should a similar mechanism exist in man, an essential role for dietary carbohydrate in the maintenance of sympathetic nervous system function could be postulated.

Electrocardiograms

On our subject's electrocardiograms, shifts to the right of the QRS (30 degrees to 60 degrees) and to a lesser extent T-wave axis (50 degrees to 60 degrees) occurred. A decrease in amplitude from 6 to 3 mm was seen in the QRS complex only in lead I.

Changes in the electrocardiogram during fasting and semistarvation are well known.[13,31,34,37,38] Changes most frequently reported include sinus bradycardia, decreased QRS complex and T-wave amplitude, and shifts to the right of the QRS and T-wave axes. In the Minnesota semistarvation study,[13] a decrease in the amplitude of all deflections (P wave, QRS complex and T wave) occurred with a shift to the right of the QRS and T-wave axes; though the QT interval and duration of mechanical systole increased, the PR and QRS intervals and the duration of the P wave did not change. In case reports of World War II prisoners suffering from severe malnutrition, reversible electrocardiographic abnormalities including pronounced prolongation of the QT interval, to a lesser extent lengthening of the PR and QRS intervals, depression of the ST segment and changes in the T wave were noted.[37] Similarly, prolongation of the QT interval and abnormal ST segment and T wave are consistent findings in patients with anorexia nervosa.[39]

The mechanism underlying these electrocardiographic changes is unknown. Atrophy of cardiac muscle has been observed in starvation.[37,38] and

many of these electrocardiographic changes may reflect decreased cardiac mass.

Natriuresis

The early high rate of weight loss in our subject cannot be explained on the basis of energy expenditure alone. If the initial 0.9 kg per day weight loss observed were to reflect loss of body fat, carbohydrate and protein, it would require an energy expenditure of 3,150 calories per day. This is far in excess of the basal energy expenditure[40] of 1,673 calories per day predicted for this man in the early fasting period. It is now well established that early accelerated weight loss during fasting is the result of salt and water diuresis.[41-43]

Because no attempt was made to equilibrate salt intake in the prefast period in our study, urinary sodium levels (as well as other electrolyte and mineral determinations) on day 1 reflect the previous unmeasured dietary intake. However, cumulative sodium loss was estimated at 325 mEq over the first seven days and the peak net urinary sodium loss was 68 mEq in one day and occurred on day 3. The sodium loss corresponded to an 0.9 kg per day weight loss and 0.9 liter negative fluid balance (insensible losses not included). Urinary chloride loss followed a similar pattern but was quantitatively less than sodium loss. Cumulative urinary sodium losses in the first week of fasting in our subject were comparable to those observed by others (200 to 350 mEq), but the peak sodium loss of 73 mEq on day 3 was somewhat less than the 100 to 150 mEq peak losses reported elsewhere to occur on fasting days 3 or 4.[30]

Numerous explanations have been offered for the early natriuresis during fasting including changes in renal tubule sodium-transport systems, glomerular filtration rate, aldosterone secretion, ketoacidosis or an osmotically induced diuresis.[30] All fail to explain this phenomenon entirely. It now appears that this natriuresis is, in large part, the result of obligatory sodium loss due to the generation and high early excretion of ketone bodies.[42,43] As liver glycogen stores are depleted and body energy requirements are met by mobilization of fat stores, serum and urinary levels of metabolically generated anions in the form of ketones increase. Excretion of these anions requires an accompanying cation that initially is sodium. Ammonium production increases under the stimulus of metabolic acidosis (ketoacidosis) and ammonium replaces sodium as the major

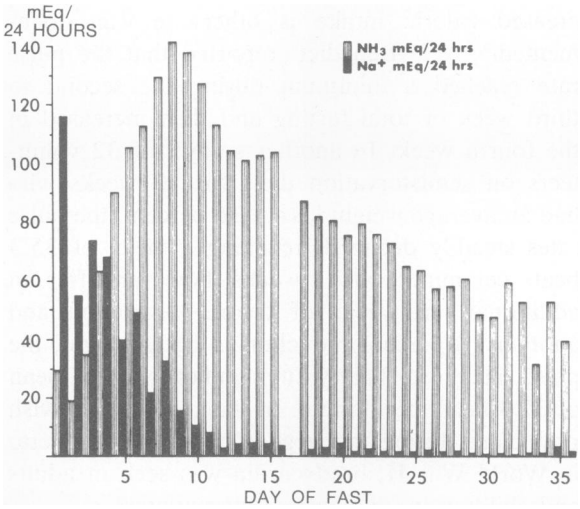

Figure 2.—Urinary sodium (Na^+) and ammonia (NH_3) losses during the fasting period.

urinary cation. During the period when urinary excretion of ammonium is lagging behind ketone excretion, peak rates of sodium excretion are observed (and maximum weight loss occurs).[42-44] This pattern was seen in our subject: urinary ammonia excretion increased through day 9 as sodium excretion gradually declined (Figure 2).

Hormonal mechanisms have also been implicated in the natriuresis of early fasting. Glucagon levels rise during this period; experimentally, infusions of physiologic doses of glucagon in nonfasting subjects induce a similar natriuresis[45] while administration of insulin can cause renal sodium retention.[46] Therefore, the rising glucagon and the falling insulin levels during the early phase of fasting may both contribute to sodium excretion.

Carbohydrate refeeding after fasting (though the diet may still be hypocaloric) produces an abrupt weight gain with an immediate reversal of urinary salt and water loss.[12,47-49] At times the sodium retention is profound, resulting in frank edema formation. Isocaloric refeeding with fat does not result in sodium retention whereas refeeding with protein produces a delayed but significant antinatriuresis.[48] The mechanism of sodium retention with carbohydrate realimentation is not well understood. Rising insulin and falling glucagon levels may be involved but are unlikely to account for frank edema formation. The aldosterone level is not consistently raised and usually falls with realimentation.[50] A reversal of this pattern of urinary excretion of solutes, namely persistent secretion of ammonium after suppression

of ketonuria by carbohydrate realimentation, could also contribute to sodium retention.

Metabolic Adaptation of Fasting

Fuel Stores

The composition of total body fuel stores in humans is well understood (Table 2). In fasting states liver glycogen is depleted in the first 18 to 24 hours.[30] Protein, which has essential enzymatic, structural and mechanical functions, constitutes 15 percent of total body energy stores.[51] Because of these essential functions, the breakdown of a third to a half of the body protein stores is believed incompatible with life.[52] Muscle, another site of glycogen stores, lacks glucose-6-phosphatase and therefore cannot release glucose directly into the bloodstream.[53] Fat in the form of triglycerides in adipose tissue provides the largest and most efficient storage of body energy and constitutes 85 percent of all potentially available calories.[51] In a 70-kg person basal caloric requirements could be met solely from fat stores for two to three months in the absence of any caloric intake.[51,53,54]

Glucose Homeostasis

In our subject blood glucose levels fell early during fasting and remained low throughout the fasting period. Insulin levels became appropriately reduced as glucagon increased significantly (Table 3).

The transition from the fed state through brief fasting and into prolonged starvation is mediated by a series of complex metabolic, hormonal and glucoregulatory mechanisms. The interrelationship between body fuel stores and the time sequence for their mobilization via glycogenolysis, gluconeogenesis, lipolysis and ketogenesis is diagramed in Figure 3. Felig[30] conveniently divided the transition from a fed to a fasted state into three stages: (1) the postabsorptive phase, 6 to 24 hours after beginning fasting, during which cerebral glucose requirements are maintained primarily via glycogenolysis, (2) the gluconeogenic phase, from two to ten days of fasting, during which glucose requirements are met using gluconeogenic amino acids, lactate, pyruvate and glycerol, and (3) the protein conservation phase beyond ten days of fasting, characterized by decreasing protein catabolism as fat stores are mobilized and tissue use of free fatty acids and ketones increases.

In the postabsorptive state, total glucose use is

TABLE 2.—*Body Fuel Stores of Healthy Humans**

Body Fuel Source	*Kg*	*Calories*	*Percent of Total Fuel*
Fat (adipose)	15.0	141,000	85.00
Protein (mainly muscle) .	6.0	24,000	14.50
Glycogen (muscle)	0.150	600	0.35
Glycogen (liver)	0.075	300	0.15

*Modified from Cahill et al.[51]

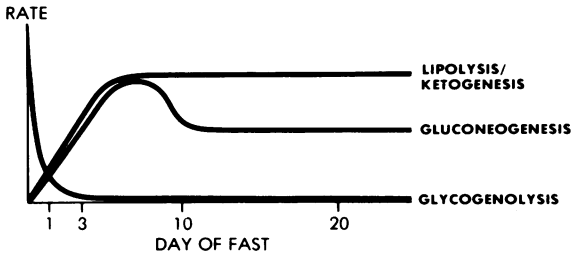

Figure 3.—A schematic of the changes in rates of glycogenolysis, gluconeogenesis, lipolysis and ketogenesis that are required to maintain caloric homeostasis during the transition from brief to prolonged fasting.

TABLE 3.—*Serum Glucose, Insulin, Glucagon, Growth Hormone, Total Lipids and Triglyceride Levels in Our Subject Before, During and After Fasting*

Day of Study	*Glucose (mg/dl)*	*Insulin (μIU/ml)*	*Glucagon (pg/ml)*	*Growth Hormone (ng/ml)*	*Total Lipids (mg/dl)*	*Triglycerides (mg/dl)*
Prefast Period						
	96	13.5	138.7	0.73	530	72
Fasting Period						
5	63	2.91	222.1	2.92	430	118
12	74	5.31	161.8	4.10	440	122
19	71	2.64	248.5	7.95	410	136
26	77	1.50	327.8	9.86	400	101
33	76	1.34	727.8	3.12	470	111
36	56	2.55	198.2	4.51	400	124
Postfast Period						
7	135	16.0	218.9	0.82	500	314
12	90	...	...	...	470	125

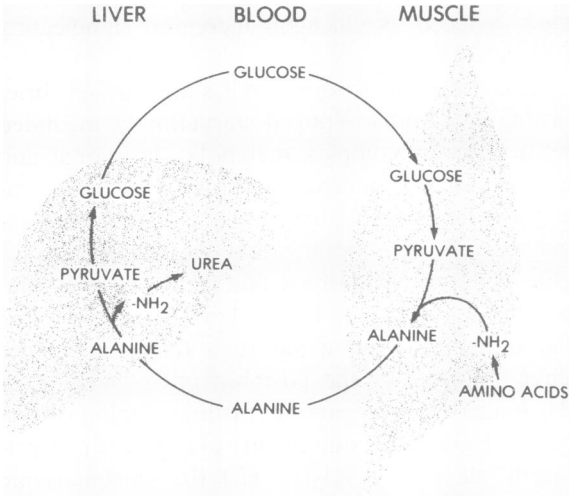

Figure 4.—The glucose-alanine cycle. Glucose released by the liver is taken up by muscle where it is converted to pyruvate and transaminated to form alanine. The alanine thus synthesized is released by muscle and taken up by the liver where its carbon skeleton is reconverted to glucose, thus completing the cycle (from Felig[55]).

150 to 250 grams per day.[55] The brain consumes the largest fraction, about 125 to 150 grams, while resting muscle cells and obligate anaerobic cells in bone marrow, blood, peripheral nerve and renal medulla consume the remainder.[55] Hepatic glycogenolysis provides about 75 percent of the glucose requirements early in fasting from its glycogen reserve of 70 grams.[55] The remainder comes from gluconeogenic precursors: amino acids (10 percent to 15 percent), lactate and pyruvate (10 percent to 15 percent) and glycerol (1 percent to 2 percent).[55] Muscle glycogen is metabolized to lactate that is released into the circulation and is resynthesized into glucose by the liver and kidney. Although this process (the Cori cycle) results in no net production of glucose, an advantage exists in that glucose synthesis from protein catabolism is reduced and the energy for resynthesis is derived from the oxidation of free fatty acids, a plentiful and readily available energy source.[56] Glycerol, a by-product of the hydrolysis of triglycerides and release of free fatty acids, provides a small but significant nonprotein-derived gluconeogenic precursor in prolonged fasting.[55] Thus, although humans cannot synthesize glucose directly from fat, the energy derived from oxidation of free fatty acids facilitates glucose synthesis from lactate and glycerol.

As mentioned earlier, gluconeogenesis from protein-derived amino acids provides 10 percent to 15 percent of the substrate in the early fasting period. Although all amino acids except leucine are potentially gluconeogenic, a specific pattern of precursor availability occurs. Alanine, which constitutes no more than 7 percent to 10 percent of all amino acid residues in skeletal muscle, accounts for 30 percent to 40 percent of amino acids released from muscle after an overnight fast.[55] It is now well established that this increased output represents de novo alanine synthesis in muscle by transamination of pyruvate.[55]

Felig and associates[57] noted that the concentrations of branched chain amino acids (valine, leucine, isoleucine) are increased early in fasting, reaching a peak at approximately the fifth day. These amino acid and serum alanine levels rose early during the fasting period in our subject. The branched chain amino acids appear to be preferentially catabolized in muscle and provide the nitrogen source for the transamination of pyruvate to alanine.[58] Subsequently, the alanine released by muscle is taken up by the liver and kidney where it is resynthesized into glucose.[57] The amino groups are converted to urea, which is excreted in the urine. This glucose-alanine cycle, which is comparable to the Cori cycle discussed earlier, represents a major glucohomeostatic mechanism in the early fasting period (Figure 4). This cycle provides a source of alanine that the liver uses, more efficiently than it uses any other amino acid, to make glucose.[57] It also establishes several control points for feedback inhibition of gluconeogenesis—that is, insulin reduces gluconeogenesis by inhibiting hepatic alanine uptake,[57] and ketosis inhibits gluconeogenesis[59] by decreasing the degradation of branched chain amino acids that in turn removes the source of nitrogen for alanine synthesis.

As fasting progresses, plasma glucose levels fall significantly whereas the level of glucagon rises.[60] The fall in plasma glucose level is greater in female than in male subjects.[61] Merimee and Tyson[61] noted a mean plasma level of glucose of 47.8 ± 2.9 mg per dl in 12 nonobese women who fasted for 72 hours compared with 66.4 ± 2.9 mg per dl in 12 nonobese men who also fasted for 72 hours. The reason for this sex difference is not clear. Relative muscle compartment size[62] (women have a lower lean body mass-to-adipose ratio) and estrogen and progesterone modulation of tissue uptake[63] and use of glucose have been suggested as possible explanations. Women are also known to become ketotic more rapidly than men

during fasting, and ketosis appears to decrease gluconeogenesis, thereby indirectly affecting plasma glucose levels.

Protein Conversion

Nitrogen Balance

In our subject, total urinary excretion of nitrogen fell from 10 to 12 grams per day in the first week to 5 to 7 grams per day after the third week (Figure 5). In prolonged starvation survival depends on conserving protein stores while energy for essential metabolic functions is maintained. Evidence that protein catabolism is reduced with continued fasting is reflected by the decrease in total urinary excretion of nitrogen. As expected, the urinary nitrogen excretion in our subject was somewhat greater than the losses of 3 to 6 grams per day observed in fasting obese persons.[64] Cerebral adaptation to ketone use lowers glucose requirements, thereby reducing the need for gluconeogenesis.[65] The fall in urea excretion (Figure 5) suggests decreased hepatic gluconeogenesis from amino acids.[64] In addition, the hyperketonemia of starvation may exert a direct inhibitory effect on gluconeogenesis. Sherwin and co-workers[59] found a reduction in serum alanine levels of 30 percent after one-hour infusions of β-hydroxybutyrate in obese persons who fasted for five to ten weeks (Figure 6).

Along with this fall in blood alanine level, total urinary nitrogen excretion decreased 30 percent. As discussed previously, alanine is the major amino acid gluconeogenic precursor during fasting. A reduction in alanine formation results in decreased gluconeogenesis and hence a decrease in protein catabolism. Thus it would appear that the hyperketonemia of starvation exerts a direct protein-sparing effect by reducing alanine release from muscle. Although the exact mechanism is not known, it has been suggested that ketones may directly inhibit the oxidation of branched chain amino acids in muscle, thereby stopping the synthesis of alanine and turning off the glucose-alanine cycle.[59]

Conversely, recent evidence indicates that alanine may inhibit ketone production directly, suggesting the presence of a ketone-alanine cycle.[66] The importance of substrate cycling in homeostatic control of intermediary metabolism has only recently been appreciated, and in the case of a ketone-alanine cycle further investigation to elucidate its full significance is required.

Also apparent in Figure 5 are the changes in urinary ammonia levels. Ammonia production and excretion increase steadily (maximal by day 10) under the stimulus of ketoacidosis.[64] As discussed earlier, the major obligate cation lost early in fasting (to compensate for the increased excretion of metabolically generated anions) is sodium. As fasting progresses, sodium conservation is

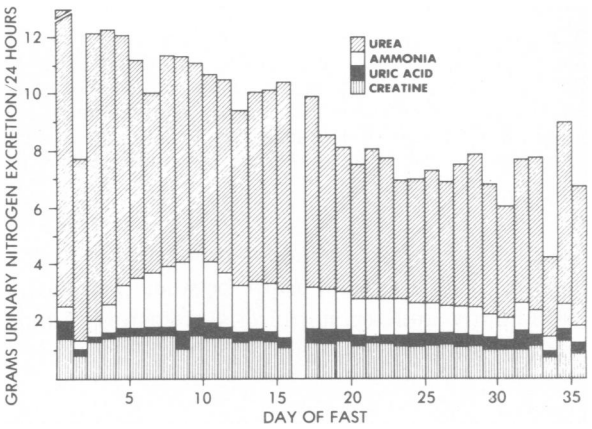

Figure 5.—Total urinary nitrogen excretion. Note the gradual increase and then decrease of urinary excretion of ammonia and the absolute reduction in total nitrogen excretion as fasting progresses.

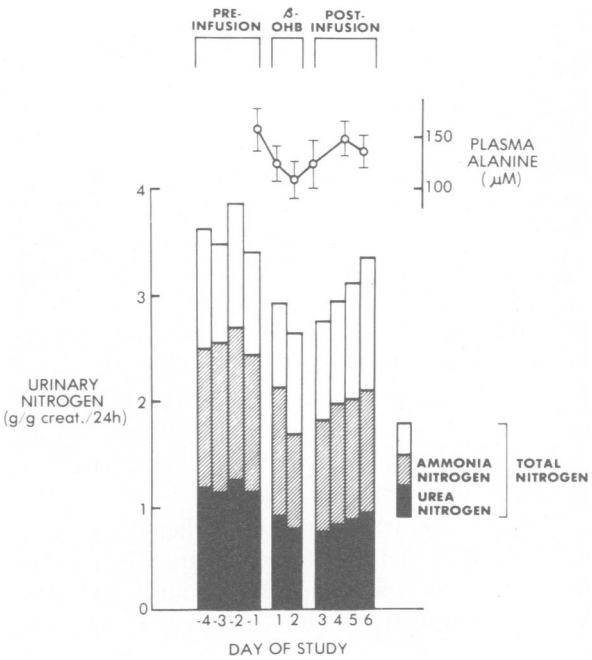

Figure 6.—The effect of an infusion of β-hydroxybutyrate (β-OHB) on urinary nitrogen excretion and plasma alanine concentration during prolonged (five to ten weeks) fasting. Infusions were for 12 hours (9 AM to 9 PM) on each of two consecutive days, and data presented are mean values for five subjects. Plasma alanine and urinary nitrogen levels fell significantly ($P<.025$) in response to the infusion (from Sherwin et al[59]).

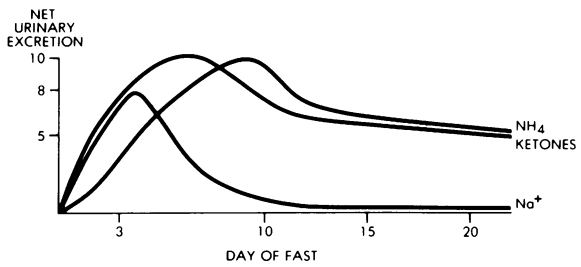

Figure 7.—A schematic of the relationship between ketonuria, ammoniuria and the natriuresis of fasting. Sodium (Na^+) losses decrease as ammonium (NH_4) becomes available as a cation to be excreted with ketones. Ketone losses decrease due to increased renal reabsorption; this is accompanied by a decreased ammonium excretion.

linked to increased ammonia production and excretion.[42,43] The relationship between ketonuria, ammoniuria and the natriuresis of fasting is diagramed in Figure 7.

Lipolysis and Ketogenesis

In our subject total lipid levels fell slightly whereas triglyceride levels rose (Table 3). Also, a pronounced increase in triglycerides was seen on refeeding as fuel stores were rapidly replenished in the hypercaloric state.

In the transition from a fed to a fasted state, fat stores are rapidly mobilized. Lipolysis, which is the hydrolysis of triglycerides to free fatty acids and glycerol, is stimulated by a fall in insulin levels and a rise in glucagon levels. In the postabsorptive state free fatty acids are mobilized at the rate of about 7 grams per hour and are taken up by the liver at about 3 grams per hour where they are terminally oxidized to CO_2 (β-oxidation), partially oxidized to ketone bodies (ketogenesis) or resynthesized into triglycerides (lipogenesis).[30] The major ketone bodies are β-hydroxybutyrate and acetoacetate, which may rise 70-fold during prolonged fasting.[64] Regulation of ketogenesis is dependent on substrate availability (that is, free fatty acids) and transport into the hepatic or renal mitochondria where oxidation occurs. The enzyme responsible for this transfer, carnitine acyltransferase, is indirectly stimulated by glucagon in the absence of insulin.[30] As fasting continues, increased cerebral use of ketone bodies occurs as greater ketonemia develops.[65,67] Serum levels of ketone bodies rise steadily during three to four weeks,[68] whereas lipolysis and ketogenesis are maximal by three days.[69] This discrepancy between increasing serum levels and stable production rates is explained by the decreased peripheral uptake and decreased renal excretion of ketones.[68] Muscle uptake of ketones falls by 75 percent from early to prolonged fasting as energy for muscle metabolism shifts from ketones to free fatty acids.[70] In addition to increasing plasma ketone levels, the increased reabsorption of ketones by the kidney has a nitrogen-sparing effect by decreasing the ammonia excretion required to titrate urinary ketone losses.[68] Thus, in addition to providing substrate, the ketonemia of starvation provides feedback inhibition of protein catabolism.

Sex Differences and Body Size in the Development of Fasting Ketosis

As early as 1931 differences during fasting between men and women have been shown.[71] It was not until the late 1950's, however, after Bloom[15] reintroduced fasting as a treatment of morbid obesity, that interest in and study of fasting metabolism became widespread. Rapid weight loss under medical supervision became a major incentive for prospective volunteers; as a result, most of the information collected during prolonged fasts during the past two decades is from studies with obese persons. Unfortunately, in these studies and in fasting studies with nonobese persons, the data generally were not analyzed for possible differences based on sex or body size. Not until 1974 was it recognized that there are differences in plasma glucose levels between fasting nonobese men and women,[61] and apparently the influence of sex and body size must be considered before interpreting any findings.

Deuel and Gulick[71] first reported that fasting ketosis develops more rapidly in women than in men. Also, serum free fatty acids and ketone levels increase at a greater rate in women than in men during fasting.[72,73] This sex difference, however, disappears with increasing body weight.[74,75] Maximal mobilization of free fatty acids occurs only at reduced levels of insulin. However, in obese persons both basal and fasting levels of insulin are raised.[64] Although insulin is known to be less sensitive in obese persons,[76] at least for its primary action, its secondary or antilipolytic effect could be a predominant factor in the reduced rate of lipolysis. In addition, little or no rise in growth hormone is seen after prolonged fasting in obese subjects[77-79]; this hyperinsulinemia and lower growth hormone level would be expected to make fat mobilization more difficult in an obese person. Conversely, growth hormone

levels in nonobese persons are raised during fasting,[79,80] and in the presence of lower insulin and higher glucagon levels lipolysis is enhanced. One might postulate that in a nonobese fasting person the stimulus for mobilization of free fatty acids and ketogenesis is greater due to lower plasma glucose, lower insulin, and elevated glucagon and growth hormone secretion.

Other sex differences include the glucagon level, which has been shown to be higher in nonobese fasting women than in men.[81] A role for glucagon in the explanation of the sex-based variation in fasting ketosis has been suggested.[81] As discussed earlier, ketosis has been shown to decrease the release of amino acid gluconeogenic precursors (especially alanine) from muscle and may represent another important control point in the regulation of intermediary substrate cycling. Merimee and associates[81] found lower but not statistically significant reductions in serum alanine levels between nonobese men and women after 24 and 48 hours. Their subjects, however, were chosen based on previous studies showing similar fasting insulin levels. They suggested that if women with lower fasting plasma glucose levels (and hence lower insulin production) are studied, a difference in the release of amino acid gluconeogenic precursors might be evident. Furthermore, if a decreased release of gluconeogenic precursors in fasting women is found, a lower plasma glucose level could be explained. Further investigation is necessary to resolve this issue.

Other explanations for the greater ketosis in fasting women include sex differences in body composition,[62] estrogen effects,[63] and differential use or conversion of free fatty acids to ketones.[62] The mobilization of fuel stores during fasting depends on the energy requirements and the hormonal milieu. Previous explanations may have oversimplified the role of certain hormones. A partial list of differences between men and women and lean and obese persons is shown in Table 4.

Hormonal Changes

The important roles of insulin and glucagon in the adaptation to fasting have already been discussed and have been reviewed extensively by others.[30] Other endocrine changes that also occur during fasting are as follows.

Growth Hormone

We observed a progressive rise in growth hormone level through day 26 followed by a significant fall thereafter with a return to baseline levels during realimentation (Table 3). Growth hormone plays a key role in protein, carbohydrate and fat metabolism. It also has known lipolytic effects[87] and may be diabetogenic in large doses or in smaller amounts in the absence of insulin.[88] Its secretion fluctuates widely during the day with a major increase during early sleep.[88] Other known stimuli to growth hormone secretion besides fasting include hypoglycemia, exercise, certain amino acids (for example, arginine and other

TABLE 4.—*Differences in Metabolism During Fasting Related to Sex and Body Size**

	Obese Subjects		*Nonobese Subjects*		
	Women	*Men*	*Women*	*Men*	*References*
Substrate					
Glucose	↓↓↓	↓↓	↓↓↓	↓	61,62,64,81
Free fatty acids	↑↑	↑	↑	↑	62,72,73,75,78,81
Ketones	↑↑	↑	↑	↑	62,71-75,78,81
Amino acids (especially alanine)	0†	0†	?	?	81
Hormones					
Insulin	↓↓	↓↓	↓	↓	61,62,64
Glucagon	↑↑‡	↑	↑	↑	55,62,81
Growth hormone	↑↑↑‡	↑↑	0	0	78-80,82
Miscellaneous					
Rate of weight loss	↓↓↓	↓↓↓	↓	↓↓	83-85
Total urinary nitrogen excretion	↓↓	↓↓	↓	↓	72,83,85
Total urinary mineral excretion (calcium, magnesium, phosphorus, sodium, potassium)	↑	↑	↑↑	↑↑	73,86

0 = no change
? = unknown

*Arrows indicate a relative quantitative change. This table represents a summary of data in an area that has not been adequately studied.
†Although no change was noted by Merimee et al,[81] it has been shown that infusions of β-hydroxybutyrate stimulating the hyperketonemia of fasting results in a decrease in amino acid gluconeogenic precursors, especially alanine[59]; on that basis some sex difference might be expected. Additional studies are necessary.
‡Basal growth hormone levels (after an overnight fast) are raised in women compared with men, but no significant increase occurred in women after 72 hours of fasting.[80]

TABLE 5.—*Serum Thyroxine (T_4), Luteinizing Hormone (LH) and Follicle-Stimulating Hormone (FSH) Before, During and After Fasting*

Day of Study	T_4 (μg/dl)	LH (mIU/ml)	FSH (mIU/ml)
Before Fasting			
	5.9	47	6
Fasting			
5	6.5	20	6
12	6.4	16	4
19	5.5	12	3
26	5.3	10	3
33	3.9	9	2
36	4.9	10	2
After Fasting			
7	2.6	8	3
12	4.4	..	..
Normal Range	4.5-12.5	6-30	5-25

mIU = milli-international units.

basic amino acids), catecholamines, stress (for example, fever or surgical procedures) and certain drugs (for example, L-dopa, vasopressin).[89]

In addition, the secretory pattern of growth hormone in response to provocative stimuli appears to vary among obese and nonobese persons.[79,90] In obese persons, little or no rise in growth hormone has been reported after fasting from 14 to 38 days.[64,77,78] Conversely, in other studies mean serum growth hormone values rose within three days and then fell in nonobese persons during fasting from three to ten days.[60,80,91] The progressive rise in the level of growth hormone beyond day 10 is surprising in view of the previous reports, but we are unaware of growth hormone determinations in nonobese persons fasting beyond ten days.

In an interesting study by Merimee and coworkers,[92] six normal and ten growth hormone-deficient dwarfs fasted for six days. Four of the growth hormone-deficient dwarfs received growth hormone replacement during the fasting period. Glucose levels fell 15 mg per dl in the normal and growth hormone-treated dwarfs but fell 50 mg per dl in the untreated dwarfs. The insulin level also fell whereas free fatty acid and serum ketone concentrations increased to a greater degree in the untreated dwarfs compared with the normal and treated dwarfs. Although growth hormone may have a lipolytic effect, these studies suggest that it is not primary. The higher level of free fatty acids and ketones noted in the untreated dwarfs was probably related to the lower plasma insulin levels. Nevertheless, it is apparent that glucose homeostasis during fasting is dependent in part on the presence of growth hormone.[93]

Thyroid Hormone

Values for serum thyroxine (T_4) in our subject over the fasting and realimentation periods are shown in Table 5. The T_4 level showed only a slight decline from the early to the late fasting periods, and remained depressed at the end of the first week of realimentation. Serum triiodothyronine (T_3), thyrotropin (thyroid-stimulating hormone, or TSH) and reverse T_3 were not measured.

In starvation and fasting states, T_4 has been reported to be unchanged,[94] increased slightly[95] or decreased slightly,[91] whereas serum T_3 falls dramatically.[95] Spaulding and colleagues[96] and Portnay and associates[95] showed a reduction of free T_3 levels by approximately 50 percent in persons who fasted for one to four weeks. This reduction in T_3 is due to an increased production of reverse T_3, an inactive metabolite, and to a lesser extent to a decrease in the peripheral conversion of T_4 to T_3.[97] It also appears to be related to the carbohydrate content of the diet.[96,98] Spaulding and co-workers[96] were able to prevent the fall of T_3 levels in persons fed hypocaloric diets containing at least 50 grams of carbohydrate but not in the same persons fed hypocaloric protein, fat or mixed protein-fat diets.

Despite the fall in T_3 levels, clinical hypothyroidism does not develop. Thyrotropin values do not rise, as might be expected in primary thyroid dysfunction; in fact, basal TSH concentrations may decrease in short-term fasting[98] or remain unchanged in prolonged (more than three weeks) fasting.[95] In addition, TSH response to thyrotropin-releasing hormone infusions may be blunted[98,99] or unchanged.[95]

The diversion of T_4 metabolism from T_3 to reverse T_3 is an adaptive mechanism that reduces caloric requirements by lowering the basal metabolic rate and thereby indirectly reducing the need for glucose derived from protein catabolism. The protein-sparing effect of this physiologic fall in T_3 has been well studied.[94,100] In obese persons given physiologic doses of exogenous T_3 to prevent the normal fall of the T_3 level during fasting, a significant increase in total urinary nitrogen excretion has been found.[100] No change in total urinary excretion of nitrogen occurs in persons receiving normal nutrition given similar doses.[100] In another study of lean fasting men given 5 mg

of T_3 every 3 hours for 80 hours to maintain normal serum T_3 levels, excretion of urea increased 9.1 percent from earlier fasting control values.[94] Another marker of protein catabolism, 3-methylhistidine, a component of actin and myosin that cannot be used again for protein synthesis and is excreted almost entirely in the urine, has been shown to increase paralleling nitrogen losses in fasting persons in response to exogenously administered T_3.[100,101]

In persons given larger doses of T_3 (150 mg every 12 hours) for 72 hours before and during a 72-hour fast, excretion of urea increased 2 to 2½ times whereas creatinine excretion increased six to nine times above control levels.[102] In addition, plasma glucose, free fatty acids, serum ketones and urinary ketone excretion increased significantly, suggesting accelerated gluconeogenesis, lipolysis, β-oxidation and ketogenesis in response to exogenous T_3 in a fasting but not a fed state.[101]

In anorexia nervosa, as in fasting and other malnourished states, T_4 and T_3 levels are reduced and TSH levels are unchanged, whereas reverse T_3 values may be increased.[103-105] In six patients with anorexia nervosa in a study by Moshang and coworkers,[103] T_4 levels were reduced slightly whereas T_3 levels were 50 percent lower than the levels of normal control subjects. The basal TSH concentration and response to thyrotropin-releasing hormone were not different in anorexic patients when compared with normal control subjects.

Gonadotropins

Serum luteinizing hormone and follicle-stimulating hormone (FSH) values are shown in Table 5. Both hormone levels fell during fasting and remained low after the first week of realimentation.

We are unaware of comparative findings in nonobese men during a similar period. Many of the data on gonadotropin response to weight loss comes from studies of patients with anorexia nervosa and self-imposed nonpsychopathologic weight loss or simple weight loss. Boyar and colleagues[106] studied the secretory pattern of luteinizing hormone in nine patients with anorexia nervosa by measuring luteinizing hormone levels at 20-minute intervals for 24 hours. They found a luteinizing hormone secretory pattern resembling that of prepubertal and pubertal children that reverted to a "mature" pattern with weight gain. More recent studies have reported low levels of serum luteinizing hormone and FSH[104] in patients with anorexia nervosa with a delayed response to exogenous luteinizing hormone-releasing hormone.[107-109] A delayed response to luteinizing hormone-releasing hormone has also been noted in simple weight loss, but the response was intermediate in extent between that in anorexia nervosa patients and normal persons.[109] The response to luteinizing hormone-releasing hormone in both conditions of weight loss returns to normal[110] or becomes supranormal[108] with weight gain, but resumption of menstruation in anorexia nervosa may not occur immediately, suggesting that other factors (most likely psychologic) are also involved.[105] Thus it appears that hypothalamic dysfunction in patients with anorexia nervosa and to a lesser degree in patients who have undergone nonpsychopathologic weight loss is related to the extent of weight loss.

Frisch and McArthur[111] postulated that a minimal weight-for-height ratio representing a critical

TABLE 6.—*Serum Sodium (Na^+), Potassium (K^+), Magnesium (Mg^{++}), Calcium (Ca^{++}) Phosphorus (P), Zinc (Zn) and Uric Acid Levels Before, During and After Fasting*

Day of Study	Na^+ (mEq/liter)	K^+ (mEq/liter)	Mg^{++} (mg/dl)	Ca^{++} (mg/dl)	P (mg/dl)	Zn (μg/dl)	Uric acid (mg/dl)
Before Fasting	138	4.6	1.7	10.3	3.6	104	5.5
Fasting							
5	134	4.8	1.4	9.6	2.6	255	11.2
12	132	3.9	1.4	10.1	2.6	...	12.6
19	131	4.1	1.2	10.0	3.0	342	12.5
26	130	4.7	1.5	10.5	2.8	307	10.5
33	134	4.8	1.5	10.2	3.8	284	8.4
36	122	...	1.6	9.8	3.0	364	8.0
After Fasting							
7	136	5.3	1.6	9.1	3.0	117	2.0
12	139	4.3	...	9.4	4.0	...	3.5
Normal Range	(134-146)	(3.5-5.3)	(1.5-2.9)	(8.8-10.8)	(2.0-4.7)	(80-120)	(2.5-8.5)

adipose store must be attained before onset and maintenance of normal menstrual cycles. As with anorexia nervosa, simple weight loss and protracted strenuous exercise all deplete adipose stores, resulting in menstrual irregularities. Amenorrhea, oligomenorrhea and anovulatory cycles have been reported in long distance runners,[112,113] ballet dancers,[114] and female participants in strenuous sports,[115] as well as in cases of anorexia nervosa and simple weight loss. Because infant survival depends on birth weight, which is affected by maternal weight both before and during pregnancy, successful reproduction including lactation depends on adequate maternal energy stores. Teleologically, this represents an adaptive mechanism that limits reproduction when body energy stores are suboptimal.[116]

Whether or not the changes in luteinizing hormone or FSH levels that we observed are consistent findings in fasting nonobese men and are analogous to the changes seen in women needs to be studied further. Changes commonly seen in men during periods of reduced caloric intake include loss of libido, decreased volume of prostatic fluid, and decreased sperm number and motility.[13]

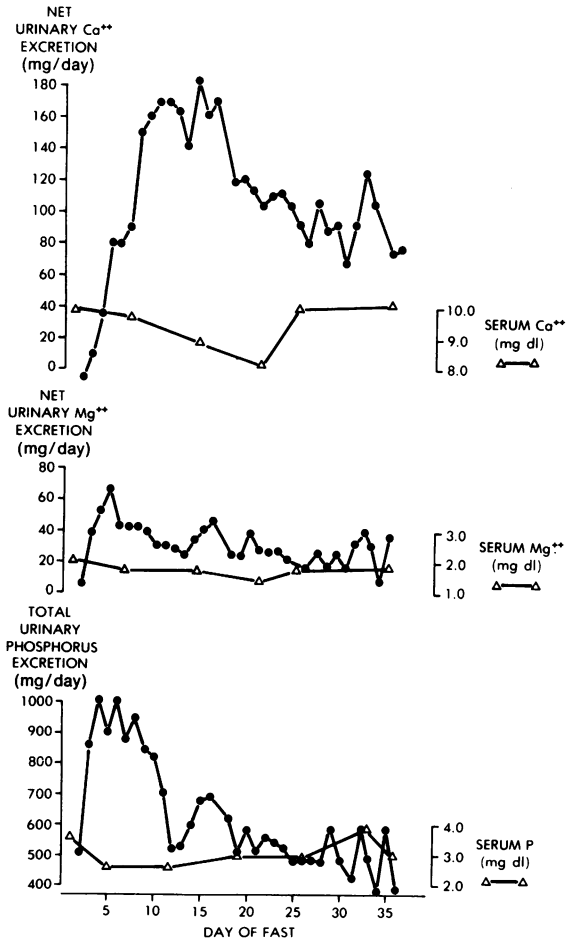

Figure 8.—Net urinary calcium (Ca^{++}) and magnesium (Mg^{++}) excretion and total urinary phosphorus (P) excretion over the fasting period. Serum levels are shown on the right.

Mineral Changes

Potassium

Serum potassium levels remained essentially unchanged in our subject (Table 6), but there was a net total urinary loss of potassium of 37.6 mEq per day for the first ten days or 729.6 mEq over the entire 36-day fast. Serum potassium levels may decline slightly, but rarely fall below 3.0 mEq per liter even after two or more months of unsupplemented fasting.[86] Urinary potassium losses observed by others[86] in the early fasting period (first ten days) were similarly large, averaging 33 to 41 mEq per day in lean persons. Consolazio and associates[117] noted a mean loss of 39.1 mEq per day during a ten-day fast in six normal men. Benedict[9] reported a similar pattern of urinary potassium excretion with an average daily loss of 19.9 mEq per day in a 31-day fast. In obese persons fasting a month or longer, potassium losses are less than half those of lean persons.[86] Because net potassium loss is primarily from lean tissue, these decreased losses in obese persons may represent more efficient protein sparing as fat stores are mobilized.

Magnesium

Serum magnesium levels were remarkably stable, whereas urinary excretion of magnesium increased over the first five days and then fell gradually to approximately 2 to 3 mEq per day by the end of the fasting period (Figure 8). Total net urinary magnesium excretion equaled 2.6 mEq per day or 93.6 mEq over the 36-day fast.

Magnesium deficiency in persons with protein-calorie malnutrition is well recognized.[118-120] Signs and symptoms compatible with magnesium deficiency include weakness, emaciation, anorexia, insomnia, hyperirritability, atrophic skin changes and hypocalcemia.[121] Electrocardiographic changes include nodal or sinus tachycardia and flat or inverted T waves in the lateral precordial leads.[121] In children with severe protein-calorie malnutrition and clinical signs and symptoms of magnesium deficiency, magnesium-supplemented realimentation results in dramatic and rapid improvement in

serial electrocardiograms along with a return of appetite, resumption of a normal sleep pattern and stabilization of vital signs.[121]

In cases of acute starvation, evidence of magnesium deficiency generally is not seen. In obese persons fasting up to 60 days, serum levels may be slightly increased, decreased or remain the same.[86] Consolazio and colleagues[117] observed a pattern of urinary magnesium excretion during fasting that was similar to our subject's. Benedict[9] reported an average magnesium loss of 6.0 mEq per day over a 31-day fast. Gamble and co-workers[122] noted a net total loss of 51.2 mEq of magnesium after a 15-day fast of nonobese epileptic children, whereas after 15 days in our study net total magnesium loss equaled 50.1 mEq. Urinary magnesium excretion is somewhat higher in obese persons, averaging 13 mEq per day over the first seven days, thereafter receding to a stable minimum excretion of 7 to 10 mEq per day.[86]

Calcium

In our subject, serum calcium levels fell slightly (Figure 8) by the third week but returned toward the baseline level by the end of the fasting period. Serum calcium levels have not been reported to be significantly altered by fasting, probably due to the large bony reserves. Urinary excretion of calcium increased steadily through the second week of fasting and then fell gradually before stabilizing at around 4 to 5 mEq per day (Figure 8). The average net urinary calcium excretion for the 36-day fast was 5.3 mEq per day or 190.8 mEq.

Calcium losses during fasting vary. The calcium loss in our subject compared quite favorably with findings in nonobese fasting persons.[9,117,122] Consolazio and co-workers[117] reported a 6.4 mEq daily loss during a ten-day fast of nonobese men that was comparable with a loss in our study of 5.3 mEq per day. Benedict[9] noted a net urinary calcium loss of 10.9 mEq per day over the 31-day fast of nonobese Mr. L. Gamble and colleagues[122] reported a total urinary loss of calcium of 51.2 mEq at day 15 in four epileptic children, which was comparable with the 50.1 mEq loss over the same time period in our subject. In obese subjects, Drenick[86] reported total urinary losses between 550 and 900 mEq (11 to 18 mEq per day) during a 50-day fasting period with a pattern of excretion similar to that of magnesium. In another study of three obese women, net calcium excretion during fasting periods of 12, 20 and 24 days amounted to total losses of 3.5, 10.2 and 14.7 mEq per day, respectively.[123]

The source of this calcium is presumed to be bone, though actual analysis of bone for calcium content change during fasting has not been carried out in humans.[86] Osteoporosis with hypercalciuria is a well-documented consequence of immobilization.[124] Therefore, considerable variation in calcium losses might occur between physically active versus inactive fasting persons. Our subject was fully ambulatory throughout the fasting period, as are most persons studied during fasting.

Phosphorus

Serum phosphorus levels and total urinary phosphorus excretion in our subject are shown in Figure 8. Serum phosphorus levels did not change significantly. Peak urinary phosphorus losses occurred on days 4 through 6, decreasing steadily thereafter to approximately 0.5 gram per day by the end of the fast.

Phosphate losses during fasting in obese persons are initially quite high, up to 80 mEq per day, before falling to average daily losses of 20 to 30 mEq after 15 to 20 days.[86] Rapoport and associates[125] noted similar losses closely paralleling the curve of titratable urinary acidity and suggested that phosphate might play a role in buffering the metabolic acidosis of starvation.

Because sufficient quantities of phosphorus are readily available in almost all foodstuffs, dietary phosphorus deficiency under normal conditions is uncommon in humans.[126] However, a phosphorus-depletion syndrome from prolonged antacid therapy, chronic alcoholism, diabetic ketoacidosis, thermal burns, hyperalimentation or severe respiratory alkalosis has been described.[126-128]

Zinc

Serum zinc levels in our patient are shown in Table 6. A prompt and sustained increase was noted throughout the fasting period. With alimentation, serum levels fell to within the normal range. Urinary excretion of zinc was not measured in our subject.

Few studies of zinc metabolism during fasting have been reported. We are unaware of any such studies in nonobese persons fasting for prolonged periods. Spencer and co-workers[129] reported a twofold increase in urinary zinc excretion in the first six days of total fasting in an obese person. Thereafter, zinc excretion remained high, averaging a 4.6 mg per day loss throughout a 60-day

starvation period. Despite these large urinary losses, serum zinc levels rose slightly, but not to the extent observed by us. The source of this zinc is presumed to be from tissue catabolism and bone resorption.

Zinc is an essential cofactor or forms a metalloenzyme for more than 70 known enzymes.[130,131] It plays a role in protein, carbohydrate, lipid, and nucleic acid synthesis and degradation. An excellent review of zinc metabolism and its clinical implications has been published recently.[132]

Zinc deficiency was first suspected in 1961 by Prasad,[133] who reported a syndrome of dwarfism, hypogonadism, hepatosplenomegaly and parakeratosis in men from Iran. Zinc-deficient states have since been reported in a variety of clinical conditions. Zinc deficiency has been associated with abnormal growth, abnormal sexual maturation and function, anorexia, hypogeusesthesia, dysgeusia, hyposmia, dysosmia and impaired wound healing.[132,133] Total body zinc stores are about 1.5 to 2.5 grams with about 60 percent found in muscle and 30 percent found in bone.[132,134] Under normal conditions, these reserves are not thought to be readily available, thereby necessitating a minimum daily requirement. For adults this is about 15 mg per day, increasing to 20 to 25 mg per day during pregnancy or lactation.[132]

Uric Acid

In our subject, serum uric acid levels rose rapidly over the first two weeks, stabilized during the third week and fell thereafter to the upper limit of the normal range (Table 6). Urinary excretion of uric acid averaged 400 mg per day after the first week of fasting and changed very little thereafter (Figure 5). Most other studies have reported urinary uric acid excretion to decrease with fasting.[135,136] This fall in serum uric acid that occurred in our patient while renal excretion was stable may represent decreased uric acid production as protein-sparing mechanisms are activated later in fasting.

Hyperuricemia is a well-established consequence of fasting.[136-138] In a nonobese person studied in the last two days of a 45-day fast, a serum uric acid level of 9.0 mg per dl (normal 3 to 4 mg per dl) was recorded.[11] We are otherwise unaware of serum uric acid levels measured in nonobese persons during prolonged fasting. In another study of obese patients who fasted for up to four months, serum levels of uric acid increased progressively for the first 15 to 20 days to levels of 12 to 18 mg per dl (normal in men, 4.0 to 8.5 mg per dl) reaching an average maximum of 21.8 mg per dl as fasting extended beyond two months.[139]

Explanations for the hyperuricemia of fasting include increased production[140] or decreased excretion due to decreased glomerular filtration rate,[136] altered renal tubular transport systems[136] or ketoacidosis.[141] Uric acid and keto acids are thought to compete for renal tubular transport sites. Infusions of β-hydroxybutyrate to simulate the ketonemia of starvation have been shown to produce a pronounced renal retention of uric acid.[141,142] Acute episodes of gouty arthritis and urate nephrolithiasis with subsequent renal insufficiency have also been reported.[139,142] Probenecid and allopurinol have been used to control the hyperuricemia of fasting and prevent these complications,[143] but were not used in our study.

Psychologic and Neurologic Effects

Our subject remained lucid throughout the fast and maintained a rigorous schedule of daily meetings, conferences and worship while keeping a detailed journal of activity and subjective response to physical changes. Appetite was noted to diminish, but total anorexia did not develop. The sight and smell of food remained subjectively pleasant.

In conventional short-term calorie-deficient diets, persistent hunger has been a major obstacle to patient compliance. However, loss of appetite (after one to four days) along with a sense of well-being has been reported frequently in persons on short total fasts for weight reduction.[15-17,144] Others[18] have reported euphoria without total anorexia. Ketosis, which develops rapidly during fasting, was commonly believed to be responsible for the anorexia.[16] More recently, β-endorphin, an endogenous opiate that has been linked to feeding regulation and satiety, has been postulated to be involved in this physiologic adaptation to fasting.[145]

The sense of well-being that may occur during short-term total fasting is in contradistinction to that seen during prolonged periods of semistarvation when mental lethargy, apathy and irritability are common.[13,33] To explain the euphoria, Bloom[15] postulated that accumulation of acetoacetic acid produces a mild intoxication similar to ethanol. Phillips[146] from studies in animals speculated that the accumulation of isopropyl alcohol in neural tissue might be responsible for fasting-induced religious, mystical or hallucinatory ex-

periences. One must also consider the positive psychologic benefits of significant daily weight loss in persons who have had lifelong histories of obesity previously refractory to any treatment.

Electroencephalographic studies in fasting persons have been limited. Owen and associates[65] reported no change in the findings on electroencephalograms of three obese persons who fasted for 38 to 41 days. In patients who fasted for psychosomatic disorders, fast-wave activity on electroencephalograms was reported to increase.[147] In studies of children suffering from kwashiorkor, electroencephalographic tracings showed abnormal slow-wave frequencies[148] or a high incidence of abnormal tracings in the temporal lobe.[149] In both studies a return of the electroencephalographic findings toward normal was reported with nutritional rehabilitation.

In other types of dieting, including liquid protein and protein-sparing modified fasting, anorexia is purported to be a prominent feature.[150,151] In a study of patients with Prader-Willi obesity who fasted on a protein-sparing hypocaloric regimen, the high degree of outpatient compliance obtained in these mentally deficient patients, who do not normally experience satiety, was believed to be due to an appetite-suppressant effect of the ketogenic diet regimen.[151]

Medical Complications of Prolonged Fasting

Complications reported during prolonged fasting for weight reduction are summarized in Table 7. Although prolonged fasting is generally well tolerated with few and relatively minor complications,[152] several reports of death after or during total fasting have appeared.[153,157-161] In addition to morbid obesity, two of six reported fatal cases had severe prefast symptoms of congestive heart failure (which initially improved with fasting) and one had focal stenosis of the coronary arteries at autopsy.[157,160] In another case a small bowel obstruction developed in the fasting person and death from complications occurred on the 13th day.[153] An abrupt onset of renal failure followed by death in another patient after 14 days of a total fast has been reported; chronic glomerulonephritis was found at autopsy.[161] In the sixth fatal case, the patient, who otherwise was in good health, had been given small amounts of protein supplements (essential amino acids) for 103 days of a 210-day fast, but died of intractable ventricular dysrhythmias on the eighth day of realimentation.[158] In this case, as is common in deaths of patients while on liquid protein fasts,[162] an otherwise unexplained prolongation of the QT interval was reported along with gross fragmentation of myocardial fibrils at necropsy. Although the cause of the dysrhythmias in these patients is unknown, perhaps this case represents the first reported though unrecognized death during protein-supplemented fasting.

TABLE 7.—*Complications During Prolonged Acaloric Fasting*

Complication	*References*
Nonfatal	
Headaches	15-18,152,153
Light-headedness	16,18,152
Nausea	15,16,144,152
Abdominal pain	153
Weakness	16,152,154
Cramps	86,152
Orthostatic hypotension	17,152,153
Acute gout	17,139,152
Urate nephrolithiasis	139
Renal insufficiency	139
Oliguria	18,144,152,153
Edema	18
Atrial flutter	152
Anemia	17,144
Amenorrhea	13,111
Alopecia	154
Porphyria	155
Parotitis	18
Polyneuritis	154,156
Vitamin deficiency	17,154
Fatal	
Intractable ventricular arrhythmia	157-159
Lactic acidosis	160
Small bowel obstruction with complications	153
Renal failure	161

Liquid protein diets, recently promoted heavily in the lay press[150] for weight reduction, are now known to be associated with serious complications including intractable ventricular dysrhythmias and sudden death.[163-165] Isner and colleagues[165] reviewed findings on 17 unexpected deaths in otherwise healthy obese persons using liquid protein diets. In all of nine patients for whom adequate electrocardiographic information was available, the QT interval was prolonged. Seven of the cases did not have the usual causes of QT interval prolongation—that is, hypocalcemia, hypomagnesemia, drugs or congenital anomaly. In another study of three persons with no previous history of cardiac disease who were on a liquid protein-fasting regimen, the QT intervals were prolonged, the ST segments and T waves were abnormal, and intermittent syncopal episodes due to ventricular tachycardia and ventricular fibrillation occurred for up to three months after discontinua-

tion of the diet.[166] All patients had electrocardiographic features of atypical ventricular tachycardia (torsades de pointes*); two of the patients died.[166] These studies suggest a causal relationship between liquid protein diets and delayed repolarization (prolonged QT interval), serious ventricular arrhythmias and risk of sudden death.

In an effort to assess the dysrhythmogenicity of liquid protein diets, six obese patients were given 300 kcal per day of a commercially prepared liquid protein hydrolysate for 40 days and were observed weekly with 12-lead electrocardiographic and 24-hour Holter monitoring.[167] No abnormalities were seen using standard 12-lead electrocardiographic monitoring in any patient before, during or after the fasting period. However, with 24-hour Holter monitoring, persistent and multiple ventricular dysrhythmias occurred in three of six patients after the tenth day of supplemented fasting. These dysrhythmias were noted to increase in frequency and complexity as the fasting period progressed. After resumption of normal diet, no further disturbances were seen with either standard 12-lead electrocardiograms or Holter monitoring in any of the patients. Although these findings are intriguing, unfortunately no control group was examined nor are there available comparative studies of Holter monitoring in persons undergoing other forms of dietary restriction such as total fasts, protein-sparing modified fasts or hypocaloric mixed diets. Although the cause of the life-threatening dysrhythmias seen in patients on protein diets is unknown, deficiencies of trace elements,[168,169] micronutrients[170] and essential amino acids,[171] as well as electrolyte disturbances[172,173] and biologically poor protein sources,[174,175] have all been suggested.

Summary

Early in fasting, weight loss is rapid, averaging 0.9 kg per day during the first week and slowing to 0.3 kg per day by the third week. During the period of rapid weight loss, there is significant negative sodium balance, probably due to losses of the sodium salts of keto acids in the urine. As mild starvation ketoacidosis develops, ammonia production is stimulated, providing ammonium for excretion with keto acids and thus sparing sodium loss. This leads to a decrease in the rate of weight loss. Carbohydrate-free fasts tend to cause orthostatic hypotension due to the sodium losses plus a degree of autonomic insufficiency. Other physical features such as the amplitude and axis on the electrocardiogram change, probably reflecting loss of cardiac mass, and bradycardia develops.

The early days of fasting are characterized metabolically by a high rate of gluconeogenesis, chiefly with the use of amino acids, especially alanine, as substrates. The stimulus for gluconeogenesis appears to be decreased insulin production and increased glucagon. As fasting continues, progressive ketosis develops due to mobilization and oxidation of fatty acids. At higher blood levels of ketones, the brain is able to use ketones as a primary energy source, thereby decreasing the need for gluconeogenesis. The specific feedback is probably by ketones on release of alanine from muscle. The ketotic phase of fasting is then associated with protein sparing. Lean persons become ketotic earlier than obese persons, and women become ketotic more rapidly than men.

Other hormonal changes occur. Serum levels of T_3 promptly fall with a reciprocal rise in reverse T_3, which contributes to protein sparing. Changes in the blood level of growth hormone during fasting are varied and may differ depending on whether the person is obese or nonobese. Changes in the blood level of gonadotropin are not well characterized; luteinizing hormone and FSH levels fall, at least in the patient reported herein.

Potassium losses decrease after ten days of fasting though some losses persist. Magnesium calcium and phosphorous losses are minimal after the first week.

Changes in trace metal balance are poorly defined. Serum zinc levels rose through the fasting period in the patient reported herein, but the significance of this change is unknown.

Hyperuricemia occurs in fasting obese persons and also occurred in our nonobese subject. This is probably due to increased production of uric acid from tissue catabolism and decreased urinary excretion of uric acid from competitive inhibition of tubular uric acid secretion.

The subjective psychologic effects of fasting may produce a sense of well-being or euphoria. Neurologically, there is evidence that ketosis may increase seizure thresholds in patients with epilepsy. Electroencephalograms in chronic protein-calorie malnutrition show diffuse slowing and abnormal temporal lobe tracings.

*Torsades de pointes means "twisting of the points" and is believed to represent an especially malignant form of ventricular tachycardia characteristically seen in association with a prolonged QT interval in which polarity of ventricular complexes swings between the positive and the negative directions.

Rare medical complications of short-term fasting include gout, urate nephrolithiasis, postural hypotension and cardiac dysrhythmias. The particular association of liquid protein-supplemented fasting and sudden cardiac death is well reported, though the mechanism is still unknown.

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