

# Nutritional Aspects of Body Water Dislocations in Postoperative and Depleted Patients

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Measurements of plasma volume with  $^{125}\text{I}$  human serum albumin, extracellular water (ECW) with  $^{82}\text{Br}^-$ , and total body water (TBW) with  $^3\text{H}_2\text{O}$  were made on 16 postoperative patients, 15 depleted patients, and three control subjects. Intracellular water (ICW) was calculated as the difference between TBW and ECW. The observed findings for the series as a whole showed no change in blood volume, an increase of 3.7 l in ECW, and a decrease of 1.5 l in ICW as compared to predicted values based on current weight. Compared to predicted values based on normal (pre-illness) weight, the observed body weight decreased 16% and ICW decreased 22%; this suggests that body weight consistently underestimates the extent of nutritional depletion. Severe depletion seen in postoperative patients indicates that frequently earlier use of total parenteral nutrition would be beneficial. ICW was found to be the most reliable single index of moderate or severe nutritional depletion; errors in estimating normal values interfere with its use in mild depletion. The ratio of ECW:TBW best reflects distortion of body water composition; it is largely independent of weight, and is a more sensitive index than absolute values of ICW. Repeat measurements of body composition were made on 9 patients given total parenteral nutrition for an average period of 18 days. On the average, there was an ECW decrease of 1.8 l, a body weight increase of 2 kg, and an ICW increase of 3.2 l after parenteral nutrition. The increased ICW represents the repletion of half of the average initial deficit of 6 l. The initial ratio of ECW:TBW of 0.58 was reduced to 0.50, returning it about three-quarters of the way to the expected normal value of 0.48. Intravenous administration of 5% glucose as sole source of calories may be a factor in distortion of body water compartments.

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CURRENT PRACTICES in intravenous feeding seriously lag behind advances in both nutritional understanding and techniques. Many nutritionally depleted persons are starved for weeks by the administration of small amounts of glucose as the sole source of calories, despite the ready availability of adequate intravenous diets. Furthermore, a growing body of evidence suggests that a daily dose of 50-200 g glucose as sole calorie source may have harmful effects; e.g., extensive information comes from studies on malnutrition in children of undeveloped countries,<sup>3,41,42</sup> and in experimental animals.<sup>32</sup> These studies show two main types or extremes of protein-calorie deficiency corresponding approximately to the syndromes of marasmus and kwashiorkor. Marasmus arises from inadequate intake of a diet in which protein and total calories are in approximate balance; there is wasting and failure to grow, but body composition remains relatively normal. Kwashiorkor results from intake of little or no protein with more or less adequate calories derived mainly if not entirely from carbohydrate. In this condition there is marked expansion of extracellular water (ECW) with pitting edema, ascites, and anasarca. There is also decreased cell mass, decreased plasma albumin, marked changes in plasma amino acid and enzyme patterns, fatty liver, and loss of hair pigment. One week of carbohydrate feeding can produce the fully developed kwashiorkor syndrome in an already undernourished child.<sup>41</sup>

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TABLE 1A. *Clinical Data of Postoperative Patients*

| No. | Age, Sex | Diagnosis                                                                                    | Operation                                                   | Estimated Blood Loss (ml) | Intraoperative Urine Output (ml) | Intraop & immediate postop Fluid Replacement (ml) |
|-----|----------|----------------------------------------------------------------------------------------------|-------------------------------------------------------------|---------------------------|----------------------------------|---------------------------------------------------|
| 2   | 30, M    | Ulcerative colitis and thrombocytopenia                                                      | Subtotal colectomy                                          | 500                       | 300                              | 4,000 Saline                                      |
| 3   | 30, M    | Obesity (340 lbs.), multiple hepatic abscesses                                               | Laparotomy, drainage of abscesses                           | 1,000                     | 600                              | 500 Blood, 750 Albumin, 1,700 Saline              |
| 5   | 20, M    | Renal artery stenosis                                                                        | Vein graft from aorta to left renal artery                  | 2,500                     |                                  | 1,500 Blood                                       |
| 6   | 80, M    | Sigmoid carcinoma with intestinal obstruction, perforated cecum, peritonitis and dehydration | Colostomy                                                   | 500                       |                                  | 1,000 Saline                                      |
| 7   | 82, M    | Strangulated inguinal hernia                                                                 | Hernioplasty                                                | 300                       | 150                              | 500 Blood, 1,000 Saline                           |
| 8   | 68, F    | Chronic esophagitis with stricture                                                           | Thoracotomy and esophagogastrectomy                         | 1200                      | 200                              | 1,500 Blood, 1,000 Saline                         |
| 9   | 35, F    | Aneurysm, right posterior Communicating artery                                               | Aneurysmal clipping                                         | 700                       | 1,500                            | 2,000 Saline                                      |
| 13  | 81, M    | Carcinoma of stomach, cardia                                                                 | Esophagogastrectomy, pyloroplasty                           | 2,000                     |                                  | 4,000 Saline, 500 Blood                           |
| 16  | 46, M    | Stomal ulcer, upper GI bleeding                                                              | Thoracotomy, vagotomy                                       | 1,250                     | 200                              | 2,000 Saline                                      |
| 20  | 81, M    | Carcinoma, rectum                                                                            | Abdominoperineal resection                                  | 350                       | 138                              | 1,500 Blood, 1,700 Saline                         |
| 21  | 71, F    | Aortic aneurysm                                                                              | Aortofemoral bypass                                         | 2,500                     | 454                              | 2,500 Blood, 2,100 Saline                         |
| 22  | 73, F    | Upper GI bleeding, cholecystitis                                                             | Gastrectomy, Cholecystectomy                                | 500                       | 150                              | 1,700 Saline                                      |
| 27  | 60, F    | Cerebral hemangioma                                                                          | Craniotomy                                                  | 1,200                     | 450                              | 2,700 Saline                                      |
| 29  | 60, F    | Rupture aneurysm of post communicating artery                                                | Craniotomy and clipping of aneurysm, Evacuation of hematoma | 800                       | 300                              | 2,000 Saline                                      |
| 30  | 77, M    | Meningioma, frontal area diarrhea, Na hypoproteinemia                                        | Removal of frontal meningioma                               | 600                       | 720                              | 1,500 Saline                                      |
| 31  | 45, F    | Meningioma, recurrent                                                                        | Craniotomy                                                  | 800                       | 350                              | 1,200 Saline                                      |

The implications for intravenous feeding of patients seem obvious. If carbohydrate feeding has such marked effects on children and experimental animals, it may be presumed to have some effects on adults. Intravenous administration of glucose as sole calorie source will be harmful if given in sufficient quantities over sufficient periods. It remains to determine what quantities over how long are required to do damage, and how the extent of damage is affected by the prior nutritional state of the patient.

Body composition measurements can be useful in diagnosis and evaluation of the degree of nutritional depletion. Deficits of intracellular water should closely approximate losses of body cell mass. Expansion of ECW also occurs with undernourishment and may reflect the effects of predominantly carbohydrate diets.

Frequently, knowledge of the changes in total body water (TBW) and its distribution is of crucial importance in the day-to-day care of the critically ill patient. Since these fluid abnormalities often cannot be inferred from clinical observation at the bedside, direct quantitative measurements are needed to define the major problems

and to suggest possible improvements in therapeutic approaches.

The present study documents body composition measurements in critically ill postoperative and nutritionally depleted patients. The possible relationships of the body water dislocations to protein-calorie deficiencies and to prior intravenous therapy are explored.

## Materials and Methods

### Protocol and Clinical Material

We studied blood volumes (BV), TBW and ECW in 31 patients suspected of fluid dislocations during the 18 months from December 1971 to June 1973. Prior reports were made of certain aspects of the data from some of these patients.<sup>10,18,36,37</sup> The patients have been divided into groups: (a) 16 critically ill postoperative patients (postoperative group); (b) 11 patients with severe nutritional depletion from chronic wasting diseases (depleted group); and (c) 4 depleted patients who also had clinical evidence of dehydration (depleted-dehydrated group). We also studied a control group of two normal subjects

TABLE 1B. Clinical Data of Depleted Patients

| No. | Age, Sex | Diagnosis                                                                                                                                                            |
|-----|----------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 1   | 59, M    | Recurrent cerebellar tumor                                                                                                                                           |
| 10  | 44, M    | Extensive abdominal and vertebral A-V malformations since the age of 3 yrs., recent bleeding into spinal canal; kyphoscoliosis, paraplegia, weight loss and debility |
| 11  | 27, F    | Regional ileitis                                                                                                                                                     |
| 12  | 36, F    | Chronic meningitis, revision of ventriculo-pleural shunt 5 months previously                                                                                         |
| 14  | 37, F    | Ulcerative colitis, weight loss, chronic wasting                                                                                                                     |
| 23  | 65, M    | Carcinomatosis with severe weight loss and chronic wasting                                                                                                           |
| 25  | 72, M    | Terminal carcinomatosis (colon)                                                                                                                                      |
| 26  | 71, F    | Diabetes mellitus, weight loss, anorexia                                                                                                                             |
| 28  | 67, M    | Upper GI bleeding, acute renal failure, gastric fistula                                                                                                              |
| 33  | 75, F    | Debility, carcinomatosis                                                                                                                                             |
| 34  | 63, M    | Giant duodenal ulcer, previous ileal resection with short bowel syndrome (debility and weight loss)                                                                  |

and one patient with myasthenia gravis who was otherwise healthy.

Repeat studies were made on 10 patients after varying periods (mean 18 days) of therapy; Patients were given 60 to 80 kcal per kg per day by standard total parenteral nutrition ("hyperalimentation") technique.<sup>16,36</sup> When bowel function returned, oral or tube feeding was started and gradually increased. When 2000 kcal was well tolerated orally, intravenous feeding was gradually curtailed. In 8 patients, exchangeable potassium (Ke) was measured. The clinical data are summarized in Table 1.

### Body Composition Measurements

**Plasma volume and blood volume** were measured by dilution of <sup>125</sup>I-radioiodinated human serum albumin. Three to five microcuries ( $\mu$ Ci) were accurately measured and injected. Blood was sampled prior to and at 5, 10 and 20 minutes after injection. Duplicate 1 ml aliquots of plasma were counted together with standard dilutions of the injection fluid in a well type  $\gamma$ -scintillation counter. The zero time value was obtained by extrapolation from the 5, 10 and 20 minute samples. Blood volume was calculated from plasma volume and hematocrit with correction factor (0.874) for the packing fraction and large vessel/whole body hematocrit ratio.

**Total body water (TBW) and extracellular water (ECW)** were determined simultaneously by dilution of tritiated water and <sup>82</sup>Br respectively using a procedure modified from that of Moore et al.,<sup>27</sup> 100  $\mu$  Ci of <sup>3</sup>H<sub>2</sub>O and 8  $\mu$  Ci of NH<sub>4</sub><sup>82</sup>Br were accurately measured and injected. Blood and cumulative urine samples were collected prior to and at 2, 3 and 5 hours after injection.

The radiobromide of 2 ml aliquots of plasma and urine was counted in a well type  $\gamma$ -scintillation counter in duplicate together with appropriate dilutions of the injection

TABLE 1C. Clinical Data of Depleted-Dehydrated Patients

| No. | Age, Sex | Diagnosis                                                             |
|-----|----------|-----------------------------------------------------------------------|
| 17  | 43, F    | Ulcerative colitis with chronic diarrhea                              |
| 19  | 56, F    | Gastric fistula, anorexia, weight loss                                |
| 32  | 67, M    | Intracerebral hemorrhage, with coma, diarrhea and chronic wasting     |
| 35  | 38, F    | Insulinoma of pancreas with hypoglycemia diarrhea and chronic wasting |

fluid. Bromide remaining in the body was taken to be the injected dose less cumulative urinary losses; bromide space was calculated from that remaining and the specific activity in plasma. The 3 and 5 hour samples were averaged and corrected for Donnan effects and erythrocyte content<sup>27</sup> to give extracellular water.

For tritium determination, duplicate samples of plasma, urine and standards were vacuum distilled. One ml aliquots of the distillate were added to 20 ml of a liquid scintillator solution and counted in a  $\gamma$  scintillation counter. The injected dose of tritium was corrected for measured urine losses and estimated insensible losses. The average of the 3 and 5 hour samples was used to calculate total body water.

**Intracellular water (ICW) was taken to be TBW-ECW.**

**Exchangeable potassium (Ke)** was determined with <sup>42</sup>K.<sup>27</sup> One hundred and fifty  $\mu$  curies ( $\mu$ Ci) was injected. Urine was collected for 12 hours prior to and three days after injection. Concentration of K<sup>+</sup> was determined with a flame photometer. Radioactivity of 2 ml aliquots of urine was measured in a well type scintillation counter. On day 2 and 3, when counts were very low, the potassium from 15 to 30 ml of urine was adsorbed on a 2 ml slurry of cation exchange resin for counting purposes. Standard dilutions of the injection fluid were also counted. The injected dose was corrected for urinary losses and divided by the specific activity (cpm/mEq) to give total Ke. Calculations were usually made for those urine samples collected from 20-28, 36-44, and 60-68 hours after injection. These values were plotted against time. If the plot indicated that complete equilibration was nearly approached, the value for the 60-68 hour sample was taken as the Ke.

### Counting Procedure and Isotope Interference

All samples were counted until the counting error [ $(200 \times \sqrt{N})/N$ ] was between 1 and 2%. Both <sup>82</sup>Br and <sup>42</sup>K emit radiation over a broad and overlapping range. Radiation from <sup>125</sup>I is confined to a narrow low energy band. All counting was performed in a 2 channel system. One window was set to include most of the <sup>82</sup>Br and <sup>42</sup>K peaks but no radiation from <sup>125</sup>I. When <sup>125</sup>I was counted in the presence of <sup>82</sup>Br a correction could be made for <sup>82</sup>Br radiation in the <sup>125</sup>I window. <sup>125</sup>I or <sup>82</sup>Br were never counted in the presence of <sup>42</sup>K. This was quite feasible,

TABLE 2. Body Composition Data of Postoperative and Depleted Patients and Control Subjects Compared to Expected\* Values Based on Patient's Observed Current Weight.

| Patient                          | Body Weight (kg) |      |        | ECW (liters) |      |        | TBW (liters) |      |       | ICW (liters) |      |       |
|----------------------------------|------------------|------|--------|--------------|------|--------|--------------|------|-------|--------------|------|-------|
|                                  | Obs              | Exp  | Diff   | Obs          | Exp  | Diff   | Obs          | Exp  | Diff  | Obs          | Exp  | Diff  |
| Postoperative Patients           |                  |      |        |              |      |        |              |      |       |              |      |       |
| 2                                | 70.0             | 70.3 | - 0.3  | 16.0         | 17.4 | - 1.4  | 37.1         | 40.9 | - 3.8 | 21.1         | 23.5 | - 2.4 |
| 3                                | 155.0            | 79.4 | +75.6  | 45.8         | 21.9 | +23.9  | 71.0         | 51.6 | +19.4 | 25.2         | 29.7 | -4.5  |
| 5                                | 86.0             | 81.2 | + 4.8  | 29.8         | 20.3 | + 9.5  | 52.1         | 44.8 | + 7.3 | 22.3         | 24.6 | - 2.3 |
| 6                                | 52.0             | 68.9 | -16.9  | 19.1         | 14.5 | + 4.6  | 35.7         | 28.8 | + 6.9 | 16.6         | 14.3 | + 2.3 |
| 7                                | 46.0             | 61.2 | -15.2  | 18.2         | 13.1 | + 5.1  | 28.1         | 25.9 | + 2.2 | 9.9          | 12.8 | - 2.9 |
| 8                                | 36.5             | 62.2 | -25.7  | 14.1         | 9.4  | + 4.7  | 23.7         | 19.0 | + 4.7 | 9.6          | 9.6  | 0     |
| 9                                | 53.0             | 64.4 | -11.4  | 16.3         | 13.0 | + 3.3  | 27.3         | 27.5 | - 0.2 | 12.4         | 14.5 | - 2.1 |
| 13                               | 61.0             | 68.9 | - 7.9  | 16.9         | 16.3 | 0      | 33.6         | 32.2 | + 1.4 | 17.3         | 15.9 | + 1.4 |
| 16                               | 57.0             | 77.2 | -20.2  | 19.0         | 15.2 | + 3.8  | 36.1         | 33.7 | + 2.4 | 17.1         | 18.5 | - 1.4 |
| 20                               | 63.0             | 73.5 | -10.5  | 15.3         | 16.8 | - 1.5  | 33.0         | 33.1 | - 0.1 | 17.7         | 16.3 | + 1.4 |
| 21                               | 73.0             | 67.6 | + 5.4  | 18.0         | 15.4 | + 2.6  | 38.9         | 31.1 | + 7.8 | 20.9         | 15.7 | + 5.2 |
| 22                               | 51.0             | 80.3 | -29.3  | 19.5         | 14.2 | + 5.3  | 30.0         | 28.7 | + 1.3 | 10.5         | 14.5 | - 4.0 |
| 27                               | 68.0             | 71.2 | - 3.2  | 13.9         | 15.1 | - 1.2  | 23.3         | 30.8 | - 7.5 | 9.4          | 15.7 | - 6.3 |
| 29                               | 51.3             | 67.6 | -16.3  | 15.6         | 12.4 | + 3.2  | 27.1         | 25.4 | + 1.7 | 11.5         | 13.0 | - 1.5 |
| 30                               | 51.0             | 70.1 | -19.1  | 17.2         | 14.3 | + 2.9  | 28.6         | 28.6 | 0     | 11.4         | 14.3 | - 2.9 |
| 31                               | 52.7             | 65.8 | -13.1  | 13.2         | 12.9 | + 0.3  | 25.5         | 26.9 | - 1.4 | 12.3         | 14.1 | - 1.8 |
| Mean                             | 64.2             | 70.6 | - 6.5  | 19.1         | 15.1 | + 4.0  | 34.4         | 31.8 | + 2.6 | 15.3         | 16.7 | - 1.4 |
| P†                               |                  |      | .01    |              |      | .01    |              |      | NS    |              |      | .04   |
| Depleted Patients                |                  |      |        |              |      |        |              |      |       |              |      |       |
| 1                                | 65.5             | 78.0 | -12.5  | 19.4         | 17.0 | + 2.4  | 33.5         | 36.1 | - 2.6 | 14.1         | 19.1 | - 5.0 |
| 10                               | 48.0             | 63.5 | -15.5  | 18.0         | 13.2 | + 4.8  | 29.0         | 29.5 | - 0.5 | 11.0         | 16.3 | - 5.3 |
| 11                               | 68.0             | 67.6 | + 0.4  | 16.4         | 14.7 | + 1.7  | 29.3         | 29.4 | - 0.1 | 12.9         | 14.7 | - 1.8 |
| 12                               | 37.0             | 54.9 | -17.9  | 13.0         | 9.9  | + 3.1  | 21.1         | 21.4 | - 0.3 | 8.1          | 11.5 | - 3.4 |
| 14                               | 45.0             | 62.6 | -17.6  | 18.1         | 11.6 | + 6.5  | 27.0         | 24.7 | + 2.3 | 8.9          | 13.2 | - 4.3 |
| 23                               | 53.0             | 70.3 | -17.3  | 18.3         | 14.6 | + 3.7  | 32.3         | 30.3 | + 2.0 | 14.0         | 15.7 | - 1.7 |
| 25                               | 59.0             | 67.1 | - 8.1  | 18.6         | 16.0 | + 2.6  | 34.8         | 32.5 | + 2.3 | 16.2         | 16.5 | - 0.3 |
| 26                               | 50.0             | 60.3 | -10.2  | 22.8         | 12.1 | +10.7  | 34.0         | 24.3 | + 9.7 | 11.2         | 12.2 | - 1.0 |
| 28                               | 70.5             | 66.3 | + 4.2  | 31.1         | 18.0 | +13.1  | 46.5         | 37.3 | + 9.2 | 15.4         | 19.3 | - 3.9 |
| 33                               | 31.8             | 62.2 | -30.4  | 12.0         | 8.4  | + 3.6  | 22.2         | 16.8 | + 5.4 | 10.2         | 8.4  | + 1.8 |
| 34                               | 40.7             | 70.3 | -29.7  | 15.5         | 11.8 | + 3.7  | 31.2         | 24.6 | + 6.6 | 15.7         | 12.8 | + 2.9 |
| Mean                             | 51.7             | 65.7 | -14.1  | 18.5         | 13.4 | + 5.1  | 31.0         | 27.9 | + 3.1 | 12.5         | 14.5 | - 2.0 |
| P†                               |                  |      | .03    |              |      | < 0.01 |              |      | NS    |              |      | .03   |
| Depleted and Dehydrated Patients |                  |      |        |              |      |        |              |      |       |              |      |       |
| 17                               | 57.3             | 63.1 | - 5.8  | 13.7         | 14.8 | - 1.1  | 34.8         | 35.7 | - 0.9 | 20.9         | 20.8 | + 0.1 |
| 19                               | 47.7             | 62.4 | -14.7  | 7.2          | 11.9 | -4.7   | 20.5         | 24.8 | -4.3  | 13.3         | 12.9 | + 0.4 |
| 32                               | 65.0             | 77.2 | -12.2  | 16.1         | 17.1 | -1.0   | 30.7         | 35.9 | -5.2  | 14.6         | 18.8 | -4.2  |
| 35                               | 33.2             | 61.7 | -28.5  | 10.6         | 8.9  | +1.7   | 20.6         | 18.4 | +2.2  | 10.0         | 9.5  | + 0.5 |
| Mean                             | 50.8             | 66.1 | -15.3  | 11.9         | 13.2 | - 1.3  | 26.7         | 28.7 | - 2.0 | 14.7         | 15.5 | - 0.8 |
| All Patients                     |                  |      |        |              |      |        |              |      |       |              |      |       |
| Mean                             | 58.0             | 68.3 | -10.3  | 18.0         | 14.3 | +3.7   | 32.2         | 30.0 | +2.2  | 14.3         | 15.8 | - 1.5 |
| P†                               |                  |      | < 0.01 |              |      | < 0.01 |              |      | NS    |              |      | .015  |
| Control Subjects                 |                  |      |        |              |      |        |              |      |       |              |      |       |
| 18                               | 82.0             | 89.5 | - 7.5  | 19.4         | 19.4 | 0      | 47.1         | 45.2 | +1.9  | 27.7         | 25.7 | + 2.0 |
| 36                               | 89.2             | 90.7 | - 1.5  | 21.0         | 20.7 | +0.3   | 48.5         | 45.4 | +3.1  | 27.5         | 24.7 | + 2.8 |
| 37                               | 82.0             | 80.3 | + 1.7  | 19.0         | 19.7 | -0.7   | 44.0         | 42.7 | +1.3  | 25.0         | 22.9 | + 2.1 |
| Mean                             | 84.4             | 86.8 | - 2.4  | 19.8         | 19.9 | -0.1   | 46.5         | 44.4 | + 2.1 | 26.7         | 24.5 | + 2.2 |

\*Expected values derived by procedures described in text.

†See text for derivation of probability that difference between averages of observed and expected values are statistically significant.

even on repeat determinations, because of the short half-life (12 hours) of  $^{42}\text{K}$ . When  $^{42}\text{K}$  was counted in the presence of  $^{82}\text{Br}$ , the bromide was removed by passing the urine over an anion exchange resin. In most instances, contamination of  $^{125}\text{I}$  with  $^{82}\text{Br}$  was avoided by injecting the bromide just after completing the plasma volume determination. Contamination of tritium by the other isotopes was completely eliminated by the distillation procedure. This also eliminated problems of variable quenching.<sup>28</sup>

### Derivation of Expected and Normal Values

Expected values for blood volume were obtained from the equations of Nadler et al.<sup>30</sup> based on height, weight and sex.

Expected values for TBW were derived from age, weight and sex, using the nomogram of Moore et al.<sup>27</sup> Expected values for ECW, ICW and Ke were obtained from age, sex and the value for TBW according to the regression equations of the same authors.

Expected normal values for weight were derived from height and sex using age-height-weight tables for insured persons in the United States.<sup>14</sup> In 11 instances, normal pre-illness weights were obtained as part of the patient's history. The mean of values obtained from history were  $7 \pm 15\%$  (S.D.) less than that of the tables; this difference was not statistically significant. The standard deviation indicates that for a series of 11 patients, the uncertainty in mean values will be of the order of 4%, and does not negate any of the conclusions.

### Statistical Methods

The probability (P) that a given set of observed values belong to the same population as the corresponding expected values was calculated from a sign test. For example, in Table 2 there were 16 observations of ECW for postoperative patients. There were 13 positive and 3 negative differences. From the binominal distribution, the likelihood that three or less negative values would occur by chance is 0.01 indicating that, statistically, the observed values are significantly above the expected values.

TABLE 3. Observed and Predicted Ratios of Extracellular to Total Body Water for Patient and Control Subjects

|                     | Number of Subjects | Observed | Predicted | Difference |
|---------------------|--------------------|----------|-----------|------------|
| Postoperative       | 16                 | 0.55     | 0.48      | + .07      |
| Depleted            | 11                 | 0.59     | 0.48      | + .11      |
| Depleted-dehydrated | 4                  | 0.45     | 0.46      | -.02       |
| All patients        | 31                 | 0.55     | 0.48      | + .07      |
| Controls            | 3                  | 0.43     | 0.45      | -.02       |

## Results

### Changes in Body Composition from Predicted Values Based on Current Body Weight

In comparing average values for the entire series of patients to predicted values based on current weight, there was no change in blood volume,\* an ECW excess of 3.7 L ( $P < 0.01$ )\*\* and an ICW deficit of 1.5 L ( $P < 0.015$ ) (Table 2). The slightly increased TBW, which was not statistically significant, reflected a balance between increased ECW and decreased ICW.

The depleted and postoperative groups considered separately had similar patterns to each other and to the series as a whole; both groups had marked body water dislocations in which the ECW was greatly expanded compared to the ICW or TBW. Expected ratios of ECW:TBW are a function of age and sex and ranged from 0.40 for a 15-year-old boy to 0.50 for 80-year-olds of either sex,<sup>27</sup>

The mean expected values varied between 0.45 and 0.48 for the several groups of patients and control subjects (Table 3). The observed values of 0.55 and 0.59 for the postoperative and depleted patients, respectively, were markedly increased above predicted values. By contrast, the depleted-dehydrated patients had no change in this ratio and relatively normal water distribution.

### Changes in Body Weight

Observed weights in all 3 patient groups were significantly less than predicted normal values (Table 2). The control subjects were slightly decreased from expected values, but this was not statistically significant. The weight loss of the postoperative patients was obscured by patient 3 who was very obese. Without patient 3 the mean weight loss for this group was 11.9 instead of 6.5 kg. This was not significantly different from the weight losses of the depleted and depleted-dehydrated groups (mean 14.4 kg).

### Changes in Body Composition from Expected Normal Values

The deficits in ICW shown in Table 2 were relatively

\*We previously reported a blood volume deficit averaging 0.53 l for a subset of the patients reported here.<sup>37</sup> This discrepancy is largely due to the choice of expected values. We formerly used the method of Davis<sup>13</sup> which assumes a direct proportionality between blood volume and surface area. The method of Nadler et al.<sup>30</sup> used in the present report is derived by regression of blood volume against either surface area or  $\text{ht}^2 \times \text{wt}$ , and gives much better predictions in a large number of normal subjects than the Davis procedure. Applied to the entire series of subjects reported here, predictions by the Davis procedure averaged 0.4 l more than those by the Nadler method.

\*\*Reports of postoperative contraction of "functional" extracellular water<sup>35</sup> are not in conflict with these findings. "Functional" ECW refers to that part of the total ECW with which the tracer,  $^{35}\text{SO}_4$ , is in rapid equilibration. Contraction of "functional" ECW has been observed to occur simultaneously with expansion of total ECW.

TABLE 4. *Observed Body Composition Values Expressed as Per Cent Deviation from Predicted Values Based on Current as well as on Normal Expected Weight*

|                     | No. of Subjects | Per Cent Deviation from Predicted Values Based on |                    |     |     |                   |                   | ICW |
|---------------------|-----------------|---------------------------------------------------|--------------------|-----|-----|-------------------|-------------------|-----|
|                     |                 | ECW                                               | Current Weight TBW | ICW | Wt. | Normal Weight ECW | Normal Weight TBW |     |
| Postoperative       | 16              | +25                                               | + 7                | - 7 | -10 | +11               | - 4               | -18 |
| Depleted            | 11              | +39                                               | +13                | -12 | -22 | +15               | - 7               | -28 |
| Depleted-dehydrated | 4               | - 8                                               | - 6                | - 4 | -24 | -27               | -24               | -22 |
| All patients        | 30              | +25                                               | + 7                | - 9 | -16 | + 7               | - 8               | -22 |
| Controls            | 3               | - 1                                               | + 5                | + 9 | - 3 | - 3               | + 2               | + 7 |

modest and by themselves understate the extent of nutritional depletion. A better estimate was obtained when weight losses and relative compositional changes were combined. This was done by comparing observed values to predicted values based on normal preillness weights (Table 4). ICW deficits for all patients averaged 9% based on current weight and 22% based on normal weight. As compared to ICW losses, weight losses underestimated the extent of depletion except in the dehydrated patients. This was more marked in some individuals than in others. For instance, patient 27 had a weight loss of 4% and an ICW loss of 42% based on expected normal values.

The pattern of postoperative and depleted patients is quite similar because many of the postoperative patients were also nutritionally depleted. If one uses a 20% deficit of ICW as an arbitrary definition of severe nutritional depletion, 9 out of 16 postoperative patients and 9 out of 15 depleted patients would be classified as severely depleted. Five of the postoperative patients and one of the depleted patients had little or no nutritional depletion as indicated by less than 10% deficit in ICW. Except for the depleted-dehydrated group, all but one exhibited marked distortion of the ECW:TBW ratio.

Relative weight losses (16%) were twice as great as losses of TBW (8%). This reflects two processes: 1) proportional increase of ECW which has a high water content; and 2) use of fat depots which have a low water content.

#### *Changes of Exchangeable Potassium Compared to ICW*

Exchangeable potassium (Ke) was measured in 8 patients and 2 control subjects as an independent method for estimation of changes in cell mass. The average ICW and Ke values of the patients were -26% and -41%, respectively; the average values of the controls were +10% and +3%, respectively, of their expected norms.

#### *Effects of Parenteral Nutritional Therapy*

Body composition measurements were repeated after parenteral nutritional therapy in 9 patients, 5 were depleted and 4 were postoperative. There were modest but variable increases in weight and TBW. Changes in ECW, which were also variable, decreased 1.8 l on the average.

All but one patient had marked increased ICW which averaged 3.2 l or 27% of the starting values. The mean deficit in ICW before treatment was 6.0 l; 53% of this was restored during the 18 day period of therapy. The mean ratio, ECW:TBW, for these patients was 0.58 before and 0.50 after therapy, the predicted normal value being 0.48. Thus, therapy returned this ratio about three quarters of the way back toward expected normal values (Table 5).

Concurrent with these body compositional changes were pronounced clinical improvements in all patients. Several patients who were comatose at the start of parenteral nutrition returned to a conscious state within periods ranging from a few days to a few weeks. During therapy, the subjects changed from negative to positive potassium balance and exhibited substantial improvement in serum albumin and sodium concentrations.

### **Discussion**

#### *Intracellular Water as an Index of Nutritional Status*

Estimation of nutritional status in seriously ill patients is difficult, particularly in protein-calorie malnutrition for which there are no highly specific tests. Weight loss, nutritional history, and plasma sodium and albumin concentrations are the most readily available indices. Sodium and albumin concentrations are affected by other than nutritional changes and at best provide only a rough index of malnutrition. Likewise, nutritional history provides only a gross qualitative picture of nutritional status. Weight change, which probably is the most reliable and quantitative of these indices, also has drawbacks. The preillness weight, which usually is obtained by questioning the patient, may be unreliable and current weight may be hard to obtain in the bed ridden subject. Weight loss may represent loss of either fat or lean body mass with quite different nutritional implications. Most importantly, expansion of the ECW, whether from nutritional or other causes, may obscure losses of body cell mass. Thus, in our series of patients, weight loss averaged 16% as compared with 22% ICW loss. In individual cases this discrepancy was much greater.

Loss of body cell mass is more appropriate than weight

TABLE 5. *Effects of Parenteral Nutrition on Body Composition*

| No.    | Patient  | Type   | Increases (+) or Decreases (–) After Parenteral Nutrition for: |        |      |     |    | Time<br>Between<br>Measurements (days) |
|--------|----------|--------|----------------------------------------------------------------|--------|------|-----|----|----------------------------------------|
|        |          |        | Body weight                                                    | ECW    | TBW  | ICW |    |                                        |
|        | kg       | liters | liters                                                         | liters | %    |     |    |                                        |
| 1      | Depleted | +6     | –9.1                                                           | –0.2   | +8.9 | +63 | 25 |                                        |
| 9      | Postop   | +1     | –1.0                                                           | +1.1   | +2.1 | +17 | 14 |                                        |
| 10     | Depleted | –1     | +2.2                                                           | +5.7   | +3.5 | +32 | 14 |                                        |
| 12     | Depleted | +3     | +1.0                                                           | +3.0   | +2.0 | +25 | 14 |                                        |
| 14     | Depleted | –4     | –5.0                                                           | –3.8   | +1.2 | +13 | 11 |                                        |
| 25     | Depleted | 0      | –5.7                                                           | +0.2   | +5.9 | +36 | 6  |                                        |
| 27     | Postop   | +7     | +0.2                                                           | +4.9   | +4.7 | +50 | 38 |                                        |
| 29     | Postop   | +6     | –0.4                                                           | –1.1   | –.7  | –6  | 27 |                                        |
| 31     | Postop   | 0      | +1.3                                                           | +2.5   | +1.2 | +10 | 11 |                                        |
| Mean   |          | +2     | –1.8                                                           | +1.4   | 3.2  | +27 | 18 |                                        |
| S.E.M. |          | 1.2    | 1.3                                                            | 1.0    | 1.0  | 7   |    |                                        |

loss as an index of protein-calorie depletion.<sup>27</sup> Two measurable quantities, closely related to body cell mass, are intracellular water and Ke. The latter may be measured directly and, given enough care and time, with considerable accuracy. However, measurement of Ke presents serious technical difficulties for critically ill patients in the routine laboratory setting. Equilibration time is three days in normal subjects and may be longer in seriously ill patients.<sup>43</sup> The maximum permissible dose of <sup>42</sup>K is 150  $\mu$ Ci, its half-life is 12 hours. By three days after injection the specific activity is so low that the potassium in urine or other fluids must be concentrated in order to minimize counting errors. Even with accurate three day counts there is no guarantee that equilibration is complete in sick patients, accurate counting on the fourth day is almost impossible, and the information is not available for use in patient management until four days after starting the determination. In addition to technical problems, there are problems in interpretation. In heart failure and other diseases, loss of potassium may be proportionately much greater than loss of body cell mass.<sup>19,29</sup> Under these circumstances, Ke ceases to be an index of nutritional depletion. In our opinion, these problems make Ke unsuitable for routine clinical estimation of body cell mass.

An alternative approach is to measure ICW. The relative composition of cells and in particular, their water content, presumably fluctuates within narrow limits. Therefore, major changes in the body cell mass are reflected in ICW changes. Acute changes in intracellular water may occur in dehydration states<sup>15</sup> and after cardiac surgery;<sup>12</sup> these are of the order of 5 to 10% of total ICW and are approximately at the limit of sensitivity of the methods used. Acute changes of this order of magnitude should not seriously interfere with use of ICW as an index of body cell mass.

Measurement of ICW must be made indirectly, as the difference between TBW and ECW. TBW is readily mea-

sured by dilution of tritiated water, ECW has been measured by dilution of a variety of tracers including inulin, sucrose, thiocyanate, and isotopically labelled chloride, sulfate and bromide. Of these <sup>82</sup>Br<sup>–</sup> is most suitable for clinical uses because it is easy to determine and reaches a quite stable concentration in plasma within a few hours even in sick patients.<sup>6,7,12,17,22,24,27,31,38,39</sup> The measurement with both tritiated water and <sup>82</sup>Br<sup>–</sup> have been shown to be highly reproducible in normal subjects.<sup>38</sup> By this procedure a complete determination of ECW, TBW and ICW may be performed within 24 hours and requires no more than four to five 16 ml blood samples.

#### *Extent of Cellular Penetration of Bromide*

Bromide does enter cells to some extent, so that it may overestimate ECW. However, in normal subjects errors due to cellular penetration appear to be small and reproducible. A potentially more serious disadvantage is that permeability of cells to bromide may increase in various severe illnesses,<sup>12,31,33</sup> so that increased bromide space in ill patients may in part reflect increased bromide penetration into cells; this overestimates the ECW and underestimates the calculated ICW. As an approach to estimating the extent of this problem, we compared Ke and ICW measurements; the data indicate that ICW calculations consistently underestimate deficits in body cell mass as compared to Ke measurements. In part, this may be due to failure of the potassium to reach complete equilibration by our procedures in a routine laboratory setting. The findings of Moore et al.<sup>27</sup> show a very close correlation of Ke with ICW in normal subjects and patients with wasting diseases. Thus, data from both laboratories indicate that bromide and tritiated water do not overestimate ICW deficits as compared to measurement of Ke.

Cleland et al.<sup>12</sup> have reported apparent increases of 1-2 liters in ECW at the expense of ICW after cardiac surgery. These changes were most pronounced in pa-

tients with preoperative cardiac failure. These were measured by changes in dilution of  $^{82}\text{Br}^-$  and  $^3\text{H}_2\text{O}$  pre- and postoperatively. They have reported similar shifts in hypoxic dogs.<sup>33</sup> Dogs were made to breathe a mixture of 5%  $\text{O}_2$ -95%  $\text{N}_2$ . Within five minutes, ECW, measured by  $^{82}\text{Br}^-$  dilution, increased by 5%, but remained stable thereafter. These shifts can be explained as due to shifts in water from one compartment to another, changes in membrane permeability to  $^{82}\text{Br}^-$ , or to both; when they occur they introduce an error in the use of ICW as an index of nutrition. This error may be as high as 10% in cardiac failure but in general appears to be smaller.

Nicholson and Zilva<sup>31</sup> have interpreted very high values of ECW, up to 50% of body weight, as indicating increased cell permeability to  $\text{Br}^-$  in preterminal carcinomatosis. We have measured both TBW and ECW in a 46-year-old woman, one week prior to death from a metastasized ovarian carcinoma. She had a body weight of 35.8 kg, TBW of 27.8 l, and ECW of 21.1 l; she was not edematous. Thus, her ECW, although 59% of body weight, was entirely consistent with an ICW of 7.7 l and total solids (obtained by subtracting TBW from body weight) of 8.0 kg. Therefore, we conclude that abnormally high values of ECW actually occur in this type of patient and cannot, per se, be considered as evidence of increased permeability to  $\text{Br}^-$ .

#### *Reproducibility of ICW Measurements and Comparison to Predicted Values*

In ill patients, variation of ECW and ICW with time is too great to test reproducibility of the method by multiple determinations in one individual, but the normal subject may be expected to have a more constant composition. Hyatt and his group<sup>38</sup> made duplicate measurements of body composition in 43 healthy young men at one week intervals. Their methods for measuring ECW with  $^{82}\text{Br}^-$  and TBW with  $^3\text{H}_2\text{O}$  were very similar to ours except that they took six samples at hourly intervals after injection and extrapolated to zero time. We, in accordance with Moore et al.,<sup>27</sup> used the average of the three and five hour sample. Our method would tend to give higher values for ECW, in part because we would include transcellular water which accounts for about 5% of ECW; extrapolation to zero time excludes most of the transcellular water. Dr. Kenneth H. Hyatt has very kindly made available to us the individual measurements on these 43 men which were not published in detail.<sup>38</sup> In 38 of the men, duplicate measurements were made of both ECW and TBW permitting calculation of ICW. The mean values for all second determinations of ICW differed negligibly (—0.04%) from the mean for all the first determinations; 19 of the second determinations were greater, 19 less than the first determination. The average difference between first and second determinations, regardless of sign, was 4.3%,

since the true value should tend to lie between the two determinations, the probable error of any one determination of ICW is less than 4%. In ill patients with fewer blood samples the probable error will undoubtedly be somewhat higher, probably in the neighborhood of 5%.

We have compared 79 estimations of ICW observed in the 43 men to the predicted values based on the regression equations derived by Moore et al.<sup>27</sup> On the average the observed values were 10.5% higher than predicted. This may be explained in large part by the differences in methodology, discussed above, since the procedure of Hyatt and co-workers<sup>52</sup> should give lower values of ECW and therefore higher values of ICW than that of Moore et al. on which the regression equations were based. Of more interest with respect to ill patients is the variability of the individual deviations. Each individual observation was compared to a predicted value corrected by adding 10.5%. The S. D. of the differences between these values was found to be 11.6%, indicating that in two-thirds of the cases, the observed values were within 11.6% of the predicted values.

These data suggest that the major source of error in the use of ICW as an index of nutritional depletion comes in predicting the normal values, and this error is only of the order of 12%. This limits the usefulness of ICW in mild depletion. When sequential measurements of body composition can be made and compared in the same individual, the major errors are technical and of the order of 5%. In our opinion, the ICW remains the single most useful index of moderate or severe nutritional depletion.

#### *Extracellular Water: Total Body Water Ratio*

This ratio, related to ICW, is largely independent of body weight or fat content and dependent only on age and sex. It is increased in illnesses reflecting expansion of ECW, contraction of ICW or both; it varies within narrow limits in the normal population.<sup>27</sup> Therefore, it is more reliable than ICW, although not a direct index of nutritional depletion. An increase of 0.05 in this ratio from predicted values suggests significant dislocation of body water.

#### *Incidence of Severe Nutritional Depletion*

The data reported here indicate that severe protein-calorie depletion remains an important problem; in 18 months, 18 of 31 patients studied were severely depleted. This includes only those patients admitted to the ICU so that these figures underestimate the actual incidence of severe malnutrition at this hospital. The high incidence of malnutrition among those patients admitted for postoperative care rather than for repletion therapy indicates that, even at this stage of depletion, the relation of malnutrition to serious illness was not suspected. While some of these patients were undernourished on admis-

sion, most of their nutritional depletion occurred in hospital. Other reports indicate that there is a low awareness of nutritional requirements in many hospitals.<sup>11</sup>

### *Diagnosis and Treatment of Severe Nutritional Depletion*

There is little doubt that severe nutritional depletion makes a substantial contribution to morbidity among surgical patients.<sup>2,16,21,23,40</sup> During the past 10 years practical procedures for adequate parenteral nutrition have become available and are effective in preventing and treating most cases of severe depletion. In this country the most readily available procedures are variants of intravenous hyperalimentation, popularized by Dudrick and co-workers.<sup>16</sup> In this procedure, hypertonic glucose with amino acid solutions, vitamins, and minerals are infused continuously through a central venous catheter. Because of the problems of long term maintenance of this catheter, total parenteral nutrition is frequently restricted to special care environments. In countries where fat emulsions are given intravenously, adequate intravenous feeding may often be achieved via peripheral veins and the need for special care facilities is lessened.

Despite its availability, adequate parenteral nutrition is not provided to all patients who would benefit from it. There are several factors which account for this. One factor is its lack of availability on general services. If adequate parenteral alimentation is only supplied in special services such as the ICU, it will be given only to patients sick enough to warrant ICU admission and, therefore, cannot be used as a preventive measure. If the depleted patients had been given adequate nutrition on the general service, many of them would not require ICU admission. Adequate parenteral nutrition availability on the floors is feasible and this would permit its wider use as a preventive rather than a therapeutic measure.

Another factor is the failure of many physicians to recognize the appropriate time for nutritional therapy. This is largely because of its limited availability; it does little good to be aware of a need which cannot be met. Ready availability of adequate intravenous nutrition would largely eliminate this problem.

A third factor is the unavailability of diagnostic methods for nutritional depletion. Physical appearance and nutritional history give qualitative assessments of depletion, but not quantitative ones. Weight loss provides useful quantitative information, but frequently underestimates the degree of depletion, since there may be a relative ECW expansion. As discussed above, the best method for quantifying nutritional depletion is estimation of the loss of body cell mass by ICW.

A fourth factor is the poor definition of what constitutes sufficient nutritional depletion to require nutritional therapy. It is clear that severe depletion contributes sig-

nificantly to mortality.<sup>2,16,21,23,40</sup> At the other end of the spectrum, mild weight loss (5-10%) is not usually considered to require nutritional therapy, although there is little objective evidence to document this position. Weight loss between 10 and 30% may be seriously detrimental, although again there is little quantitative evidence which demonstrates a correlation between degree of depletion and morbidity. The degree of depletion which requires adequate intravenous nutrition is probably in the range of 10-20% of body cell mass. It should be a major objective of further clinical investigation to define more precisely this point in terms of the correlation of nutritional depletion with morbidity.

### *Nutritional Implications of Extracellular Water Expansion*

Expanded ECW has been reported in wasting diseases<sup>27</sup> and in German soldiers on repatriation from Russian prison camps after World War II.<sup>26</sup> Findings in both these studies are very similar to those reported here. ECW was expanded on a relative and frequently on an absolute basis despite considerable weight loss, and even greater relative loss of body cell mass. Expanded ECW has been found by others after weight loss,<sup>16,21,39</sup> post-operatively,<sup>4,5,12,22,25,27,33,34</sup> and after resuscitation from trauma and hemorrhage.<sup>1,15</sup> In part, acute increases in ECW may result from administration of saline or other crystalloid solutions. However, similar treatment in normal individuals does not result in ECW expansion. Retention of administered fluids in acutely ill subjects must be partly due to other factors. One of these factors may be the administration of carbohydrate as sole caloric source. This is likely in chronic patients with weight loss, since ECW expansion is also characteristic of kwashiorkor. That intravenous glucose administration may produce fluid retention acutely is suggested by Gamble's findings<sup>20</sup> that glucose administration to fasting, healthy young men markedly reduces Na<sup>+</sup> excretion; this effect is increased when NaCl is given simultaneously.

The possibility that ECW expansion is a side effect of intravenous dextrose administration has potentially serious implications to patient management. Expanded ECW is considered undesirable, as it may contribute to the 'wet lung' syndrome.<sup>1</sup> This provides an additional impetus to find substitutes for 5% glucose as the routine intravenous fluid. One possibility is the use of 3% amino acid solutions as a supplement to, or substitute for, 5% glucose.<sup>8,9,18</sup>

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