POSTOPERATIVE NITROGEN LOSS AND STUDIES ON PARENTERAL NITROGEN NUTRITION BY MEANS OF CASEIN DIGEST*

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THE NITROGEN METABOLISM of the surgical patient has been the subject of special consideration in recent years. The possibility of parenteral administration of nitrogenous foodstuff further extends the practical aspects of this problem.

A major surgical procedure with operative manipulation of deeply situated viscera and tissues followed by a brief period of starvation and then gradual return, over several days, to ingestion of normal diet constitutes together with the complications often developing, such as shock, fever, vomiting, the presence of injured tissues, *etc.*, an altered physiologic state. Because intake of nitrogen obviously does not equal output during this period, a state of negative nitrogen balance exists for varying periods. Operative trauma itself may be the cause of increased nitrogen catabolism (so-called toxic (?) destruction of protein.)

In order to obtain some concrete conception of the extent of this loss, in 41 patients subjected to major operations of various types, nitrogen balance studies were carried out from the day of operation to and including the tenth postoperative day.

Urine, feces, excess sputum, biliary or other drainage, vomitus and gastric aspirations were collected each 24-hour period and analyzed for nitrogen (Micro-Kjeldahl), and this was compared with the nitrogen intake each day. The latter was obtained from standard dietitians' charts and this portion of the data represents, therefore, an approximation, since it was not practical to analyze each sample of food received from day to day for the exact nitrogen content.

The conditions pertaining to the postoperative management in this group of patients were: (a) Where the abdomen or thorax was not opened liquids were permitted by mouth as soon as tolerated and shortly thereafter a soft or regular diet was given, the latter being taken by the third to fifth postoperative day; and (b) where the abdomen or thorax was opened nothing was taken by mouth for the first 48 to 72 hours, fluids being given parenterally; on the third or fourth day small quantities of water were taken at hourly intervals, the next day clear liquids, and if tolerated soft to regular diet ingested by the sixth or seventh day, except in operations upon the stomach, where increase in food by mouth was more gradual.

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Blood transfusions which were given in many cases following operation have not been taken into account in calculating the nitrogen balance.

The results of the studies on net nitrogen loss (or gain) over the ten-day postoperative period are shown in Table I.

TABLE I

NET LOSS OR GAIN IN NITROGEN IN TEN-DAY POSTOPERATIVE PERIOD IN 41 PATIENTS UNDERGOING A VARIETY OF MAJOR SURGICAL PROCEDURES

Operation	Patient	Net N. Loss or Gain 10-day P.O. period
Thoracic sympathectomy	L. M.	− 27.10 Gm.
	McM.	− 68.47 Gm.
Esophagoplasty	Ril.	− 75.17 Gm.
Exploratory celiotomy	Windb.	− 65.37 Gm.
	Bernst.	− 16.86 Gm.
	Valent.	− 3.81 Gm.
Acute append. (peritonitis)	Ad.	− 49.17 Gm.
Gastric resection	Neh.	− 73.53 Gm.
	Maz.	−175.79 Gm.
Repair perforated peptic ulcer	Ly.	−136.06 Gm.
Cholecystectomy	Fish	− 24.34 Gm.
	Thomp.	− 27.78 Gm.
	Miller	− 23.18 Gm.
	Lew	− 20.74 Gm.
	Barger	− 75.90 Gm.
	Patton	− 24.73 Gm.
	Bohl.	− 68.65 Gm.
	Glynn	+ 5.91 Gm.
	Clayt.	− 36.44 Gm.
	Mal.	+ 1.13 Gm.
	Pears.	−114.09 Gm.
Radical mastectomy	Rawl.	+ 1.23 Gm.
	Meed.	− 15.68 Gm.
	Shaw	− 13.51 Gm.
Operation on extremities	Burdi.	− 9.98 Gm.
	Kit.	− 6.21 Gm.
	Gal.	− 30.00 Gm.
Thyroidectomy	Anth.	+ 4.44 Gm.
Herniotomy	Berb.	− 18.35 Gm.
Gastro-enterost	Hag.	− 47.96 Gm.
Partial colectomies	Robert.	− 20.72 Gm.
	Boyer	− 60.22 Gm.
	Zaraz	− 51.86 Gm.
	Benk	− 49.48 Gm.
	Schr.	− 69.87 Gm.
	Ehl.	+ 4.97 Gm.
	Steph.	− 41.44 Gm.
	Thomp.	− 59.88 Gm.
Operations on pancreas	Rapacz	− 39.96 Gm.
	Fait	− 24.41 Gm.
	Cullen	− 61.02 Gm.

TABLE I A

SUMMARY OF DATA IN TABLE I ON NITROGEN LOSS IN TEN-DAY POSTOPERATIVE PERIOD

(A) Group I: 18 patients lost up to 40 Gm. of nitrogen, average = 21.31 Gm.
Group II: 7 patients lost 41 to 60 Gm. of nitrogen, average = 51.4 Gm.
Group III: 11 patients lost 61 to 175.8 Gm. nitrogen, average = 89.45 Gm.
Group IV: 5 patients gained 1.13 to 5.91 Gm. nitrogen, average = 3.54 Gm.

(B) Calculated *dry weight of protein lost (Group I) = 133.19 Gm.; this represents †0.67 Kg. wet body tissue.
Calculated *dry weight of protein lost (Group II) = 321.25 Gm.; this represents †1.6 Kg. wet body tissue.
Calculated *dry weight of protein lost (Group III) = 549 Gm.; this represents †2.7 Kg. wet body tissue.

* Grams of excreted nitrogen x6.25.

† Calculated on assumption that the relationship of tissue protein to water in the tissues is 1:5 (Best and Taylor: Physiological Basis of Medical Practice. 2nd ed. Baltimore, Williams-Wilkins, pp. 915–916, 1940.)

There seemed to be no correlation between age, sex, type of anesthesia, the presence or absence of malignant neoplasm or other type of disease, and the extent of nitrogen loss. The most important factor in this connection appeared to be the period of postoperative starvation and period of limited intake of food. Moderate brief rises in temperature did not affect nitrogen excretion to a very marked degree. Indeed, the patient in whom the postoperative nitrogen loss was greatest (175.79 Gm.) had had a Pólya-type partial gastrectomy and for the ten-day period was afebrile but ate practically no food because of intractable vomiting; recovery eventually ensued. Where the individual could tolerate food relatively early and ingested a relatively liberal diet there was a small net loss or even a positive nitrogen balance at the end of the ten-day period. A study of the day-to-day nitrogen balance revealed that the major portion of the net loss occurred during the first five days postoperatively when food by mouth was not permitted or was very limited.

The practical importance of an effective method for parenteral administration of nitrogenous foodstuff in postoperative management where intake by mouth would of necessity be limited, especially for prolonged periods and in debilitated persons, is obvious. This would reduce or even prevent significant loss of nitrogen. Such a possibility would appear to be afforded by the intravenous injections of casein digest which Elman in 1937, and reporting before this Association in 1940, demonstrated for the first time to be feasible in man. Our own studies were concerned with obtaining pertinent data on the question of the clinical use of casein digests.

The casein digest (Amigen) employed by us in the observations recorded below was kindly furnished by Mead-Johnson and Company, Evansville, Ind., and represents an enzymic hydrolysate of casein (complete protein). Mueller, Kemmerer, Cox, and Barnes found that young rats on a diet, the nitrogenous portions of which consisted of the digest, grew and developed normally, and that dogs with hypoproteinemia regenerated plasma proteins with the digest given by mouth as the sole source of nitrogen. Clark, Brunschwig, and Corbin showed, for the first time, that dogs depleted of protein stores and exhibiting hypoproteinemia as a result of several weeks on a synthetic *nitrogen-free* diet regenerated plasma proteins when this diet was continued and supplemented by daily intravenous injections of the digest as the sole source of nitrogen. These experiments are summarized in Table II.

TABLE II

(Reproduced from Proc. Soc. Exp. Biol. and Med., **49** 282–285, 1942)

SUMMARY OF EXPERIMENTS ON PLASMA PROTEIN REGENERATION WITH INTRAVENOUS INJECTION OF CASEIN DIGEST (AMIGEN)

Dog	Depletion period N.-free diet, days	Duration of inj., days	Avg. daily casein digest intrav. (10% sol.), cc.		Beginning of inj. period	End of inj. period
Eddie Exp. I	47	12	165	Wt., Kg.	6.7	6.1
				Total P.P.*, Gm. %	4.06	5.64
				Hematocrit	39	34.2
				R.B.C.†, M.	6.2	5.8
Eddie Exp. II	21	17	177	Wt., Kg.	7.0	6.2
				Total P.P., Gm. %	4.66	4.91
				Hematocrit	41	32
				R.B.C., M.	8	5.8
Fuzzy Exp. I	27	21	248	Wt., Kg.	9.2	8.3
				Total P.P., Gm. %	4.74	5.12
				Hematocrit	43	35
				R.B.C., M.	7	5.0
Fuzzy Exp. II	37	15	210	Wt., Kg.	9.1	9.2
				Total P.P., Gm. %	4.31	4.97
				Hematocrit	43	35
				R.B.C., M.	6.1	6.0
Pete	77	18	309	Wt., Kg.	7.4	6.6
				Total P.P., Gm. %	5.0	5.97
				Hematocrit	37	25
				R.B.C., M.	7.5	4.7
Mike	21	11	256	Wt., Kg.	8.6	8.1
				Total P.P., Gm. %	3.98	4.99
				Hematocrit	38.2	27
				R.B.C., M.	7.5	6.14
Kate	76	7	214	Wt., Kg.	8.1	7.6
				Total P.P., Gm. %	5.31	5.7
				Hematocrit	40	36
				R.B.C., M.	5.5	6.1

* Plasma protein. † Red blood count.

The manner of injection of casein digest varied with the individual patient, the total amount of fluid to be administered, and the sensitivity of the patient to the injections. The product was received, sterile, in bottles containing approximately 1,000 cc. of a 10 per cent aqueous solution of the digest, thus representing 100 Gm. of hydrolyzed casein or approximately 12 Gm. of nitrogen. In these studies it was administered in one of the following forms:

(1) Intravenously as a 10 per cent solution (hypertonic).
(2) Intravenously with equal parts of 5 per cent or 10 per cent dextrose in distilled water (hypertonic).
(3) Intravenously with two parts of distilled water (isotonic).
(4) By hypoclysis, one part casein digest, two parts of distilled water (isotonic).
(5) Intravenously as 10 per cent solution with equal parts of normal saline or Ringer's solution.

Further data concerning the casein digest is as follows:

One hundred Gm. of digest yields approximately 12 Gm. nitrogen. One gram of digest is approximately equivalent to 3.66 calories. Studies on guinea-pigs, carried out by H. C. Hopps and J. Campbell, of the Department of Pathology, confirmed the fact that the product was not anaphylactogenic.

Additional quantities of saline or Ringer's solution may be administered to afford adequate electrolyte. Where 50 Gm. of protein were desired as supplementary nourishment, 500 cc. of the 10 per cent solution were mixed with a liter of triple distilled water and injected either by hypoclysis or intravenously.

Nitrogen equilibrium can ordinarily not be achieved on a pure protein diet, thus simple injection of a quantity of digest equivalent to the standard protein requirement of a given individual will obviously not suffice to prevent nitrogen loss. Caloric requirements must be met to a substantial degree by carbohydrate (and fat) which afford energy and thus spare, so to speak, the amino-acids for protein synthesis, otherwise the amino-acids themselves will be catabolized for sources of energy. Thus, where nourishment is given entirely by the intravenous route the casein digest must be combined with glucose.

Table III

NITROGEN BALANCE STUDIES SHOWING FAILURE TO ACHIEVE NITROGEN EQUILIBRIUM IN PATIENTS RECEIVING QUANTITIES OF PROTEIN (CASEIN DIGEST) AND INADEQUATE GLUCOSE DURING PERIODS OF OBSERVATION

	Patient, J. O.*				Patient, Schoendt†				Patient, Whit.‡			
Days	Gm.N. Excr.	Gm.N. Inj.	Gm.N. Bal.	Gm. Dext. Inj.	Gm.N. Excr.	Gm.N. Inj.	GmN. Bal.	Gm. Dext. Inj.	Gm.N. Excr.	Gm.N. Inj.	Gm.N. Bal	Gm. Dext. Inj.
1	8.91	0.00	− 8.91	...	12	5.80	+ 6.20	70	4.09	.....	4.09	...
2	6.0	9.19	− 3.19	75	19.15	12.00	− 7.15	150	10.09	6.00	−3.91	75
3	26.7	12.00	− 6.70	150	22.00	12.00	−10.00	150	12.18	6.00	−6.18	75
4	25.30	12.00	−13.30	150	21.33	12.40	− 9.33	150	14.74	6.00	−8.74	75
5	26.70	12.00	−14.70	150	14.41	12.00	− 2.41	75	14.37	6.00	−8.37	75
6	22.60	12.00	−10.00	150	18.60	12.00	− 6.60	150	10.39	6.00	−3.60	75
7	20.09	0	−20.09	150	17.51	12.00	− 5.51	150	12.15	6.00	−6.15	75
8	20.95	18.00	− 2.95	75	17.65	12.00	− 5.65	150	12.55	6.00	−6.55	75
9	23.30	18.00	− 5.30	75	20.75	12.00	− 8.75	150	9.00	6.00	−3.00	75
10	20.10	18.00	− 2.10	75	18.59	12.00	− 6.59	150	15.02	12.00	−3.02	75
11	21.60	18.00	− 3.60	75	11.80	12.00	+ .20	150	13.33	12.00	−1.33	75
12	20.03	18.00	− 2.03	75	16.50	12.00	− 4.50	150	16.95	12.00	−4.95	75
13	23.30	18.00	− 5.30	75	7.75	12.00	+ 4.23	150	14.12	12.00	−2.12	75
14	24.60	18.00	− 6.60	75	16.00	12.00	− 4.00	150	15.14	12.00	−3.14	75
15	22.9	18.00	− 4.90	75	14.04	12.00	− 2.04	150	13.91	12.00	−1.91	75
16	27.30	18.00	− 9.30	75	19.77	12.00	− 7.77	150	16.17	12.00	−4.17	75
17	17.31	12.00	− 5.31	75	18.53	12.00	− 6.53	150	12.74	12.00	− .74	75
18	13.94	12.00	− 1.94	75	17.63	12.00	− 5.65	150	10.98	12.00	+1.02	75
19	15.92	12.00	− 3.92	50	22.3	18.00	− 4.30	100	7.61	12.00	+4.39	75
20	17.18	9.00	− 8.18	75	18.49	18.00	− .49	100	12.30	12.00	− .30	150
21	14.39	18.00	+ 3.61	75	22.50	8.00	−14.50	100	13.11	12.00	−1.11	75
22	21.30	18.00	− 2.70	75	11.64	8.00	− 3.64	100	13.23	12.00	−1.23	150
23	13.45	9.00	− 4.45	150	22.80	8.00	−14.80	100	9.72	12.00	+2.28	150
24	.....	.....	....	...	Total N. loss = 119.56 Gm.				17.92	12.00	5.92	63
25	16.75	18.00	+ 1.25	75					14.12	12.00	−2.12	63
26	14.74	18.00	+ 3.26	75					Total N. loss = 70.88 Gm.			
27	20.70	18.00	− 2.70	75								
	Total N. loss = 140.05 Gm.											

* J. O., M., age 23 (274746), regional ileitis, partial enterectomy, wt. 66 Kg.

† Schoendt, M., age 36 (87546), regional ileitis, partial enterectomy, wt. 81 Kg.

‡ Whit., M., age 57 (277337), Ca. stomach, total gastrectomy, wt. 61.5 Kg.

The details of the nitrogen balance in three patients receiving nothing by mouth and glucose and amino-acids in the form of casein digests over rather prolonged periods are summarized in Table III and the failure to obtain nitrogen equilibrium is well demonstrated since, while the caloric requirements were nearly satisfied, there was obviously insufficient quantity of carbohydrate to spare amino-acids. On the other hand, in patients J.O. and Whit. some of the daily losses of nitrogen were small enough to warrant the assumption that nitrogen loss was to some extent spared by the quantity of glucose injected.

It would appear that there are individual variations in metabolism and that in the exceptional instance postoperative nitrogen loss may be consistently and appreciably reduced and nitrogen equilibrium achieved with parenteral carbohydrate and casein digest, even where the proportions of

TABLE IV

NITROGEN BALANCE STUDY OF PATIENT RECEIVING NOTHING BY MOUTH AND CASEIN DIGEST AND GLUCOSE INTRAVENOUSLY. SHOWING SPARING EFFECT OF DIGEST ON NITROGEN LOSS

Mrs. Rasg. (274120), F., age 36, Ca. stomach, resection, wt. 50 Kg.

Days	Gm.N. Inject.	Gm.N. Excret.	Gm.N. Bal.	Gm. Dext. Inject.
1	0	2.46	2.46	50
2	0	2.71	− 2.71	125
3	0	9.28	− 9.28	25
4	0	19.43	−19.43	100
5	6.00	− 9.10	− 3.10	75
6	12.00	−17.13	− 5.13	75
7	12.00	−14.64	− 2.64	100
8	12.00	−12.75	.75	75
9	6.00	−13.27	− 7.27	75
10	12.00	−11.99	+ .01	50
11	12.00	−12.79	− .79	75
12	15.60	−12.81	+ 2.79	75
13	18.00	−18.84	− .84	75
14	18.00	−18.66	− .66	75
15	18.00	−18.27	− .27	75
16	18.00	−22.72	− 4.72	75
17	18.00	19.37	− 1.37	75

Total loss N. during 12-day period of injection of casein digest = 24.80 Gm.

these two foodstuffs are not ideal. The nitrogen balance studies in such a case are summarized in Table IV. During the 13 days in which the casein digest together with glucose was administered, nitrogen equilibrium was almost achieved in five days, was achieved on one day and on one day a positive nitrogen balance obtained. The total loss of nitrogen during the 12-day period in which casein digest and carbohydrate were injected was 24.80 Gm., which is no greater than in a number of patients subjected to the routine postoperative management in regard to permission for ingestion of food as soon as possible.

Where there has been depletion of nitrogen stores because of prolonged vomiting and consequent reduced intake, casein digests and carbohydrate in proper amounts and relative proportions might facilitate replenishment of the stores where this would take a longer period by ingestion of food alone, especially where the appetite is poor.

TABLE V

SHOWING POSITIVE N. BALANCE IN PATIENT (WITH TERMINAL STAGE OF CARCINOMA) AFFORDED BY INTRAVENOUS INJECTION OF CASEIN DIGEST SUPPLEMENTING LOW PROTEIN DIET

Pt. Lak., M., age 50 (270426), wt. 60.3 Kg., inop., Ca. pancreas, prev. cholecystogastrostomy

Observation Days	Intrav. N. Gm.	N. by Mouth Gm.	N. Excr. Gm.	N. Bal. Gm.	Dext. (per os) Gm.	Fat (per os) Gm.
1		6.60	7.29	− 6.9	252	87
2		6.30	8.65	− 2.35	316	94
3		2.70	3.80	− 1.10	178	74
4	18	0	10.62	+ 7.38	0	0
5	18.00	.75	7.86	+10.89	100	18
6	18.00	.75	14.37	+ 4.38	112	26
7	14.00	.90	7.86	+ 7.04	100	32
8	12.00	1.95	13.52	+ .43	135	42
9	12.00	1.65	5.32	+ 8.33	116	50
10	12.00	1.50	7.56	+ 5.94	140	43
11	12.00	3.00	12.86	+ 2.14	160	78
12	12.00	1.20	13.65	− .45	105	35
13	12.00	1.75	9.74	+ 3.01	142	46
14	12.00	2.10	10.76	+ 3.24	162	53
15	12.00	1.95	4.85	+ 9.10	130	53
16	12.00	1.95	12.77	+ 1.18	139	53
17	12.00	1.20	14.68	− 1.48	122	34
18	12.00	1.20	15.48	− 2.28	157	30
19	6.00	1.00	5.35	+ 1.65	112	16

Net positive N. balance in 16-day period = 127.94 Gm. (Calculated equivalent to 4 Kg. of protein with water in the body.)

An example of this is afforded by the nitrogen balance studies of the patient summarized in Table V. He presented advanced carcinoma of the head of the pancreas, had had a cholecystogastrostomy some weeks previously and was brought back to the hospital because of increasing weakness and a recent severe gastro-intestinal hemorrhage. As shown in the table, the nitrogen balance was negative during a three-day period when choice of food was left to the patient. Beginning with the fourth day, a low protein diet was prescribed and casein digest injected intravenously each day. The plasma proteins were low (5.5 Gm. per cent) indicating a depletion of protein stores. On the combination of intravenous digest and diet by mouth, the patient was put into positive N. balance and at the end of the sixteenth day of the injection period, presented a net gain in nitrogen of 127.94 Gm. which is equivalent to 800 Gm. of protein dry weight and 4,000 Gm. of protein with water as body weight (or 8.8 lb.). Clinically, the patient did not make progress, continued to complain of loss of appetite and on the day following the last recorded studies died suddenly of massive hemorrhage into the bowel. Necropsy revealed abdominal carcinomatosis, and the source of the hemorrhage was neoplasm fungating into the duodenum from the head of the pancreas. However, these studies illustrate the possibility of forced nitrogen nutrition by the intravenous route and the avidity for nitrogen of an organism depleted of nitrogen, although there obtained a fatal disease process which was in the terminal stages.

In another series of observations, patients not suffering from a fatal condition and who were subjected to a major surgical procedure received casein digests postoperatively beginning with the day of operation and later in supplement to the usual postoperative dietary regimen. The purpose of these studies was to obtain data on the extent of sparing excess protein catabolism. The nitrogen balance studies are summarized in Table VI, and show that in

TABLE VI

SUMMARY OF POSTOPERATIVE NITROGEN BALANCE STUDIES IN THREE PATIENTS SUBJECTED TO MAJOR SURGICAL PROCEDURES AND RECEIVING CASEIN DIGESTS AND GLUCOSE INTRAVENOUSLY FROM THE DAY OF OPERATION AND IN SUPPLEMENT TO USUAL POSTOPERATIVE DIETARY MANAGEMENT

Patient I, Mrs. T., cholecystectomy, wt. 62.9 Kg.										
Days	1	2	3	4	5	6	7	8	9	10
N. Intrav. Gm.	6.00	18.00	18.00	18.00	0	9.6	0	0	0	0
N. Mouth Gm.	0	0	0	0	1.40	4.64	5.10	2.1	3.0	4.60
N. Excret. Gm.	−4.54	16.29	21.5	17.85	8.12	9.94	4.52	3.04	7.55	4.24
N. Bal. Gm.	+1.46	+1.71	−3.50	+ .15	−6.72	+3.30	+ .58	− .94	−4.55	+ .36
Dext. Gm.	75	75	90	105	80	81	79	65	115	107
Fat (per os) Gm.					10	47	48	21	40	43
						Net N. loss 10-day period = −8.5 Gm.				
Patient II, Mr. L., cholecystectomy, wt. 80.5 Kg.										
N. Intrav. Gm.	18	18	18	18	18	18	18	18	18	0
N. Mouth Gm.						0.45	6.70	6.70	9.6	12.6
N. Excret. Gm.	13.71	23.3	28.4	23.17	20.79	17.69	17.60	14.3	10.05	8.1
N. Bal Gm.	+4.29	−4.70	−10.4	−5.17	−2.79	+ .76	+7.10	+10.40	+17.10	+4.50
Dext. Gm.					160	24	160	213	260	337
Fat (per os) Gm.						98	107	82	140	152
						Net N. gain 10-day period = 20.39 Gm.				
Patient III, Mrs. S., cholecystectomy, wt. 76.6 Kg.										
N. Intrav. Gm.	6.00	6.00	12.00	6.00	6.00	6.00	6.00	6.00	6.00	6.00
N. Mouth Gm.	0	0	0	0	0	4.00	6.40	8.00	11.10	13.25
N. Excret. Gm.	3.32	7.54	16.57	13.26	12.00	7.16	8.59	11.36	10.98	12.00
N. Bal. Gm.	+2.68	−1.54	−4.57	−7.26	−6.00	+2.84	+3.81	+3.64	+4.12	+7.25
Dext. Gm.	150	150	300	161	175	120	161	205	190	249
Fat (per os) Gm.				4	0	33	78	75	101	108
						Net N. gain 10-day period = 4.97 Gm.				

one case the net loss of nitrogen was only 8.5 Gm., in one there was a net gain of 20.39 Gm. and in the third a net gain of 4.97 Gm. These were not selected cases and indeed did not present entirely smooth immediate postoperative courses. Patient I also suffered from severe menopausal symptoms and complained of severe nausea with frequent vomiting during the first four days (not due to ileus or postoperative dilatation of the stomach). Patient II was a chronic alcoholic and developed temperatures of 102° F. on the second and third days. Patient III was very apprenhensive following the operation and resented all parenteral fluids. The casein digest was given to this patient by hypoclysis on all but the third day.

The vast majority of patients subjected to major surgical procedures recover without special attention to nitrogen balance, since the brief period of total and relative nitrogen starvation is well tolerated by the organism and the loss is made good after return to full diet. However, following major surgical operations there is frequently a rather prolonged asthenia which is often appreciable for a few weeks after discharge from the hospital. Leriche has referred to this syndrome, which cannot be clearly defined as "maladie postoperatoire," and ascribed it to generalized disturbances of the sympathetic nervous system. It is interesting to speculate on the possible rôle of postoperative nitrogen loss in this connection. While the quantity of tissue protein lost may not be large, the source of the catabolized protein under these conditions is not known and might conceivably differ from the stores depleted, when in the course of usual activities the subject may simply refrain from protein foods and continue his activities. Patient II in Table VI in whom there was a net gain of 20.39 Gm. commented upon the fact that he felt quite well at this time and did not experience the weakness which he had expected to occur for some days following the operation. His weight a day before operation was 80.5 Kg. and on discharge on the sixteenth day was 80 Kg., a net loss of 0.5 Kg. or 1.1 pounds. It would be difficult indeed to evaluate the benefits in any large series of patients derived from substantial sparing or actual prevention of postoperative nitrogen loss, but it is understandable theoretically that in such a group the period of impaired physical actively due to postoperative asthenia might be shortened.

Minimal caloric requirements including sufficient protein (as amino-acids) may be met by intravenous nutrition and in this way facilitate operative procedures and contribute to recovery. The nitrogen balance studies shown in Table VII are of a white female patient, age 36, in whom a large fungating

TABLE VII

SUMMARY OF NITROGEN BALANCE STUDIES IN PATIENT WITH OBSTRUCTION IN SIGMOID DUE TO INFLAMMATORY MASS IN PELVIS

Mrs. R. F., age 36 (276536), wt. 50 Kg. Left tubo-ovarian abscess with adhesions to sigmoid colon producing obstruction

Days	N. Inj. Gm.	N. by Mouth Gm.	N. Exc. Gm.	N. Bal. Gm.	Carbohydrate Gm.	Fat Gm.
1	18.00	0	4.98	+13.02	300	
2	18.00	0	10.32	+ 7.68	300	
3	18.00	0	10.60	+ 7.40	300	
4	18.00	0	12.39	+ 5.61	300	
5	18.00	0	15.16	+ 2.84	300	
6	18.00	0	14.10	+ 3.90	300	
7	18.00	0	17.45	+ .55	300	
8	18.00	0	15.58	+ 2.42	300	
9	18.00	0	13.80	+ 4.20	300	
10	18.00	0	14.78	+ 3.22	300	
11	6.00	0	8.59	− 2.59	300	
12	6.00	0	7.03	− 1.03	150	
13	6.00	0	5.09	+ .91	0	
14	12.00	0	12.68	− .68	150	
15	12.00	0	16.92	− 4.92	150	
16	18.00	0	13.00	+ 5.00	300	
17	8.4	0	14.12	− 5.72	150	
18	0	1.00	8.04	− 7.0	53	15
19	0	1.98	4.41	− 2.43	99	30
20	6.00	7.00	9.15	− 1.17	126	18
21	6.00	7.2	7.57	+ 5.43	184	98
22	6.00	6.04	7.29	+ 4.75	211	93
23	6.00	6.10	5.44	+ 6.66	158	83
24	6.00		8.96			

mass was excised from the cervix on the gynecologic service. Because of the histologic diagnosis of leiomyosarcoma external radiation was given. A left adnexal mass was also palpated and regarded as an extension of the tumor with inflammation. Frequent nausea and vomiting occurred at home for a number of days after discharge from the hospital. She was readmitted and the symptoms continued for some ten days, the patient retaining almost nothing by mouth but receiving fluids parenterally. When one of us (A. B.) was requested to see the patient because of the question of low colon obstruction, there was moderate distention of the abdomen and rectal examination revealed what appeared to be constricting bogginess about the rectal colon. Barium enema revealed a high degree of obstruction over several centimeters of a redundant segment of the lower sigmoid in the pelvis. The stomach was aspirated and a small quantity of liquid recovered. Nothing was then permitted by mouth. Intravenous nutrition was carried out daily by means of the following solutions:

(A) 1,500 cc. 10 per cent casein digest } mixed in the flask
1,500 cc. 10 per cent dextrose }
(B) 1,500 cc. 10 per cent dextrose in normal saline

After solution A was injected, solution B was poured into the flask. The total period of injection lasted five to six hours, the total daily fluid intake was 4,500 cc. The patient soon learned at what rate nausea and other disagreeable sensations could be avoided and the clamp on the tube from the flask was placed within her reach so that she regulated the speed of intake herself.

The caloric content of the above solution is:

150 Gm. casein digest x 3.66 =	549 calories
300 Gm. dextrose x 4.00 =	1,200 calories
	1,749 calories

NaCl content = 13.5 Gm.

Since the patient weighed approximately 50 Kg., the caloric content equaled 35 calories per Kg., and the protein content equaled 3 Gm. per Kg. The salt content is slightly in excess of the quantity (10 to 12 Gm.) usually ingested by adults on a general diet. Thus basal dietary requirements in energy and protein seem to have been satisfied, although of course vitamins and complete variety of minerals were not provided since it was not anticipated that complete parenteral nutrition was to be maintained for an unusually prolonged period. This factor, however, may easily be adjusted. The nitrogen balance studies show a positive balance over the ten-day period when 18 Gm. of nitrogen were injected (1,500 cc. 10 per cent casein digest) each day; on the eleventh and twelfth days of observation the latter injections were reduced to 500 cc. per day. Clinically, the patient improved markedly on parenteral nutrition. Nausea and vomiting soon ceased, distention disappeared, and gas was passed per rectum. A second barium enema taken on the eleventh day of the injection period showed disappearance of the obstruction in the lower sigmoid except for one point of partial constriction. An exploratory celiotomy was performed on the thirteenth day of the study and the left lower quadrant mass found to be a tubo-ovarian inflammatory process. This was removed dissecting about 15 cm. of adherent sigmoid colon from it. As seen in Table VII, a slight positive nitrogen balance was maintained on the day of operation and a slight negative balance obtained on the following day. Due to the long period of intravenous injections, even prior to the use of casein digests, the superficial veins were rendered unfit for further intravenous therapy by the fifth day after operation. Furthermore, in view of the removal of the obstruction in the lower sigmoid, a soft diet was permitted by mouth and 1,500 cc. of 3.5 per cent casein digest injested subcutaneously as supplementary nourishment on the eighth to twelfth postoperative days. A review of the data shows that during the course of this study a positive nitrogen balance was maintained with caloric requirements throughout the 12 days prior to operation, the patient receiving nothing by mouth. A net gain in nitrogen amounting to 47.22 Gm. was observed in this period. For the 12 days postoperative, there was a daily variation in nitrogen balance, food was permitted on the sixth day and supplemented by continued parenteral nitrogenous nutrition. At the end of the twelfth day, the net nitrogen gain was 0.63 Gm. for the postoperative period; practically, nitrogen equilibrium was maintained. For the whole 24-day period during which food was taken by mouth only for the last five days, caloric requirements were for the most part met and the net nitrogen gain was 47.85 Gm.

Untoward Reactions.—While the administration of the casein digest was not in our experience with hundreds of individual injections accompanied by serious reactions (with exceptions to be noted below), minor disturbances were frequent. These include mild and occasionally severe nausea, and vomiting and a generalized disagreeable flushing sensation. In the exceptional instances, these are sufficiently pronounced to warrant discontinuation of injections after one or several attempts. On the other hand, we have observed nausea and a generalized feeling of discomfort to be present during the first few injections and to disappear subsequently as they are continued. In one patient marked nausea developed with the first injections but after several days she was observed to eat simultaneously while receiving the digest intravenously. An important factor is the speed of injection. This should be altered with each patient. Some individuals exhibited no discomfort from 500 cc. of the 10 per cent aqueous solution administered in 30 to 45 minutes. Where intravenous injections are not well tolerated, a 3.3 per cent solution in distilled water may be given safely by hypoclysis without discomfort and without reaction in the tissues. Another feature frequently encountered, is reduction in desire for food apart from any nausea or other discomfort. Patients with clinical icterus are not suitable subjects for intravenous injections of the casein digest, since in three instances severe chill, marked rise in temperature, and profound discomfort resulted from the initial injection. In another instance, a chronic alcoholic with marked liver damage, as shown by the hippuric acid liver function test, a similar reaction accompanied the initial intravenous injection but hypoclyses of the 3.3 per cent solution were well tolerated for several days. On the other hand, patients who had been icteric and the latter condition cleared, did tolerate intravenous administration of the digest. It would appear that in certain types of acute hepatitis a sudden flooding of the circulation with amino-acids is too great a physiologic load for the liver to tolerate. Postmortem studies of nine patients who received substantial quantities of casein digest during their terminal disease failed to reveal evidence of toxic effects ascribable to the digests.

SUMMARY

(1) Nitrogen balance studies in 41 patients subjected to a variety of major surgical procedures revealed a net loss of nitrogen for the first ten-day period which varied widely from 3.81 Gm. to 175.79 Gm. in 36 patients. The loss was sustained for the most part during the first five days. In five instances, there was a slight net gain of nitrogen during the postoperative period due to early return to full diet.

(2) The most important factor in the nitrogen loss is the restricted ingestion of food combined with the general physiologic disturbances accompanying a major surgical procedure.

(3) Using the nitrogen balance as criterion, casein digest administered intravenously in proper proportion with glucose is effective in reducing or even preventing postoperative net loss of nitrogen and thus spares the organism from the effects of excessive protein catabolism.

(4) Casein digest and glucose intravenously may be employed as the sole source of nutrition, affording at least minimal caloric requirements under certain conditions, and include an adequate supply of amino-acids to maintain nitrogen equilibrium, or even afford a positive nitrogen balance in patients with depleted protein stores.

(5) Whether or not a surgical procedure is performed or contemplated, intravenous administration of casein digest is a means of forced nitrogenous nutrition.

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DISCUSSION.—DR. WARREN M. COX (Evansville, Indiana): I sincerely appreciate this opportunity to comment upon the papers by Doctor Brunschwig and Doctor Elman. As a biochemist, I cannot make any comment on their clinical observations. Our attention has been centered on the hydrolysate, its preparation, and more particularly its biologic utilization. Last week some of our studies in this regard were presented at the Federation meetings in Boston, and part of those may be of interest to this group.

We were particularly interested in the synthesis of serum albumin as effected by the intravenous administration of the casein hydrolysate. Others have made observations in this regard. Thus, some years ago Doctor Elman made observations that regeneration would be effected both in animals and in a few clinical cases.

Doctor Madden, in Doctor Whipple's laboratory, made an observation that regeneration could be effected in dogs made hypoproteinemic by plasmapheresis, and Doctor Brunschwig showed his results in this regard this morning.

We were interested, however, in knowing, quantitatively, whether the casein hydrolysate administered intravenously would have the same effect as casein or the hydrolysate given by mouth. For this purpose, we followed the procedure of Weech, in which dogs are made hypoproteinemic by low protein diet. They are fed this diet for three weeks. Following this, they are given protein at an intake level of 2.5 Gm. per kilo and caloric intake level of 80 per kilo, for a period of one week. The amount of regeneration during this one week's period constitutes the measure of efficiency of the protein.

Thus, we fed one group of dogs the casein hydrolysate by mouth, and another similar group the casein hydrolysate by vein. The material was given in 10 per cent solution in sterile form, and if we may have the first slide, we can see the results.

(Slide) The albumin values are given in the first column on the left. This column gives the decline of serum albumin during the standardized depletion period. Here we have the regeneration when the material was given intravenously, and here is the assay value as employed by Weech. You have an average assay value for the casein hydrolysate given intravenously of 0.43. By mouth—this is really a total of 21 animals—you have a regeneration average of 3.5. These figures are in entire agreement with the values previously reported for casein by mouth, so that we can say that casein and casein hydrolysate by mouth and casein hydrolysate by vein have the same effect on serum protein regeneration.

In conclusion, I think we might say that this means that casein hydrolysate by vein has about the same effect as beefsteak by mouth.

DR. OWEN H. WANGENSTEEN (Minneapolis, Minn.): Owing partly to the work of Doctor Ravdin of this Association, and to Dr. George H. Whipple, of Rochester, N. Y., the attention of all of us has been focused on the great importance of meeting or attempting to meet the protein requirements of the surgical patient. It remains, however, for Dr. Robert Elman of this group to indicate that it is feasible and practical to maintain satisfactory nitrogen equilibrium with the administration of amino-acid.

Those two Danish observers, Henrique and Anderson, I think just prior to the last war, showed that in a goat that casein hydrolysate could be utilized to advantage in establishing nitrogen equilibrium.

I think most of us, with any experience at all, know that you can inject practically without any reaction and that it would be fair to say that surgeons have been quite remiss in their attitude toward the feeding of surgical patients. I think, in a sense physiologists have contributed to this dereliction or delinquency of ours, in that they have not only pointed out but have emphasized that periods of starvation may not only be well-borne but some have affected to believe that in such periods of starvation, mental and even physical efficiency are improved.

Anyone who has given the matter serious concern with reference to surgical patients will understand there is a difference. We are dealing with ill patients. We are dealing with patients who, perhaps, come to us from periods of starvation, and we as surgeons now, owing to the stimulation the problem has had from Ravdin, Whipple, Elman, and others, affect to manifest an interest in the problem. Our performance, in a sense, belies that manifested or professed interest, for we do not begin to meet caloric requirements of patients or nitrogen requirements. I think most of us have been content to meet water and electrolytic requirements only. I contend that in the immediate future surgeons must have an eye to meeting not only water and electrolytic requirements but also those of calories, nitrogen, mineral, and vitamin requirements.

The magnitude of the problem imposed upon the surgeon in trying to do this is manifest in these slides that have been shown you by the two preceding speakers.

My associates and I, as Doctor Elman said, are interested in the problem of trying to maintain nitrogen equilibrium with human plasma. More than two years ago we published a paper indicating that nitrogen balance could be maintained in such a manner. Perhaps it is necessary to point out that there is a fundamental difference in behavior when plasma is injected intravenously and when amino-acid is injected. When one uses protein plasma and the nitrogen intake of the urine is reduced to a low level through the use of glucose ingested by mouth or given intravenously, there is no augmentation of excretion of nitrogen in the urine. All the plasma given intravenously is available for storage, and you quickly raise the level of plasma protein.

On the contrary, when one injects amino-acids, only so much of the amino-acids are available for energy requirements, unless calories are given in large quantity, that you have to inject larger amounts. So the matter of dosage comes in. I suppose it would be fair to say that for a man who weighs 70 kilos an optimum requirement of protein in the order of magnitude of something like 70 Gm. is necessary to maintain nitrogen equilibrium.

There are many practical problems involved in this issue. It is obvious, of course, that we are dealing essentially with starved surgical patients. Patients with obstruction to pyloric outlet present an ideal problem about which to discuss this situation.

In our own clinic, now for more than two years, we have done no two-stage operations in such patients. We have only done one-stage operations, feeding the patient intravenously with glucose and amino-acid and plasma. I do not believe that glucose is the ideal solution. I hope sometime we will have an agent by which we can administer the required amount of calories and not thrombose the veins, as we are likely to do in using 20 per cent glucose, and not give too much fluids and overhydrate our patient, if he is very old, and lose him through the agency of pneumonia and cardiac failure.

I think the papers are very pertinent, and it is a subject in which we will all have to manifest a greater interest.

DR. HARVEY B. STONE (Baltimore, Md.): I should like to ask Doctor Elman whether he will enlighten me, in closing, on one point. Does the administration of these protein split products which may be used for regeneration, as I understand it, either of the tissue proteins or of the serum of the plasma proteins, exert the same osmotic pressure when administered as the administration of plasma does? In other words, will it serve the same purpose in the physiochemical maintenance of fluid balances between tissue spaces and circulation that can be expected from the administration of serum plasma?

DR. ALEXANDER BRUNSCHWIG (closing): There is just one more point I would like to emphasize. In our experience we have found what we think is one absolute contraindication to the injection of casein digest, and that is icterus or marked liver damage, as being discovered by appropriate liver function tests. We attempted to build up, so to speak, three icteric patients showing carcinoma of the pancreas, the icteric indices in these patients ranging from 40 to 120, and in each case a very severe chill and rise in temperature, which promptly dropped in a few hours, occurred. The patients felt very uncomfortable. Their appearance was quite alarming at the time.

In another patient, a chronic alcoholic, who had no icterus, but whose liver function, by the hippuric acid test, was very low, there was also a very severe reaction.

Apparently the liver, when it is abnormal, cannot cope with a flooding of the circulation by amino-acids, and this reaction results.

We have observed, however, that a patient who will exhibit the reaction as a result of intravenous injection does tolerate subcutaneous injections very well without reaction. In our experience a 3.3 per cent solution of casein digest in distilled water can be given repeatedly day after day, just as one would give isotonic saline or 5 per cent glucose.

We have also observed that in patients in whom the liver function test is very low and who did exhibit a reaction resulting from one of the injections of casein digest, when the hepatitis improved to some extent they could tolerate intravenous injections. One patient who had an icteric index of over 80, and in whom we did not want to risk an intravenous injection subsequently, received intravenous injections after the icteric index had been normal for about two months, without any untoward effect.

DR. ROBERT ELMAN (closing): It has, of course, been quite impossible to touch on anything but the bare essentials of all the implications of the new method of therapy.

In answer to Doctor Stone's question, these amino-acid mixtures have osmotic pressure which is similar to that of glucose. Therefore, in order to exert the same colloidal pressure as protein they would have to be synthesized in the serum protein. But the matter is not as simple as that, because we have observed on many occasions a very pronounced diuresis, a passage of fluid from edematous intestines, in intestinal obstruction, *etc.*, following the injection of amino-acids, without very much significant increase in the serum protein concentration. We have been tempted to believe that the amino-acids in some way lead to an increased nutrition of the tissues, perhaps the capillaries, which enable the food to flow in the right direction, namely, into the lumen of the blood vessels and out through the kidneys, and relieve the edema of various body tissues.

It seems sort of presumptuous to bring up this point again, which has been emphasized by Doctor Wangensteen, namely, that food is important for life, and yet we see patients on surgical wards being given all sorts of vitamins because of the emphasis and the publicity they have received, and yet many of them are starving to death.

AIR-RAID SHELTER PROPHYLAXIS

A method of prophylaxis which, we are informed, may be introduced into the shelters can be properly commented upon by a surgeon—namely, the provision that has been made for the wearing of masks to prevent the spread of droplet infection. We are told that half a million masks are ready to be distributed as and when required. Surgeons have long acted upon the view that infection can easily be transferred by means of the breath, and the wearing of masks is a routine in the operating theatre. The human nasal and pharyngeal mucosa is in some cases as susceptible to infection as an open wound, and I have often been surprised that physicians have not strongly preached, and by force of example demonstrated, that contagion of the common influenzal cold could be prevented by the wearing of an efficient mask. If in the shelter, why not in the work-room or office? Making the reasonable assumption that in Great Britain every year one million people lose one day from work as the result of a cold, the time lost from this cause annually would equal nearly 3,000 work-years. Would it not be worth attempting to reduce this time by mask prophylaxis?

—V. Zachary Cope, M.D., British Medical Journal.