Metabolism in Surgical Patients

I. NITROGEN METABOLISM IN TOTALLY GASTRECTOMIZED PATIENTS

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Several investigators have studied nitrogen metabolism in patients who have had a total gastrectomy.[1-7] However, the data with respect to the relationship between nitrogen intake and fecal or total nitrogen excretion are inadequate. It therefore seemed of value to study these aspects in a group of totally gastrectomized patients who had recovered from their operative trauma and who were under observation because of their poor nutritional status. The present paper in this series submits data on the fecal and urinary excretion of nitrogen in seven patients who were on a controlled intake during the study. Subsequent reports will deal with the metabolism of fat and minerals in these and other totally gastrectomized individuals and the effects of dietary agents and procedures on absorption after total gastrectomy.

METHODS AND MATERIAL

Seven patients who had undergone total gastrectomies from four months to five years previously were studied in a metabolic ward. The diagnoses made on these seven patients are shown in Table I. All were free of recurrent disease as far as could be determined at the time of study. One patient, B. S., developed symptoms at six months and died of metastases to the liver one year following the study. All the others are apparently free of recurrences up to two years after study.

All food items were carefully prepared in a metabolic diet kitchen. Identical diets were homogenized, and aliquots of these were analyzed in triplicate. At the beginning of the study an attempt was made to use the high and moderate fat diets proposed by Wollaeger and his associates[8, 9] in their study of fat and nitrogen absorption in normal persons and patients who had undergone partial gastrectomy. However, it was soon found that many of the totally gastrectomized patients could not comfortably tolerate these large quantities of fat. The diets appeared to be calorically adequate for persons who were in a metabolic ward and whose daily activity was at a minimum (Table I). These caloric intakes are higher than those reported necessary to prevent negative nitrogen balances in normal persons.[10]

Three-day metabolic balance periods were used in this study; fecal collections were divided by carmine markers given at the beginning and end of such a period.[11] An adjustment period of a similar or longer period on the same diet preceded each metabolic period that was subjected to analysis. All excreta were kept in an icebox until the end of the collection period. The completeness of each day's urine, which was collected under toluene, was checked by a creatinine determination,[12] and then pooled in a three-day collection. The three-day collection of stools was homogenized in distilled water, and aliquots of the final volume were used for the analyses.

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All analyses were performed in duplicate or triplicate. The nitrogen was determined by digestion with selenium-sulfuric acid-hydrogen peroxide and micro-Kjeldahl distillation.[13]

In order to compare our data with those for normal persons it was necessary to review the variability. For this reason it was decided to plot the *total excretion* in milligrams per kilogram of body weight against the intake expressed in similar units. The slope of any regression equation therefore represents the fraction excreted per unit of intake, and one

TABLE I

Fecal and Urinary Excretion of Nitrogen in Totally Gastrectomized Persons

Patient	Months between operation and study	Pathology	Age	Weight of Patient	Nitrogen*			Caloric* Intake
					Intake	Urine	Stool	
			yr	*kg*	*g/day*	*g/day*	*g/day*	*cal/day*
1. N. F.	4	Lymphosarcoma	47	58.5	15.5	12.9	2.3	2368
					15.5	12.3	3.0	2368
					15.5	12.3	2.5	2368
2. B. M.	24	Benign ulcer	39	44.4	10.2	6.8	2.0	1695
					10.2	6.5	2.0	1695
3. B. S.†	20	Leiomyosarcoma	50	57.0	8.0	8.0	2.0	1810
					8.0	7.4	1.8	1810
4. J. R.	17	Cancer	68	57.0	19.1	14.6	2.1	2515
					11.2	12.1	1.8	2984
5. J. M.	48	Cancer	63	51.0	12.6	10.9	2.9	2233
6. F. Z.	60	Cancer	58	64.0	14.9	12.5	1.9	2292
7. J. K.	12	Benign ulcer	35	65.0	21.6	16.0	2.5	2777
					12.5	12.0	3.2	3174
					24.6	19.5	3.2	2486
					24.6	16.5	3.4	2486

* Each figure represents the daily average of a three-day metabolic period.

† Developed symptoms six months after study and died one year after study of hepatic metastases.

data in the literature and evaluate them statistically in the same manner as the present data. The methods for obtaining regression equations, evaluating the significance of the correlation coefficients, comparing the regression coefficients of different equations and determining the standard error of estimated points on the lines representing the regression equations are those used in ordinary statistical work and may be found in the texts of Snedecor[14] and Johnson.[15]

RESULTS

Several investigators who have concerned themselves with protein utilization in man have expressed the nitrogen balance or protein intake as grams,[16] grams per kilogram,[17] grams per square meter,[18] or milligrams per basal calorie.[19] It may be realized that the balance represents the difference between the intake and the total excretion and therefore is subject to the same absolute difference or variability as these terms and to a greater percentage *minus* this fraction represents the utilization. The data of Table I have been treated to give the regression line $Y = 89 + 0.62X$, ($r = 0.91$; $P < 0.01$), where Y represents the total excretion and X the intake, both expressed as milligrams per kilogram of body weight per day (Fig. 1). Although many data concerning this relationship exist in normal persons, a true control group for patients of the type considered here would be normal persons who had been starved and were being repleted. Such a group exists in the data of von Hoesslin[20] and of Beattie, Herbert, and Bell.[21] We shall later consider the comparison of our group with their data.

It is generally stated that there is no relationship in normal persons between nitrogen intake and the fecal excretion of nitrogen.[22–25] The following regression line was obtained from the data in Table I, $Y = 1.44 + 0.066X$; ($r = 0.69$; $P < 0.01$), where Y is the fecal nitrogen in grams per day and X is the intake expressed in the same way (Fig. 2). This

relationship is significant, and we shall examine in our discussion how this relationship differs from that in normal persons.

The relationship between fecal nitrogen and nitrogen intake is shown in another manner in Figure 3. Forsyth and associates[26] have

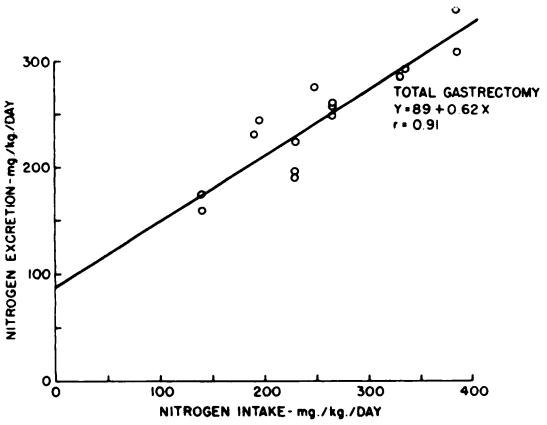

Fig. 1. Relationship between nitrogen intake and nitrogen excretion in totally gastrectomized patients. This relationship for normal persons is not represented on the graph because the two sets of normal data from the literature which were treated in a similar manner gave widely divergent equations (see Table II).

recently shown that there is a significant relationship between the intake of nitrogen and fecal excretion in normal persons. This

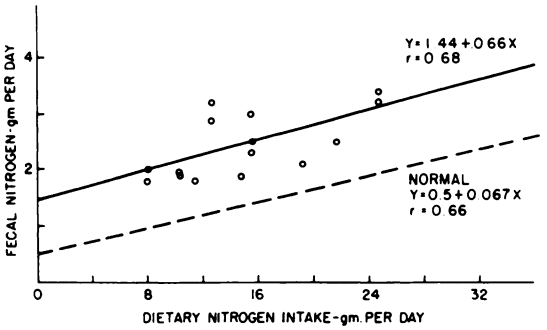

Fig. 2. Relationship between nitrogen intake and fecal nitrogen in normal persons and totally gastrectomized patients. The relationship for the normals is that of Forsyth *et al.*[26]

relationship, $Y = 0.5 + 0.067X$; ($r = 0.66$; $P < 0.01$) is shown in Figure 2. The values for the fecal nitrogen as per cent of the intake at various nitrogen intakes were calculated from the regression lines shown in this Figure 2. The sets of co-ordinate values for normal persons were plotted and the curve at the left-hand side of Figure 3 was obtained. A similar curve was drawn for the totally gastrectomized patients and is shown in the right-hand side of Figure 3. The lowest and highest percentage of nitrogen excreted in the group of totally

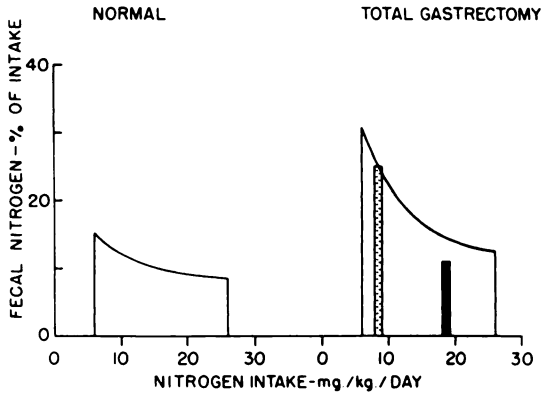

Fig. 3. Fecal nitrogen in normal and totally gastrectomized patients expressed as per cent of the nitrogen intake. Solid column: Lowest percentage of nitrogen excreted in the group of totally gastrectomized patients. Stippled column: Highest percentage of nitrogen excreted in the group of totally gastrectomized patients.

gastrectomized patients are indicated in the same figure.

DISCUSSION

The central point of interest in initiating the present study was to determine whether the overall metabolism of nitrogen in totally gastrectomized humans differed significantly from the metabolism of nitrogen in normal persons. Table II summarizes the regression equations comparing nitrogen intake and total nitrogen excretion in the present study and those of normal persons calculated from available data in the literature. It may be seen that the regression coefficient in our series differs significantly from the normal post-World War I series of von Hoesslin,[20] but not from the regression coefficient of the equation obtained by Beattie, Herbert, and Bell[21] on post-World War II men. We have no explanation for the inconsistency between these two groups of normal data.

The overall nitrogen metabolism of the patients in the present study was also compared in another way with that of normal persons.

The point at which the excretion was equal to the intake, or, in other words, the point of zero balance, was 112 mg per kilogram per day in each of the two normal groups.[20, 21] It is of interest that this point is essentially the same as that given by Sherman[27] in his analysis of the literature on normal men and women in a good nutritional state. At X = 112 mg per kilogram per day in von Hoesslin's[20] regression equation, Y = 77 + 0.31X, where X is the intake and Y the total excretion, both expressed as milligrams per kilogram per day, a region of two standard deviations about the estimated point gives a range of 93 to 131 mg per kilogram per day in the Y value. Similar statistical treatment of the equation of Beattie, Herbert, and Bell[21] yields a range of 92 to 132 mg per kilogram per day. In contrast, it was found that in the equation Y = 89 + 0.62X obtained on the totally gastrectomized patients, the range in Y values at X = 112 mg per kilogram per day was 131 to 187 mg per kilogram per day. *In other words, the nitrogen intake which is adequate for equilibrium in normal persons is insufficient for nitrogen equilibrium in totally gastrectomized patients and yields a significant negative balance.*

TABLE II

Comparison of Nitrogen Intake-Excretion Data between Totally Gastrectomized Patients of Present Study and Normal Persons

Data	Regression equation	Correlation coefficient (r)*	Comparison of regression coefficient in present study with those in normals (*t* values)	Excretion at zero balance	Calculated range of excretion at point of zero balance in normals	
					From equation for normals	From equation of patients in present study
	mg/kg/day			*mg/kg/day*	*mg/kg/day*	*mg/kg/day*
Present study	Y = 89 + 0.62X	0.91	—	234	—	—
von Hoesslin[20]	Y = 77 + 0.31X	0.96	3.5†	112	93–131	131–187†
Beattie[21]	Y = 27 + 0.76X	0.90	1.3	112	92–132	131–187†

* All correlation coefficients were significant at less than the 0.01 level.
† Statistically significant.

It will be recalled that in the present study we obtained a significant correlation, Y = 1.44 + 0.066X, between X, the dietary nitrogen intake, and Y, the fecal nitrogen, both expressed as grams per day (Fig. 2). It was of interest to see to what extent previous data in the literature agreed with this formulation. In 1952 Everson[3] collected the data on metabolic studies in totally gastrectomized persons then available in the literature. Of 46 metabolic blocks, 27 contained information on fecal nitrogen intake and excretion. Twenty-four of these metabolic blocks also had suitable data on fat excretion and hence were considered for statistical treatment. These data yielded a regression line, Y = − 0.61 + 0.313X; (r = 0.52; P < 0.01), between X, the dietary nitrogen intake, and Y, the fecal nitrogen. It may be seen that our data, as well as our recalculation of Everson's[3] data, do not support the rather generally held belief that there is no significant relationship between intake of nitrogen and fecal nitrogen excretion.[22–25] Moreover, it is of interest that a recent study of Forsyth and associates[26] in men with normal gastrointestinal function on diets ranging from 5 to 47 g nitrogen intake also revealed a definite relationship Y = 0.5 + 0.067X; (r = 0.66; P < 0.01). It is apparent that the regression coefficient, 0.066 in our study on gastrectomized patients and 0.067 in Forsyth's study on normal persons would not yield any statistically significant difference. The regression coefficient, 0.313, in Everson's study appears much greater than either of the two just mentioned, but statistical treatment showed that, because of the greater variability in Everson's[3] collected data, the difference was not significant. Accordingly, there is no statistically significant difference in the ratio of fecal nitrogen to dietary nitrogen intake between totally gastrectomized patients and control subjects such as those represented by Forsyth's[26] patients. However, as may be seen from Figure 2, at any given dietary intake

the fecal nitrogen excretion appeared to be greater in the totally gastrectomized patients of our study than in controls, and was demonstrated to be significantly higher at zero nitrogen intake.

The present work has concerned itself with the end-state of the metabolism of nitrogen rather than with the kinetics at which this state is attained. In other words, equations have been developed relating various levels of intake to the excretions at these intakes over a metabolic period of stated duration. We have seen that in the totally gastrectomized patient the steady state of nitrogen metabolism, namely, the point of zero balance, is set at a significantly higher nitrogen intake. The rates at which these end-states of metabolism are reached have naturally not been considered in this paper, but such studies, involving isotopic methods, have been performed on the normal human by a number of investigators, particularly by Rittenberg and associates[28, 29] with respect to protein synthesis. It would be of interest to conduct similar studies in totally gastrectomized patients and controls in a comparable state of nutrition.

SUMMARY

Seven patients who had had total gastrectomies were studied for 15 three-day metabolic periods from four months to five years following operation. Fecal and urinary excretion of nitrogen were determined in each metabolic period.

Fecal nitrogen was significantly related to nitrogen intake in the seven patients. The amount of dietary nitrogen necessary to prevent negative nitrogen balances was significantly greater in the gastrectomized individuals than in normal persons.

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Patients on whom these metabolic studies were conducted were a part of a group of patients being studied clinically by the Surgical Physiology Group including Drs. Kathleen Roberts, Hollon Farr, and John Anlyan. Other aspects of the problem of total gastrectomy are being presented by other members of this team in papers in press at this time.

As is the case in all metabolic studies, this work would not have been possible without the devoted aid and assistance of our technical, dietary, and nursing staff, including Mr. R. Adams, Mrs. A. Silver, and Mrs. G. Gray (technicians); Mrs. M. Turi, Miss M. O'Connor, and Miss E. Halton (nursing staff); and Mrs. L. Stroub, Mrs. R. DeSimone, Mrs. J. Schwartz, and Miss M. Resnick (dietitians).

REFERENCES

1. Buerger, M., and Konjetzny, G. E.: Ueber die Nahrungsausnutzung nach Totalexstirpation des Magens. *Zentralbl. f. Chir.* 125: 458, 1923.
2. Bull, P., and Stang, J.: Total gastrectomy for cancer with after-examinations of the absorptive capacity of the intestine. *Acta chir. Scandinav.* 75: 319, 1934.
3. Everson, T. C.: Nutrition following total gastrectomy, with particular reference to fat and protein assimilation. *Internat. Abstr. Surg.* 95: 209, 1952.
4. Kelly, W. D., Maclean, L. D., Perry, J. F., and Wangensteen, O. H.: A study of patients following total gastrectomy. *Surgery* 35: 964, 1954.
5. Rekers, P. E., Pack, G. T., and Rhoads, C. P.: Metabolic studies in patients with cancer of the gastrointestinal tract. Disorders in alimentary digestion and absorption in patients who have undergone total gastrectomy for carcinoma of the stomach. *Surgery* 14: 197, 1943.
6. Shima, K.: Allgemeine Stoffwechseluntersuchungen nach totaler Magenextirpation und ausgedehnter Darmresektion. *Beitr. klin. Chir.* 153: 275, 1931.
7. Troell, A., Losell, G., and Karlmark, E.: Fall von totaler Gastrektomie wegen Kanker. *Mitt. Grenzgeb. Med. Chir.* 40: 542, 1927.
8. Wollaeger, E. E., Comfort, M. W., Weir, J. F., and Osterberg, A. E.: The total solids, fat and nitrogen in the feces: A study of normal persons and of patients with duodenal ulcer on a test diet containing large amounts of fat. *Gastroenterology* 6: 83, 1946.
9. Wollaeger, E. E., Comfort, M. W., and Osterberg, A. E.: Total solids, fat and nitrogen in the feces: A study of normal persons taking a test diet containing a moderate amount of fat; comparison with results obtained with normal per-

sons taking a test diet containing a large amount of fat. *Gastroenterology* 9: 272, 1947.

10. SCHWIMMER, D.: Protein Metabolism Studies at Reduced Caloric and Water Intake, Annual Protein Conference, Bureau of Biological Research, Rutgers University, New Brunswick, New Jersey, February 6–7, 1948. Quoted by Allison, J. B.: Utilization of protein hydrolysates by normal and protein depleted animals. *Am. J. Med.* 5: 419, 1948.
11. CONSOLAZIO, C. F., JOHNSON, R. E., and MAREK, E.: *Metabolic Methods*, C. V. Mosby Company, St. Louis, 1951, p. 26.
12. PHILLIPS, R. A.: Cited in *Clinical Methods for Coleman Junior Clinical Spectrophotometer*, Coleman Electric Company, Maywood, Illinois, 1944.
13. HAWK, P. H., OSER, B. L., and SUMMERSON, W. H.: *Practical Physiological Chemistry* 12th ed., Blakiston Company, Philadelphia, 1947, p. 820.
14. SNEDECOR, G. W.: *Statistical Methods*, Iowa State College Press, Ames, Iowa, 1940.
15. JOHNSON, P. O.: *Statistical Methods in Research*, Prentice-Hall, New York, 1940.
16. HEGSTED, D. M., TSONGAS, A. G., ABBOTT, M. P. H., and STARE, F. J.: Protein requirements of adults. *J. Lab. & Clin. Med.* 31: 261, 1946.
17. BENDITT, E. P., WISSLER, R. W., and CANNON, P. R.: Studies of Protein Synthesis in Vivo: The Influence of the Levels of Energy and Protein Intake on Protein Synthesis, Conference on Metabolic Aspects of Convalescence—Transactions of 17th Meeting, Josiah Macy Foundation, 1948, p. 11.
18. ALLISON, J. B., and ANDERSON, J. A.: Relation between absorbed nitrogen, nitrogen balance and biological value of proteins in adult dogs. *J. Nutrition* 29: 413, 1945.
19. BRICKER, M., MITCHELL, H. H., and KINSMAN, G. M.: Protein requirements of adult human subjects in terms of protein contained in individual foods and food combinations. *J. Nutrition* 30: 269, 1945.
20. VON HOESSLIN, H.: Klinische Eigentümlichkeiten und Ernährung bei schwerer Inanition. *Arch. f. Hyg.* 88: 147, 1919.
21. BEATTIE, J., HERBERT, P. H., and BELL, D. J.: Nitrogen balances during recovery from severe undernutrition. *Brit. J. Nutrition* 1: 202, 1948.
22. REIFENSTEIN, E. C., JR., ALBRIGHT, F., and WELLS, S. L.: The accumulation, interpretation, and presentation of data pertaining to metabolic balances, notably those of calcium, phosphorus, and nitrogen. *J. Endocrinol.* 5: 367, 1945.
23. MITCHELL, H. H.: Determination of the Protein Requirements of Animals and of the Protein Values of Farm Feeds and Rations. Bulletin 55 National Research Council, 1926.
24. SMITH, M.: The minimum endogenous nitrogen metabolism. *J. Biol. Chem.* 68: 15, 1926.
25. SCHAMBERG, J. F., KOLMER, J. A., RINGER, A. I., and RAIZISS, G. U.: Research studies in psoriasis. *J. Cutaneous Dis.* 31: 802, 1915.
26. FORSYTH, B. T., SHIPMEN, M. E., and PLOUGH, I. C.: The variability of fecal nitrogen excretion with liquid and solid diets. *J. Lab. & Clin. Med.* 43: 440, 1954.
27. SHERMAN, H. C.: Protein requirement of maintenance in man and the nutritive efficiency of bread protein. *J. Biol. Chem.* 41: 97, 1920.
28. SAN PIETRO, A., and RITTENBERG, D.: A study of the rate of protein synthesis in humans. Measurement of the urea pool and urea space. *J. Biol. Chem.* 201: 445, 1953.
29. SAN PIETRO, A., and RITTENBERG, D.: A study of the rate of protein synthesis in humans. Measurement of the metabolic pool and the rate of protein synthesis. *J. Biol. Chem.* 201: 457, 1953.
30. MATTICE, M. R.: *Bridges' Food and Beverage Analyses* (3rd ed.), Lea and Febiger, Philadelphia, 1950.