Nutritional Effects of Feeding Frequency

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THIS paper is concerned with the metabolic and physiologic reactions of the organism to the rate of ingestion of the diet, apparently "complete" in its nutritive constituents. In this respect, undoubtedly, this report will differ from others in this symposium in its basic theme. We are *not* concerned primarily with the influence of dietary factors (from a qualitative and quantitative viewpoint) on the nutritional status of the individual or animal. By contrast, our work has been accomplished with presumably "optimal" diets. However, the work to be presented suggests that the *manner* of ingestion of an otherwise adequate diet may have widespread influences on the health and nutrition of the organism. From this viewpoint, it *may* be proper to consider that the frequency with which a day's nutrients are consumed may be reflected in measurements commonly used for evaluating nutritional status.

The evidence suggesting that the periodicity with which the day's allotment of protein, calories, salts and vitamins is ingested plays a significant role in the regulation of over-all body metabolism has been reviewed.[1,2] It was hypothesized that the consumption of full spaced meals (meal eating), as contrasted to frequent small feedings (nibbling), resulted in differences in the quantities of intermediary metabolites channeled over alternate and formerly rate-limiting enzymatic pathways. The sum total of the alterations in the individual enzymatic activities was considered to be reflected in the observed metabolic changes. Thus, changes in the periodicity with which the diet is ingested appears to be accompanied by differences in the manner in which the body handles its daily quota of nutrients. Consequently, we wish to emphasize two commonly neglected factors in metabolic and nutritional studies: (1) the periodicity of food intake must be considered as a possible variable in the observed results, and (2) ingested foods are *not* handled in a like fashion, irrespective of their being consumed as nibbles or as meals. Accordingly, one can visualize that different feeding experiments might result in "undernutritional," "overnutritional" or "eunutritional" states, depending on the frequency with which the same qualitative and quantitative foods are ingested.

Prior to evaluating the present knowledge of the nutritional effects of feeding frequency on man, it appears desirable to review briefly the results obtained in the experimental animal. For this purpose, the animal fed for a limited period of time during the day, or force-fed its food by stomach tube, has been considered to be the prototype of the meal eater; the animal with free access to food twenty-four hours a day that of the nibbler. Table 1 shows some of the metabolic deviations attributable to meal eating, as contrasted to nibbling.

These observations pose three problems of interest to man from a nutritional viewpoint: (1) Can man beneficially alter the quality and quantity of his animal protein sources by changing the feeding habits of the animals used

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The work performed at Michael Reese Hospital was aided by Grant A-193 (C-9) and Grant A-5686 from the National Institute of Arthritis and Metabolic Diseases, National Institutes of Health, and by Grant G-9992 from the National Science Foundation.

Presented at the Symposium on Recent Advances in the Appraisal of the Nutrient Intake and the Nutritional Status of Man at the Massachusetts Institute of Technology, Cambridge, Massachusetts, on March 6 and 7, 1962, under the sponsorship of The National Vitamin Foundation, Inc., New York, New York.

TABLE I
Metabolic Changes Produced by Meal Eating

1. With respect to body composition
   (a) Increased body fat with normal body weight* † [3–5]
   (b) Decreased body protein and water* † [4,5]
2. With respect to nitrogen balances
   (a) Increased urinary nitrogen excretion* † [6–10]
3. With respect to tissue enzymatic activities
   (a) Increased hepatic and fatty tissue hexosemonophosphate oxidative shunt activity[11,12]
   (b) Increased hepatic tryptophane pyrrolase activity* [13]
4. With respect to endocrine activities
   (a) Decreased thyroid activity secondary to decreased TSH formation or release* † [14–16]
   (b) Decreased urinary 17-ketosteroid excretion (secondary to decreased ACTH formation or release?)*
   (c) Enhancement of potential and exaggeration of actual experimental diabetes mellitus[17,18]
5. With respect to susceptibility to "metabolic" diseases
   (a) Increased severity of diabetes mellitus* †
   (b) Elevation of serum cholesterol concentrations† [19,20,27]
   (c) Enhancement of experimental atherosclerosis and an inhibition of regression of established coronary atherosclerotic lesions* [20]
   (d) The development of experimental hepatic cirrhosis with a diet high in fat but normal in its protein and vitamin content* [21]

* Demonstrated in experimental animal.
† Demonstrated or suggestive evidence in man.

for this purpose? (2) Does man react to different feeding frequencies as do other species? (3) Might eating habits be a contributing factor in the epidemiology of some of the "metabolic" diseases to which man is prone? As a corollary to the last question, it might be well to ask whether "metabolic" diseases might not be treated more efficiently by changing the customary feeding frequency of civilized man. The balance of this report will be devoted to evidence suggesting that an affirmative answer exists for all three questions.

FEEDING FREQUENCY AND FOOD SUPPLY

Data are available demonstrating that by increasing the periodicity of feeding, one can increase the lean muscle mass and decrease the fat content of swine. In the hog raising industry, this practice has been termed "limited feeding"; included in the technic is the use of three to four feeding periods daily. By employing multiple feedings, it was found that not only the efficiency of the conversion of the food consumed to body weight gain improved, but also the animals fed in this manner deposited more protein and less fat.[22,23] Obviously, these observations have a dual significance for man: (1) it appears possible to utilize more efficiently a limited grain supply for the production of greater quantities of animal protein by dividing the food intake into frequent small feedings and spreading them over a larger part of the day; (2) by producing and eating leaner meat, man would be consuming smaller quantities of saturated animal fats. With our present knowledge of the epidemiology of atherosclerosis, this situation appears to be desirable.[24]

MAN'S METABOLIC REACTIONS TO DIFFERENT FEEDING FREQUENCIES

It seems unnecessary to seek an answer to the question as to whether man is "normally" a nibbler or a meal eater. To do so is to miss the really important facet of the situation. By contrast, it seems to us that determined efforts should be made to evaluate the effects of eating patterns on man, having in mind physiologic, epidemiologic and therapeutic considerations.

Studies of Nitrogen Balances and Body Composition

As already mentioned meal eating in the experimental animal alters body composition in the direction of increased body fat and decreased body protein and water.* As might be anticipated from the results of body composition experiments, force-fed animals exhibit a greater urinary excretion of nonprotein nitrogen and urea nitrogen than control animals,

* It should be emphasized that the results observed in the force-fed animal do not appear to be attributable to any "stress" that might accompany forced feeding; the increased body lipid and decreased body protein are seen in the presence or absence of the adrenals.[3] Furthermore, neither the passage of a stomach tube twice daily nor distending the stomach twice a day in rats eating *ad libitum* altered body composition. Lastly, diurnal rhythms do not seem to play a role in the results observed since forced feeding either during the day or night yielded the same type of results.[25,27]

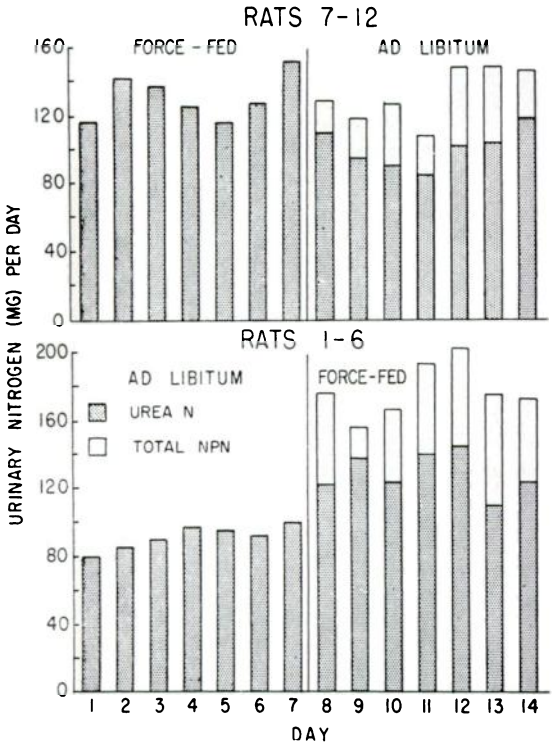

FIG. 1. Average excretion of urea nitrogen and nonprotein nitrogen of rats eating *ad libitum* and of those pair-force-fed against them. During the first seven days, rats 1 to 6 ate *ad libitum* while rats 7 to 12 were force-fed. On day eight, the feeding habits of the animals were abruptly reversed. It may be seen that the pair-force-fed rats always excreted greater amounts of urea nitrogen (and nonprotein nitrogen in one period). Data from COHN, C., JOSEPH, D., BELL, L. and OLER, L.[6]

eating *ad libitum*, against which they were pair-fed (Fig. 1).[6] Neither passing a stomach tube twice a day nor the presence or absence of the adrenals appear to play any role in these results. The effects of feeding frequencies on the nitrogen balances of man have been studied. Wu and Wu[7] and Leverton and Gram[8] a decade ago showed that, within limits, the urinary nitrogen excretion of normal subjects varies inversely with the number of meals at which protein is eaten. Cuthbertson and Munro's volunteer subject also showed a greater retention of nitrogen when placed on eight rather than two meals daily[10]; the changes in nitrogen balance, however, were not as great as in the other two studies. In human studies, each subject served as his own control; the diet was constant throughout all feeding regimens. Figure 2 has been constructed from the data of Leverton and shows the average daily nitrogen intakes and excretions of college students over nine-day periods. During period A, protein was ingested at two of the three daily meals; during period B, the protein was consumed at all three meals. It may be seen that eating the protein at only two meals resulted in nitrogen equilibrium, whereas eating the protein at all three meals was associated with a positive nitrogen balance of 1 gm. per day. One may project this data to indicate that changes did occur in body composition as a result of the varying frequencies of protein ingestion. Over a nine-day period, the students gained approximately 56 gm. of protein (or about 225 gm. of protein-containing tissue); since body weights did not change, about 200 gm. of fat (225 gm. of fat tissue) were replaced. The similarity of these calculations and the results seen in the experimental animal are striking.

Studies of Endocrine Activities

Thyroid Activity. The twenty-four hour thyroidal I^{131} uptakes and thyroidal I^{131} decay rates of the force-fed animal are decreased as compared to the animal eating *ad libitum*.[14,15] These results are not dependent on increased adrenal cortical activity in the meal-eating animal since the same results are seen in the absence of these glands. Studies of the influence of feeding frequency on thyroid activity in man are extremely limited in number—to three individuals whom we have cycled through nibbling and meal-eating regimens (Table II). These volunteer subjects have responded with an elevation in thyroid activity during the nibbling phases of the study. We are the first to admit that the changes are not dramatic in magnitude; on the other hand, we believe that the changes seen are significant because they consistently reflect the different eating habits.

17-Ketosteroid Excretions. In a limited number of rats, forced feeding was associated with a decrease in the twenty-four hour urinary excretion of 17-ketosteroids. The human counterpart of these studies have yet to be accomplished.

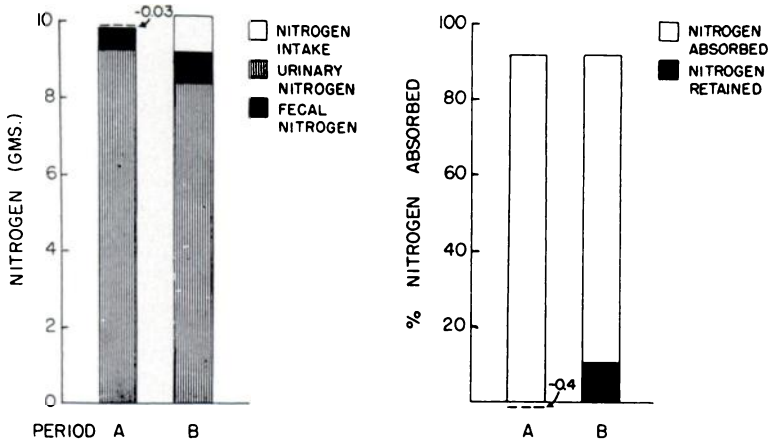

FIG. 2. Effect of number of meals containing protein on nitrogen balances of college students. During period A, two of three meals contained protein while during period B, all three meals included protein. Data from LEVERTON, R. M. and GRAM, M. R. *J. Nutrition*, 39: 57, 1949.[8]

Susceptibility to "Metabolic" Diseases

Serum Cholesterol Levels and Eating Frequency. Further evidence that man is a biologic-reacting kin to the rat and chicken may be found in the results of serum cholesterol levels as influenced by eating frequency. The female rat, trained to eat her food for a limited time period daily, responded with an elevation in serum cholesterol levels.[19] An even more dramatic increase in the serum cholesterol levels, accompanied by increased incidence and severity of coronary atherosclerosis, has been reported in the meal-eating chicken.[20]

Man's reactions to different eating habits, in regard to serum lipid levels, appear to be the same as that of other species. One subject with idiopathic hyperlipemia and hypercholesterolemia reacted to a change from a meal-eating to a nibbling regimen with a drastic fall in his elevated serum lipid levels.[16] Hashim et al.[27] have noted that subjects placed on a six-times-a-day formula diet, after having been on a three meals a day hospital diet, responded with decreased serum cholesterol levels, regardless of the fat in the diet; the type of fat in the diet, however, did influence the magnitude of the fall.

Eating Frequency and Diabetes Mellitus. The severity of experimental diabetes mellitus is increased by forced feeding; it is not influenced by the passage of a stomach tube twice daily.[18,26] To our knowledge no controlled studies to evaluate the effect of feeding fre-

TABLE II
Effect of "Meal Eating" and "Nibbling" on Indices of Thyroid Function in Man

Dietary Regimen	Index of Thyroid Function		
	24 Hour Thyroidal I^{131} Uptake (%)	Plasma Protein-Bound Iodine	Red Cell Uptake of Thyroidal I^{131}
Patient D. J.			
Meal eating	19	6.0	...
Nibbling	24	8.4	...
Meal eating	17	6.6	...
Nibbling	21	7.8	...
Patient L. B.			
Meal eating	21	5.6	17.4
Nibbling	31	6.2	18.8
Meal eating	25	5.2	12.8
Nibbling	30	5.4	17.3
Patient E. B.			
Meal eating	17	4.2	...
Nibbling	20	5.0	...

quency and the control of human diabetes mellitus have been documented. All students of the disease agree that increased feeding frequency is desirable during the course of therapy of complications of the disease, and to prevent hypoglycemic reactions. Furthermore, during the course of therapy of diabetic acidosis, the use of intravenously administered fluids and glucose may be considered to be a truly nibbling regimen. Our attempts to study the influence of feeding habits on human diabetic subjects under controlled conditions are preliminary in nature. One subject with juvenile onset diabetes has shown a fall in insulin requirements (from 55 to 35 units of protamine zinc insulin daily) with a decrease in glycosuria and hypoglycemic reactions and with more "normal" blood sugar levels when he changed from eating three meals to six meals daily. This "improvement" has continued for over nine months. Ellis[28] has shown that diabetic patients receiving glucose and insulin every hour around the clock had a decrease in insulin requirements from 200 to 9 units a day; such improvement in control persisted only during the period of frequent feedings.

From these data emerge the general biologic principle of metabolic regulation by the periodicity of nutrient intake. The somewhat scattered results now available suggest that man's reaction to feeding frequency is qualitatively similar to and often indistinguishable from that of other species. It is clearly apparent that a number of studies remain to be accomplished under controlled conditions, a number of gaps in the picture to be completed; however, the framework on which to accomplish further work is clear, as are the possible implications of the results.

Several general practical problems need to be considered. Thus, from a purely nutritional viewpoint, it is suggested that work be accomplished to evaluate protein and vitamin needs as influenced by the periodicity of food intake. Might not the advocated allowances be too high (or too low) as a result of the metabolic reactions to the feeding frequencies employed during the course of the studies designed to establish such requirements?

One might ask what problems might be anticipated in attempting to increase, in a practical way, the number of times daily that a diet is ingested, or to alter eating habits? (1) Foremost is the social custom of eating three meals per day. It is our opinion that inroads have been made into this habit by means of the so-called "coffee-break." All that is needed to augment this new habit, from a nutritional viewpoint, is to include nutritious food within the "break." (2) The provision of dietary regimens that will actually increase the periodicity of ingestion of balanced nutrients. This situation may be achieved by dividing the day's quota of food into three equal feedings and, in turn, subdividing each such meal into two or three feedings. (Such a practice abrogates the present custom of the average American to divide his food intake into $^1/_8$, $^1/_8$ and $^3/_4$ between his three meals. And this latter situation is "normal?") We have found that for persons working in offices or in industry, a number of the six or nine feedings daily can be carried as sandwiches[11]; no need exists for continuously seeking restaurants. For workers whose institutions include kitchens, and for housewives, small frequent meals pose no problem. (3) The provision of dietitians trained in preparing menus and in aiding and supervising those seeking an increased number of meals daily. If there be truth in the concept of feeding frequency and health and disease, the opportunity for the training of these specialized nutritionists should be created.

SUMMARY

Data contrasting the metabolic effects of full-spaced meals and of frequent feedings have been reviewed. The available results suggest that man may be benefited by increasing the periodicity of his food intake. The advantages that may accrue to man from this altered feeding schedule include (1) a decrease in protein requirements; (2) a decrease in susceptibility to "metabolic" diseases (obesity, atherosclerosis and diabetes mellitus); and (3) an increase in the efficacy of therapy of "metabolic" diseases. In addition, animal breeders may also benefit both their livestock and man in general by feeding the animals at frequent intervals. Using such a technic, it may be

anticipated that there will be (1) an increase in the animal's total body protein with the consumption of the same amount of grain; (2) a qualitative change in the marketed meat in the direction of decreased fat content; and (3) smaller quantities of animal fat provided to the meat-consuming public. The final and quantitative conclusions to these and other questions will require much more work but should prove a challenge to those interested in nutrition.

REFERENCES

1. Cohn, C. and Joseph, D. Role of rate of ingestion of diet on regulation of intermediary metabolism ("meal eating" vs. "nibbling"). *Metabolism*, 9: 492, 1960.
2. Cohn, C. and Joseph, D. Effects on metabolism produced by the rate of ingestion of the diet. "Meal eating" vs. "nibbling." *Am. J. Clin. Nutrition*, 8: 682, 1960.
3. Cohn, C., Shrago, E. and Joseph, D. Effect of food administration on weight gains and body composition of normal and adrenalectomized rats. *Am. J. Physiol.*, 180: 503, 1955.
4. Cohn, C. and Joseph, D. Changes in body composition attendant on forced feeding. *Am. J. Physiol.*, 196: 965, 1959.
5. van Putten, L. M., van Bekkum, D. W. and Querido, A. Influence of hypothalamic lesions producing hyperphagia and of feeding regimens on carcass composition in the rat. *Metabolism*, 4: 68, 1955.
6. Cohn, C., Joseph, D., Bell, L. and Oler, L. Feeding frequency and protein metabolism. In preparation.
7. Wu, H. and Wu, D. Y. Influence of feeding schedule on nitrogen utilization and excretion. *Proc. Soc. Exper. Biol. & Med.*, 74: 78, 1950.
8. Leverton, R. M. and Gram, M. R. Nitrogen excretion of women related to the distribution of animal protein in meals. *J. Nutrition*, 39: 57, 1949.
9. Rakes, A. H., Lister, E. E. and Reid, J. T. Some effects of feeding frequency in the utilization of isocaloric diets in young and adult sheep. *J. Nutrition*, 75: 86, 1961.
10. Cuthbertson, D. P. and Munro, H. N. The relationship of carbohydrate metabolism to protein metabolism. I. Roles of total dietary carbohydrate and of surfeit carbohydrate in protein metabolism. *Biochem. J.*, 33: 128, 1939.
11. Cohn, C. and Joseph, D. Effect of rate of ingestion of diet on hexosemonophosphate shunt activity. *Am. J. Physiol.*, 197: 1347, 1959.
12. Hollifield, G. Hyperlipogenesis in adipose tissue of rats limited to a daily two hour feeding period. (Abstract.) *J. Clin. Invest.*, 39: 997, 1960.
13. Bakshy, S. Unpublished observations.
14. Cohn, C., Joseph, D., Oliner, L. and Morton, J. V. Hypothyroidism produced by the forced feeding of normal rats. *Endocrinology*, 62: 251, 1958.
15. Kalant, N., McIntyre, W. C. and Wilansky, D. L. Thyroid function in experimental nephrotic syndrome. *Endocrinology*, 64: 333, 1959.
16. Cohn, C. Meal eating, nibbling and body metabolism. *J. Am. Dietet. A.*, 38: 433, 1961.
17. Houssay, B. A. and Martinez, C. Experimental diabetes and diet. *Science*, 105: 548, 1947.
18. Cohn, C. and Joseph, D. Comparison of "meal eating" and "nibbling" on severity of alloxan diabetes. *Proc. Soc. Exper. Biol. & Med.*, 105: 575, 1960.
19. Okey, R., Scheier, G. and Reid, R. Food restriction and cholesterol metabolism. *J. Am. Dietet. A.*, 36: 441, 1960.
20. Cohn, C., Pick, R. and Katz, L. N. Effect of meal eating compared to nibbling upon atherosclerosis in chickens. *Circulation Res.*, 9: 139, 1961.
21. Wilgram, G. F. and Ingle, D. J. Dietary method for induction of cirrhosis and obesity in rats. *Fed. Proc.*, 19: 187, 1960.
22. Swine Information Service. Bulletin E 13. National Hog Farmer, May 1960.
23. Hogcast, Bonus Report, February 1961.
24. Ad Hoc Committee on dietary fat and atherosclerosis: dietary fat and its relation to heart attacks and strokes. *Circulation*, 23: 133, 1961.
25. Cohn, C., Joseph, D. and Shrago, E. Effect of diet on body composition. I. The production of increased body fat without overweight ("nonobese obesity") by force feeding the normal rat. *Metabolism*, 6: 381, 1957.
26. Cohn, C. and Joseph, D. Unpublished observations.
27. Hashim, S. A., Arteaga, A. and Van Itallie, T. B. Effect of a saturated medium-chain triglyceride on serum lipids in man. *Lancet*, 1: 1105, 1960.
28. Ellis, A. B. Increased carbohydrate tolerance in diabetes following hourly administration of glucose and insulin over long periods. *Quart. J. Med.*, 3: 137, 1934.