A MECHANISM OF REGULATION OF FOOD INTAKE*

JACK L. STROMINGER† AND JOHN R. BROBECK‡

Regulation of food intake is a term which includes all of the reactions through which an animal (i) maintains a constant intake while environmental and metabolic conditions are constant, and (ii) adjusts its intake whenever environmental or metabolic conditions are altered. What an animal eats and how much are usually thought to be determined by the energy requirements of the body; but every careful observer who has conducted feeding experiments knows that there are many circumstances in which the amount of food eaten is not related to energy expenditure. For example, most mammals will not eat when they are deprived of water, because the demand for energy is secondary to preventing dehydration. They also fail to eat when placed in a hot environment with free access to water and food. There is, therefore, no simple correlation between energy needs and food intake which is valid under all conditions, and it is our purpose now to present the hypothesis that the important factor in regulation of food intake is not its energy value, but rather the amount of extra heat released in its assimilation. Our data do not exclude the possibility that there are other bases for this regulation; as there are several factors in regulation of respiration (CO_2 tension, pH, O_2 tension, etc.), so there may be more than one factor in regulation of feeding. Yet the intake of energy as food seems to a large extent to be regulated indirectly via the heat liberated in assimilating food, much as oxygen intake is regulated via carbon dioxide concentration and pH of the blood.

Other theories of hunger, appetite, and satiety, based on Cannon's[9] and Carlson's[10] studies of sensation from the stomach, do not account in a quantitative way for regulation feeding, nor explain the observation that animals eat different amounts of different diets. The ability of animals to change their intake when the composition of food is altered suggests that animals recognize some quality in food, and that this quality may be correlated with regulation of the amount of food eaten. This quality we have arbitrarily called the intrinsic food factor, and we have concluded that it may be identical with the specific dynamic action, since it cannot be any one of the more obvious dietary constituents, including the caloric value of the food. Following feeding, the heat production is greater than before the food

* From the Laboratory of Physiology, Yale University School of Medicine, and the Department of Physiology, School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania.
† Present address: National Institutes of Health, Bethesda 14, Maryland.
‡ M.D. 1943, Yale University School of Medicine; Editor, 1949-52, The Yale Journal of Biology and Medicine.
Received for publication March 12, 1953.

was taken. This extra heat, called the "specific dynamic action" by earlier physiologists (Rubner), must be disposed of in some way, along with the calories, protein, carbohydrate, fat, vitamins, and minerals of the food. As shown by the data of Strang and McClugage,[31] this increase in heat production is rather abrupt, especially when the rate of change of heat production is plotted graphically against time. Booth and Strang[4] further noted in human subjects that the S.D.A. of food brings about a postprandial rise in skin temperature. By measuring the rate of this rise and correlating it with the amount of food eaten by thin, by normal, and by obese subjects, they concluded that warming of the skin is an essential part of satiety reactions. Rony[27] later criticized their concept on the grounds that the quantity of heat produced was too small to warm the body by the amount that Booth and Strang had noted, but it appears that Rony failed to consider the possibility that the skin becomes warmer, not because it is directly warmed by the extra heat, but because in response to the elevated heat production there is an active cutaneous vasodilatation.

The S.D.A. is known to vary with the metabolic state of the animal[8, 21] which is determined, in part, by the metabolic mixture which the animal consumes.[19, 20, 28] During adjustment to a new diet the activity of various enzyme systems changes,[20, 28] and there may be at the same time, perhaps associated with alterations in metabolic pathways, some modification in the amount of heat liberated from food. It is important to recall that the S.D.A. of a diet is not the same as the sum of the S.D.A.'s of the individual constituents of the diet, but depends, rather, upon the relative proportions of protein, carbohydrate, and fat.[14, 16] Thus, the specific dynamic action of protein, alone, is different from its S.D.A. when fed in a mixture with other foodstuffs. If the S.D.A. is the intrinsic food factor which the animal takes in constant amount from day to day via its food, a change in the magnitude of the S.D.A. of any component of the diet would result in a corresponding change in the amount of food eaten. Changes of this type would occur gradually in company with the gradual metabolic changes, and therefore a latent period of some days would intervene before an animal previously stabilized on one diet would make a final adjustment to a new food mixture. In our experiments where fat, carbohydrate, or protein was added to a mixed diet, such gradual changes in food intake did occur.[32] The nature of these adjustments was as follows: On the first day following the change, the intake (in grams or calories) might be quite different from the animal's previous intake, but when the number of S.D.A. calories was calculated (using published data for the S.D.A.) for the control period and for the first day following the change in diet, values for intake were obtained which were more nearly constant. On the succeeding 3-8 days, gradual changes occurred in intake during the interval when changes in metabolism would be expected to result from the altered metabolic mixture. Our data suggest that the reason that the caloric intake is mistakenly believed to be the

factor regulated by animals is that on a diet of constant composition the caloric value and S.D.A. are always proportional; consequently, in the absence of any metabolic change it may be impossible to decide which of the two factors is being maintained at a constant level.

As an example of the type of calculation that can be made in studying this regulation, Lusk's figures for S.D.A. (i.e., 30% for protein, 4.9% for carbohydrate, and 4.1% for fat)[21] have been applied to the food intake of normal rats receiving a diet made up of a mixture of natural foods (G.L.F. calf meal), and subsequently diluted with various proportions of fat.[32] When the percentage of added fat was increased from zero to 14, 43, and 57% by weight, the total caloric intake per day more than doubled on the first day;

TABLE 1

SPECIFIC DYNAMIC ACTION OF FOOD EATEN IN 18 HOURS WHEN LARD WAS ADDED TO DIET

May 2, 1946—Sprague-Dawley Males (300-325 gm.)

% Lard added to diet	*Total caloric intake*	*Partition of caloric intake*			*Calculated SDA, kcal.*			*Total SDA, kcal.*
		Protein	*CH_2O*	*Fat*	*Protein*	*CH_2O*	*Fat*	
0	54.8	13.2	36.7	4.9	4.0	1.8	0.2	6.0
14	66.4	11.0	30.9	24.5	3.3	1.5	1.0	5.8
43	90.0	7.2	19.8	63.0	2.2	1.0	2.6	5.8
57	116.3	5.8	17.5	93.0	1.7	0.9	3.8	6.4
86	110.0	1.6	4.4	104.0	0.5	0.2	4.3	5.0
100	104.6	0.0	0.0	104.6	0.0	0.0	4.3	4.3

but the total estimated S.D.A. remained nearly constant at 6.0, 5.8, 5.8, and 6.4 kcal./day, respectively (Table 1). Using data for S.D.A. obtained from other sources, however, the results of certain of our experiments are less uniform, and some of our results do not yield constant amounts of extra heat per day even when Lusk's figures are used in the calculation. In spite of the many experiments performed by other investigators measuring the S.D.A., we have not been able to determine with certainty from published data what the S.D.A. may be when both the composition of the diet and the metabolic state are varying. It appears that in order to test the hypothesis further, measurements of the S.D.A. of the mixed diets will have to be done simultaneously with the experiments in which food intake is measured. But in spite of this limitation of our knowledge, of all of the variables which we measured, the estimated S.D.A. was the most nearly constant on the first day of changed dietary composition—much more nearly constant than factors such as caloric intake, total weight of food, bulk of food eaten, or the intake of either protein, carbohydrate, or fat.

Energy obtained from food is utilized by animals to do work, to increase bodily stores of carbohydrate, protein, and fat, and to maintain body temperature—all of which are accompanied by the loss from the body of rather considerable amounts of heat. Since heat production is common to all of these avenues of expenditure, it is reasonable to suppose that their regulation must be related in some manner to the body's temperature regulation, and that they must undergo some integration so that no one of these factors is allowed to vary independently of the others. An example of the interdependence existing among these reactions may be noted in female rats, where cycles of body temperature, body weight, food intake, and spontaneous activity (running) are correlated with the estrous cycle.[7] Similarly, in male rats, food intake is altered by changes in environmental temperature,[6] as it is also in other species, including cattle (Brody)[8] and human infants (Cooke).[11] All of these variations appear consistent with the idea that food intake is regulated by way of the extra heat produced in its assimilation, in that the intake decreases when the animal is having difficulty in losing heat in a warm environment, or when heat production rises because of increased activity at a constant temperature.

The experiments of Grossman, Ivy, and their associates,[15, 17, 29] the data of Anand and Brobeck,[3] and our own results all indicate that the regulation of food intake is accomplished by the central nervous system, rather than by the stomach (Carlson)[10] or by the stomach and duodenum (Alvarez).[2] In brief, the nervous system apparently serves for the integration of a number of mechanisms having the following functions:

1. Motor activity, especially locomotion;
2. Feeding reflexes;
3. Facilitation of feeding reflexes, and of locomotion;
4. Inhibition of feeding reflexes, and of locomotion;
5. Recognition of food.

Of these, the term "feeding reflexes" is generally used and probably does not need further definition, except to say that it should be applied only to a reaction initiated by some definite sensory stimulation. The stimulus may be visual, olfactory, auditory, tactile, or through taste, and may serve to direct the organism to an object, may lead to "mouthing" or oral investigation, to chewing and swallowing. If the object is not appropriate for food, a normal animal will reject it somewhere along this series of reactions, whereas an animal deprived of portions of the cerebral cortex, particularly the "visceral" cortex, will not reject it but will eat it as though it were food (Pribram).[26] This observation is responsible for the impression that in higher animals the recognition of food is primarily a cortical function.

The nervous system evidently drives, impels, or urges the individual to eat; this drive becomes apparent as restlessness, locomotion, searching, or "rooting," depending upon the species and age of the animal. From this drive arises the hyperactivity which Sherrington[30] and, more recently,

Wald[34] interpreted as a useful reaction, increasing the likelihood that food will be encountered. A satiated animal under natural conditions is not likely to discover more food because it fails to move about; hence, the urge to locomotion is an essential preliminary to feeding. In human infants, restlessness, irritability, and crying serve the same purpose, since the mother performs the movements necessary to bring the baby near to the source of food. If it were not for the storage capacity of the gut, eating probably would not be periodic, and the "normal" or habitual waking state would be a roving one, a moving from place to place, investigating, mouthing, and feeding whenever possible.

Hetherington's[18] observation (which we have confirmed) that rats with hypothalamic lesions often show reduced locomotor activity, as well as Miller, Bailey, and Stevenson's[24] discovery that similar animals, although they may exhibit hyperphagia, are unwilling to work for their food, together point to the conclusion that at least certain portions of the hypothalamus take part in maintaining the urge to locomotion and motor activity. On the other hand, the complete aphagia in the presence of food noted by Anand and Brobeck[3] in rats and cats with lesions in the lateral hypothalamus suggests that the hypothalamus also has some more specific function in feeding, a function which is most conveniently described as facilitation of feeding reflexes. Magoun[22] has shown that the hypothalamus contains an important part of the "bulbar facilitatory mechanism," a neural system capable of determining whether or not other parts of the nervous system can become active, as well as their level of activity. An afferent stimulus too weak to excite a reflex action may produce a response if the facilitatory mechanism is excited simultaneously. In the hypothalamus the facilitatory mechanism occupies the same lateral location as the "feeding center" of Anand and Brobeck—a localization suggesting that feeding reflexes may require central facilitation. The sensations produced by hunger contractions may have similar effects, viz., increasing motor activity and facilitating feeding reflexes, since both Sherrington and Carlson noted that "hunger" is associated with generalized hyperexcitability of the central nervous system.

Another function of the hypothalamus may be the inhibition of eating. When lesions are placed in the medial hypothalamus, animals become hyperphagic and obese[5] even though their "drive" or "urge" to eat has been reduced. The hyperphagia may be a result of destruction of cells normally responsible for the inhibition of feeding. It is conceivable that they inhibit either the facilitatory portion of the lateral hypothalamus, or possibly the feeding reflexes directly. Whether stimuli from the gastro-intestinal tract in normal animals act on the hypothalamus or at the reflex level is unknown. Whereas hunger contractions appear to increase activity and to facilitate feeding reflexes, distention of the stomach and intestine seems to inhibit both motor output and reflex activity. Yet Grossman's[15] results using animals with denervated gastro-intestinal tracts show that feeding can proceed

normally without sensation from stomach and intestine, presumably because the central mechanisms are affected by factors other than visceral stimulation. Sherrington[30] and Pavlov[25] suggested some years ago that feeding may be regulated in a manner analogous to respiration, where the excitatory state of the respiratory center is modified by the composition of the blood, by impulses arising peripherally in the lungs, and by activity in other portions of the neural axis. In terms of the hypothesis which we propose, the specific dynamic action of food would play in the regulation of food intake a rôle analogous to the chemical changes which act centrally to modify respiratory exchange. Any increase in the total amount of heat in the body, acting through thermal gradients and thermal receptors, would initiate impulses inhibiting the mechanisms responsible for feeding. An increase in environmental temperature would do the same. When environmental temperature decreased, or when heat production diminished, a reversal of the thermal gradients would remove the inhibition so that the animal would once again become active, searching for food and ready to eat. The hypothalamic mechanisms conceivably might be sensitive to temperature changes in the blood, as Magoun and his associates[23] demonstrated in their studies of the responses following direct heating of the hypothalamus. Data now available do not exclude the possibility, however, that some other reaction may be interposed between the released heat and the neural activity—possibly some movement of water or electrolytes, some change in cellular permeability, or in the rate of certain chemical reactions within the sensitive cells. Verney[33] has proposed a concept similar to this to explain his results with perfusion of the hypothalamic region in dogs. He suggested that alterations in the osmotic pressure of the carotid blood are adequate stimuli for the supraoptico-hypophysial complex, via osmoreceptors whose rate of discharge is affected by gradients of water concentration. He mentioned no observations upon thermoregulation of his animals during the experiments, although there is other evidence that water balance, food intake, and regulation of body temperature are interdependent.[12] Darrow and Yannet[13] found that animals subjected to depletion of their extracellular electrolyte (following injection intraperitoneally of isotonic glucose solution) failed to eat and drink, while Cort[12] observed aphagia following subcutaneous injection of small amounts of hypertonic saline. Whether this failure to eat was caused directly by shifts of body water and electrolyte is unknown, and these experiments are mentioned here only to emphasize the point that generalized changes in composition of body fluids are capable of affecting the activity of mechanisms regulating energy exchanges between animals and their environment.

Summarizing our hypothesis, we suggest that a normal animal when "hungry" is driven by his central nervous system into extra locomotion and searching, while his feeding reflexes are brought into a facilitated state. Following feeding, the locomotion decreases and the reflexes are no longer facilitated, in fact, they may be actively inhibited. Stimuli reaching the

central nervous system from the gut apparently modify both the level of motor output and the state of feeding reflexes. But factors acting upon other parts of the body, possibly directly upon the central nervous system, are equally important in feeding behavior. One such factor is represented by the conditions of temperature regulation which, through the specific dynamic action (S.D.A.) of food and by way of environmental temperature, appear to have important effects upon food intake. Other factors undoubtedly exist, with the result that the central regulation of feeding is accomplished through integration of a variety of types of disturbances and reactions within the organism or between it and its environment.

References

1 Adolph, E. F.: Urges to eat and drink in rats. Am. J. Physiol., 1947, *151,* 110.

2 Alvarez, W. C.: *An introduction to gastro-enterology.* New York, Hoeber, 1940, 778 pp.

3 Anand, B. K. and Brobeck, J. R.: Hypothalamic control of food intake in rats and cats. Yale J. Biol., 1951, *24,* 123.

4 Booth, G. and Strang, J. M.: Changes in temperature of the skin following the ingestion of food. Arch. Int. M., 1936, *57,* 533.

5 Brobeck, J. R.: Mechanism of the development of obesity in animals with hypothalamic lesions. Physiol. Rev., 1946, *26,* 541.

6 Brobeck, J. R.: Effects of variations in activity, food intake and environmental temperature on weight gain in the albino rat. Am. J. Physiol., 1945, *143,* 1.

7 Brobeck, J. R., Wheatland, Mary, and Strominger, J. L.: Variations in regulation of energy exchange associated with estrus, diestrus and pseudopregnancy in rats. Endocrinology, 1947, *40,* 65.

8 Brody, S.: *Bioenergetics and growth.* New York, Reinhold Publishing Corp., 1945, 1023 pp.

9 Cannon, W. B. and Washburn, A. L.: An explanation of hunger. Am. J. Physiol., 1912, *29,* 441.

10 Carlson, A. J.: *Control of hunger in health and disease.* Chicago, Ill., University of Chicago Press, 1916, 2d impression, 319 pp.

11 Cooke, R. E.: Behavioural response of infants to heat stress. Yale J. Biol., 1952, *24,* 334.

12 Cort, Ruth L.: Interrelationship of hunger and thirst. Yale University, School of Medicine, Thesis submitted 1951.

13 Darrow, D. C. and Yannet, H.: Metabolic studies of the changes in body electrolyte and distribution of body water induced experimentally by deficit of extracellular electrolyte. J. Clin. Invest., 1936, *15,* 419.

14 Forbes, E. B. and Swift, R. W.: Associative dynamic effects of protein, carbohydrate and fat. J. Nutrit., 1944, *27,* 453.

15 Grossman, M. I., Cummins, G. M., and Ivy, A. C.: The effect of insulin on food intake after vagotomy and sympathectomy. Am. J. Physiol., 1947, *149,* 100.

16 Hamilton, T. S.: The heat increments of diets balanced and unbalanced with respect to protein. J. Nutrit., 1939, *17,* 583.

17 Harris, S. C., Ivy, A. C., and Stearle, Laureen M.: The mechanism of amphetamine-induced loss of weight. J. Am. M. Ass., 1947, *134,* 1468.

18 Hetherington, A. W. and Ranson, S. W.: The spontaneous activity and food intake of rats with hypothalamic lesions. Am. J. Physiol., 1942, *136,* 609.

19 Lundbaek, K. and Stevenson, J. A. F.: Reduced carbohydrate intake after fat feeding in normal rats and rats with hypothalamic hyperphagia. Am. J. Physiol., 1947, *151,* 530.

20 Lundbaek, K. and Stevenson, J. A. F.: The effect of previous carbohydrate deprivation on the carbohydrate metabolism of isolated muscle. Fed. Proc., Balt., 1948, *7,* 75.

21 Lusk, G.: *The elements of the science of nutrition.* Philadelphia, W. B. Saunders Co., 1928, 4th ed., Chapt. XII, pp. 276-308.

22 Magoun, H. W.: Caudal and cephalic influences of the brain stem reticular formation. Physiol. Rev., 1950, *30,* 459.

23 Magoun, H. W., Harrison, F., Brobeck, J. R., and Ranson, S. W.: Activation of heat loss mechanisms by local heating of the brain. J. Neurophysiol., 1938, *1,* 101.

24 Miller, N. E., Bailey, C. J., and Stevenson, J. A. F.: Decreased "hunger" but increased food intake resulting from hypothalamic lesions. Science, 1950, *112,* 256.

25 Pavlov, I. P.: *Lectures on conditioned reflexes.* New York, International Publishers, 1928, 414 pp.

26 Pribram, K. H.: Cited in Fulton, J. F.: *Frontal lobotomy and affective behavior.* New York, W. W. Norton & Co., 1951, pp. 78-79.

27 Rony, H. R.: *Obesity and leanness.* Philadelphia, Lea and Febiger, 1940.

28 Samuels, L. T.: Body adaptation to change in diet. J. Am. Diet. Ass., 1946, *22,* 843.

29 Sangster, W., Grossman, M. I., and Ivy, A. C.: Effect of d-amphetamine on gastric hunger contractions and food intake in the dog. Am. J. Physiol., 1948, *153,* 259.

30 Sherrington, Sir Charles: Cutaneous sensation, in: *Textbook of Physiology,* (Sharpey-) Schaefer, E. A., Ed., Edinburgh, Pentland, Vol. 2, 1900, pp. 920-1001.

31 Strang, J. M. and McClugage, H. B.: The specific dynamic action of food in abnormal states of nutrition. Am. J. M. Sc., 1931, *182,* 49.

32 Strominger, J. L., Brobeck, J. R., and Cort, R. L.: Regulation of food intake in normal rats and in rats with hypothalamic hyperphagia. Yale J. Biol. (To be published)

33 Verney, E. B.: Absorption and excretion of water. Lancet, Lond., 1946, *251,* 739.

34 Wald, G. and Jackson, Blanche: Activity and nutritional deprivation. Proc. Nat. Acad. Sc., U. S., 1944, *30,* 255.