

## SATIETY AND BEHAVIORAL CALORIC COMPENSATION FOLLOWING INTRAGASTRIC GLUCOSE LOADS IN THE RAT<sup>1</sup>

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Glucose solutions were administered intragastrically to rats having free access to food except during the first hour after intubation. The distribution of meals after intubation indicated that effects of glucose both prolong satiety and contribute to its initiation, during the dark or the bright phase of the lighting cycle. From about 5 hr. after intubation and from the start of the second meal, the net cumulative inhibition of food intake amounted to apparently close to exact caloric compensation for the glucose load. Feeding was not differentially inhibited by control loads of the same volume as the glucose load, whether the control was air, water, sodium chloride, urea, or 3-methylglucose. The results provide the first demonstration in support of a theory of short-term behavioral regulation according to an energostatic signal generated from glucose.

Booth, Lovett, and Simson (1970) recently observed strikingly exact caloric compensation for both freely drunk and gastrically intubated glucose solutions in the subsequent 24-hr. food intakes of rats having free access to food. The present experiments were partly an attempt to define the time course of this apparently regulatory response to a transient excess in caloric input.

If there is relatively precise net cumulative inhibition of feeding to match the caloric value of glucose administered in an unfamiliar manner, the initial satiating effects of glucose by possibly imprecise mechanical and colligative mechanisms must eventually develop into an adjustment of pauses between meals or of meal sizes which balances energy exchange. This adjustment could be controlled by generation of some precalibrated chemoreceptor response specific to glucose and molecules of very similar structure. Alternatively signals could be generated by glucose utilization, e.g., the level of intracellular energy sources.

However, satiety induced by chemically specific or metabolic effects of glucose has

been surprisingly little investigated. Indeed, a purely osmotic theory of glucose-induced satiety was advocated because of the observation that an intragastric load of 1 M glucose can produce a decrease in food intake over the subsequent 1 and 2 hr. in 22-hr. food-deprived rats which is similar to that produced by an equal volume of equiosmolar sodium chloride (Smith, 1966; Smith & Duffy, 1957; Smith, Pool, & Weinberg, 1959; Smith, Salisbury, & Weinberg, 1961). However, it was known that drinking for 1-2 hr. is induced by administration of sodium salts in osmolar concentrations at which glucose has no such effect (Fitzsimons, 1961) and it had long been supposed (Harper & Spivey, 1958; Hsaio, 1967; Lepkovsky, Lyman, Fleming, Naguno, & Dimick, 1957; Schwartzbaum & Ward, 1958) and has now been established (Gutman & Krausz, 1969; Kakalewski & Deaux, 1970) that the extracellular hypertonicity which induces drinking also inhibits feeding. It would therefore have been more appropriate to conclude that glucose inhibits feeding by noncolligative effects to an extent as great as the hypertonic anorexia induced by saline. In any case it has since been shown that hypertonic glucose loads do not appreciably affect extracellular tonicity (Jacobs, 1963; Yin, Hamilton, & Brobeck, 1970). An additional consideration is that gross behavioral signs of distress can be seen with "control" .5 M saline intubations which are

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not evident with the 1 M glucose intubations (Jacobs, 1964). The proper control would be a completely nonmetabolizable analog of glucose which is no more excluded from cells than is glucose itself. 3-*O*-Methylglucose was used in one of the present experiments. Alternatively, a small molecule which is not metabolized for energy and which induces relatively small amounts of drinking would be better than a sodium salt. Urea is such a substance (Fitzsimons, 1961). It has been little used for this purpose since McCleary (1953) concluded for a purely osmotic theory after investigating the effects of urea and glucose on feeding, even though his data provided no direct comparison of these substances' effects on absolute intake inhibition.

Yet another consideration is that the starved animal would be expected to have fast gastric clearance and intestinal absorption (Hindmarsh, Kilby, Ross, & Wiseman, 1967) and to utilize absorbed glucose very rapidly. Thus, for example, gastric intubation of 1.5 gm. of glucose in a 4-hr. food-deprived rat gives blood glucose levels of 125–140-mg/100-ml at 15 min. in my experience (D. A. Booth, unpublished results) whereas 18-hr. fasted rats barely exceed 95-mg/100-ml after this dose (Curtis-Prior, Trethewey, Stewart, & Hanley, 1969). This rapid disappearance of extracellular glucose might preclude the maintenance or even the generation of effective chemospecific and metabolic satiety signals. Also, food intake should be measured for longer than the 2 hr. from intubation generally used in previous work, because a considerable proportion of absorbed glucose is converted to glycogen, fat, and protein which then release energy-yielding and glucose-sparing metabolites with a delay of many hours. Only about 50% of the glucose has been oxidized to carbon dioxide within 2 hr. of a 10 gm/kg load (Jansen, Hutchison, & Zanetti, 1966).

The effects of stomach loads of glucose were, therefore, examined in rats having virtually unbroken access to food and water, with intakes being measured every 1–2 hr. for 7–8 hr., and indeed at 1 and 2 days after intubation. In most experiments food was withheld for 1 hr. after intubation but access

to water was maintained, in order to allow both the decay of tonicity effects and their compensation by drinking—thus preventing their interaction with feeding. Water intakes were measured in addition to food intakes to provide some basis for distinguishing satiety from nonspecific behavioral inhibition, e.g., by distress or drowsiness.

In addition, the effects of intubation in the bright and dark phases of the lighting cycle were compared for technical and theoretical reasons. The high feeding rate at night could involve so great a variability as to obscure satiating effects of moderate doses of glucose. Yet on the other hand there might be so little feeding during the day that dose-response relationships could not be observed. The safest strategy was to try both. The other sort of consideration was that a difference between night and day would be expected in the pattern of glucose utilization, because of metabolic consequences of the difference in feeding pattern (Cohn & Joseph, 1960; Tepperman & Tepperman, 1965) and because of feeding-independent circadian variations in hormonal (Mills, 1966) and metabolic status (Scott & Potter, 1970). Thus it was conceivable that the time course and even perhaps the net cumulative effect of glucose-induced satiety differed between the two phases of the cycle.

## GENERAL METHOD

### *Maintenance Conditions*

The subjects were male albino rats of a Sprague-Dawley strain supplied by Scientific Products Farm, Canterbury, England. They were housed individually in 52 × 26 × 18 cm. mesh cages, and accommodated to a lighting schedule for at least 3 wk. before experiments. Rats receiving intubations during the bright phase were kept in a general purpose holding room in which (to suit experimenter convenience in other concurrent work) the lights came on at 8:30 A.M. and were turned off at 10:30 P.M. The room was dependent on the building ventilation heating system, giving a temperature range of 17°–20° C. Rats receiving dark-phase intubations had full illumination from 10 P.M. to 10 A.M. and dim red lighting from 10 A.M. This special purpose room was fully air-conditioned, at 21°–22° C.

For at least 10 days before experiments, the rats were accommodated to continuous access to water delivered through a metal spout from inverted 100-ml. measuring cylinders, and to powdered Autoclaved Small Animals Diet (Spillers, London) pre-

sented in 9-cm.-high glass jars with a 5-cm.-diam. hole in the lid.

### *Intubation Procedure*

In the week before the experiment, each rat was intubated 2-3 times without injection. A polyethylene infant-feeding tube (French-gauge 6 catheter; Portex, Hythe) marked at 13 cm. from the tip was used. The rat was restrained with one hand and the tube inserted into the throat by a twisting or jabbing motion using the animal's oral reactions to ease entry, without forcing the mouth open. Passage of the tube to within 1 cm. of the mark precluded intubating the lungs. On experimental days, the tube and attached syringe were filled with the material to be intubated, the tip of the tube washed and wetted with water, and the load delivered at about 2 ml/sec to the stomach. The rats were generally placid throughout the whole procedure.

Glucose solutions were prepared by dilution of a concentrated solution of anhydrous D-glucose (British Drug Houses) in deionized water, which had been made at least 18 hr. before intubation and stored at 0°-5° C.

Each experiment involved a group of 12 rats, with a body weight range of 25 gm. or less—group means in the range 230-400 gm. Stomach loads of a constant volume for a given experiment (unless stated otherwise) were given between 10 and 11 A.M. at least 48 hr. apart. Except in Experiment 2 food was withheld for 1 hr. after intubation. The rats never experienced any other food deprivation. Water (to the nearest milliliter) and food (to the nearest .1 gm.) remaining were measured every 1 or 2 hr. for 7 or 8 hr. following intubation, at 24 or 25 hr., and generally at 48 hr. from the time of intubation.

### *Meal Patterns*

An approximate meal-pattern analysis was derived for experiments in which hourly food-intake data had been collected for 7 consecutive hr. In three successive pairs of replications of a procedure of intubating 5 ml. of water in the light phase or 10 ml. of water in the dark phase and then withholding food for 1 hr. (in Experiment 1), an hourly intake value of .7 gm. was never observed (nor a value of .8 gm. in the 10-ml. dark-phase conditions). Yet all other .1-gm. intervals of hourly intake value were represented in the data, from zero up to 2.6 gm. in the light and 3.1 gm. in the dark. The distributions were therefore taken to be bimodal. Hour intervals producing intakes less than .7 gm. were classified as being between meals and hourly intakes above .7 gm. were taken to be part of a meal. When food intake had been observed in what was classified as an "intermeal interval," the intake was added to the intake of the immediately adjacent hour having intake greater than .7 gm., if there was one. If both adjacent hourly intakes were above .7 gm., the intervening intake was divided equally between them. Less

than 1% of the observed food intake remained unassigned to "meals" by this procedure.

### *Statistics*

Except where stated otherwise, the *p* values quoted in the text or figures are derived from two-tailed correlated *t* tests between the named pairs of conditions within a group of animals.

### *EXPERIMENT 1*

The purpose of the first experiment was to compare the effect on feeding of a moderate volume of 1 M glucose with the effects of the same volume of various control loads. One group was gastrically intubated early in the bright phase of the lighting cycle and another at the start of the dark phase.

### *Method*

Intubations of 1 M glucose, .5 M sodium chloride, and 1 M urea were compared in the first part of the experiment using a Latin-square design. In the second part, 1 M glucose was paired in turn with water and with air, half the group having the comparison with water first, half air, and also in each comparison half the subgroup having glucose first, half control first. Intakes on a day without intubation were measured between the two parts of the experiment. Volumes of 5 ml. were used throughout in the light phase. The first part of the experiment in the dark phase also involved 5-ml. loads, but, because the resulting differences between glucose and saline or urea proved to be rather small, 10-ml. loads were used for the glucose vs. water and glucose vs. air comparisons.

### *Results*

#### *Light Phase*

On a day without gastric intubation the average feeding rate over the 7 hr. of hourly intake measurements during the light phase was fairly constant at a mean rate of .38 gm/hr (Figure 1). The food intake in the third hour after intubation of saline or water (but not air) was above this rate in 10 or more rats out of the group of 12 (bold data lines in Figure 1). A later hour period of decreased intake appeared for both saline and urea intubations. Glucose intubation produced a decreased feeding rate with the same degree of reliability at hour periods from the second to fourth hour after intubation.

A reliable cumulative depression of food intake relative to control conditions devel-

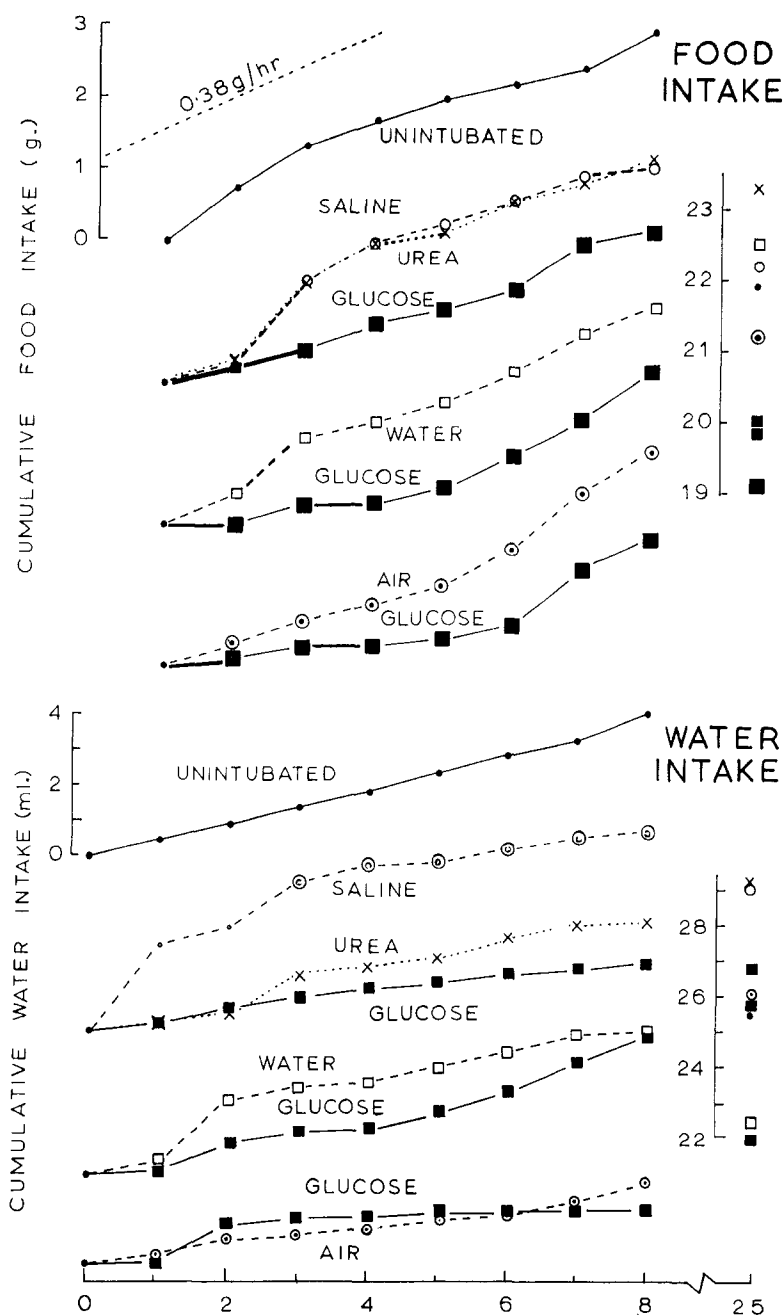


FIG. 1. Cumulative food and water intakes after 5-ml. intubation in the bright phase of the lighting cycle (Experiment 1). (Solid squares—1 M glucose; open circles—.5 M sodium chloride; crosses—1 M urea; open squares—water; dotted circles—air. The lines with filled circles give intakes on an unintubated day. A bold line to the left of a data point indicates that the group intake for that hour was reliably different from the mean unintubated rate; a large glucose data point is a mean reliably different from the control mean. The large saline-water-intake points are reliably different from water intake after either urea or glucose.)

oped in the second or third hour after glucose intubation and remained thereafter (large glucose data points in Figure 1:  $ps < .02$ ). In the cases of water and air controls this appeared before any increase in feeding rate in the control condition. The cumulative relative depression after glucose appeared to increase to a maximum at about the third or fourth hour after intubation (even later with air as control): The increases in cumulative inhibition were reliable ( $ps < .05$ ) between the second and third hours after liquid intubations. In the light of the results of Experiment 3 below, one might note the suggestion in addition of a decrease of net cumulative inhibition from that maximum which appears after 6 hr. from intubation, at least in the case of liquid controls. At 25 hr. the depressions of food intake after glucose appeared larger relative to fluid injections than to air injection, but only the depressions relative to urea and saline were reliable.

The consistent depression of food intake after glucose intubation relative to control intubations was not paralleled in the water intakes (lower part of Figure 1). Non-reliable depressions of cumulative water intake after glucose intake appeared later than feeding depressions. A large and reliable augmentation of cumulative water intake appeared only after saline intubation and was mainly attributable to drinking in the hour immediately after intubation during which food was withheld.

Estimates of meal sizes and intermeal intervals derived from the hourly food-intake measures indicated that, relative to the liquid control intubations (median delay to first meal: 1 hr.), glucose increased the incidence of long feeding latencies (median: 4 hr.) after restored access to food ( $p < .05$  overall, chi-square test). The median size of the first meal after glucose intubation (1.9 gm.) was close to that after control intubations (2.0 gm.). No indication of later effects on the meal pattern was observed.

### *Dark Phase*

On the day without intubation the feeding rate during the hourly measurement period in the dark-phase group was practically

constant at a mean of 1.21 gm/hr (Figure 2). This was about three times the rate in the light phase. Reliable changes of feeding rate in individual hour periods were not seen consistently in this group. However, as in the light, a reliable cumulative depression of food intake relative to control conditions developed in the second or third hour after glucose intubation and remained thereafter, in both cases of 10-ml. comparisons but not in the 5-ml. comparisons (Figure 2). The mean differences remained in the same direction to approximately the same extent at 25 and 48 hr. after 10-ml. intubations, but were not so consistently reliable as earlier. The food intakes 25 hr. after 5-ml. intubations were all practically identical to that seen in the unintubated condition.

Once again there was neither a consistent parallelism nor an inverse relation to feeding in the water intakes (Figure 2). Mean differences showed a pattern very similar to that seen in the light-phase group, but they were not statistically reliable.

The median feeding latency after the larger glucose loads (1 hr.) was larger than that after control loads (0 hr.). The size of the first meal after intubation was definitely smaller following the larger glucose loads (median: 2.0 gm.) than following control loads (median: 3.9 gm.) in this group ( $p < .01$  by Wilcoxon test), and a difference in the same direction, although not reliable, appeared after the smaller loads (glucose median: 2.5 gm.; control median: 4.8 gm.). No effects on the feeding pattern were evident after the first meal.

### *Discussion*

Control intubation of liquids appeared to have an effect of its own, especially evident after light-phase intubation. Saline, urea, and water all produced faster feeding in the third hour, with some tendency for it to be compensated in the subsequent hours, but the 25-hr. intake values indicating a possible residual overall hyperphagia. Perhaps fluid can accelerate the passage of chyme past satiety-maintaining gastrointestinal receptors and even affect the efficiency of absorption or utilization under some conditions. A difficulty in clearing air from the

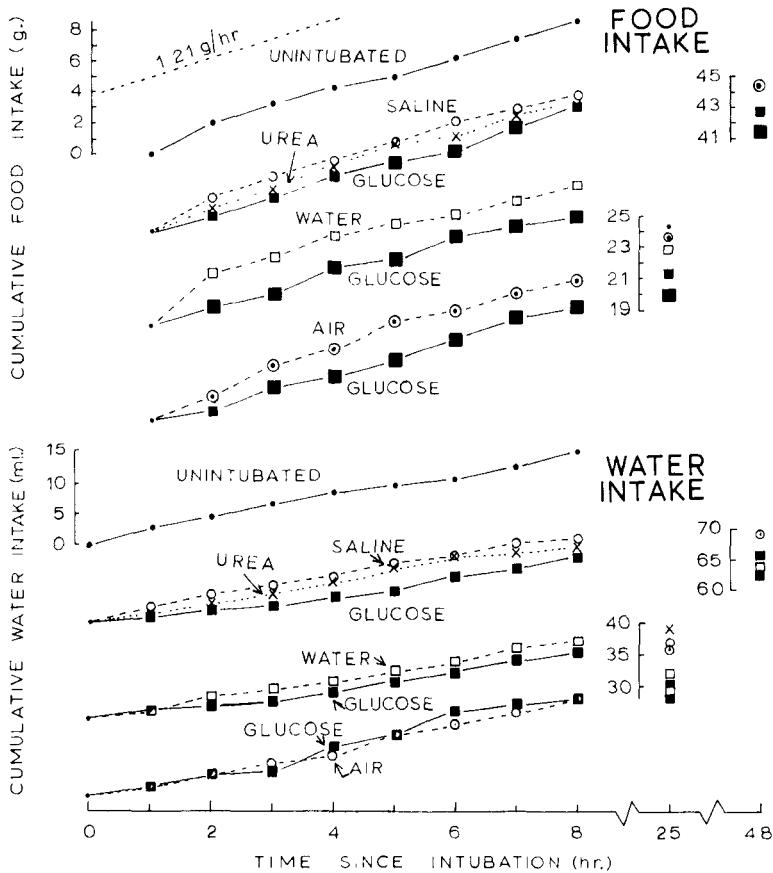


FIG. 2. Cumulative food and water intakes after dark-phase intubations (Experiment 1). (Symbols as in Figure 2 [significant glucose depressions are relative to saline in top panel]. The loads for the comparison in the top panel were 5 ml. The lower two comparisons involved 10-ml. loads.)

gut in the rat (Oatley & Dickinson, 1970) may account for the protracted development of glucose-induced feeding inhibition relative to that control in the light and in the dark.

After light-phase intubation, a temporal dissociation was observed between increases in drinking and decreases in feeding, which confirmed that the glucose-induced reduction in food intake cumulated over several hours was not merely hypertonic anorexia. The timing of feeding inhibition also failed to correlate with drinking inhibition, weighing against attribution of the feeding inhibition to distress factors. A possible late phase of slight drinking inhibition is presumably to be expected as maintenance food contains salts and protein, which would

make more demands than glucose does on urinary volume.

In the light, the approximately asymptotic cumulative food-intake inhibition several hours after glucose intubation relative to all control loads (and at 24 hr. relative to air intubation) was in the range .9–1.2 gm. of chow, which had a digestible energy of 3.43 kcal/gm according to the manufacturer. The glucose load was .9 gm. and the calorific value of glucose is 3.74 kcal/gm (McCance & Widdowson, 1960). Thus there was a net decrease in cumulative food intake which was calorically equivalent to the amount of glucose administered (1.09 gm. of chow per gram of glucose).

In the dark phase, a feeding rate three times that in the bright phase goes with an

increase in the variability of food-intake measures and so reliable effects with a 5-ml. load of 1 M glucose were not observed with a group of 12 rats in this experiment. With double that dose, however, reliable depressions of cumulative intake relative to controls were observed. In this phase of the lighting cycle, as in the light, the effect on the meal pattern appeared complete after the first meal and the cumulative inhibition had reached asymptote within a few hours of intubation. Also the asymptotic compensation approximated to caloric equivalence (1.6–1.8 gm. of chow at 8 hr. after intubation and 1.6–2.9 gm. at 25–48 hr. after 1.8-gm. glucose loads). Thus it appears that, despite the higher feeding rate in the dark, food-intake control in the rat is about as rapidly and as intensively responsive to glucose loads in the dark as in the light.

### EXPERIMENT 2

3-Methylglucose is an unmetabolizable analog of glucose (Csáky & Glenn, 1957). It moves into cells as does glucose and indeed interacts with the insulin-dependent cell uptake system in a way similar to glucose (Crofford & Renold, 1965; Morgan, Regan, & Park, 1964). Thus its osmotic and membrane effects should be distributed through the gut and the rest of the body initially very like those of glucose, but without the latter's metabolic effects. Therefore 1 M 3-methylglucose was intubated in a fresh group of rats, under light-phase conditions to minimize the amount of glucose analog that had to be expended to get behavioral effects. As 3-methylglucose was expected to have only small colligative effects postabsorptively, as does glucose (Fitzsimons, 1961), the technique of withholding food for the first hour after intubation to minimize osmotic effects on feeding was not used in this experiment.

### Method

3-O-Methyl-D-glucopyranose (Sigma), D-glucose (both 1 M), and water were compared in a group of 12 rats according to a Latin-square design, intubating volumes of 5 ml. in the bright phase of the lighting cycle. In this experiment, food as well as water was present immediately after intubation and food intake was measured at 1 hr. Intake measurements were omitted for convenience

at 4 and 6 hr. after intubation as it was expected that cumulative intake differences would settle down by that time.

### Results

Food intake in the first hour after intubation was less after both glucose and 3-methylglucose than after a water load (Figure 3). The glucose load practically eliminated all feeding in the first hour, but some remained after 3-methylglucose ( $p < .05$ ), although the food-intake difference between the two solute loads was not reliable at this time ( $p > .1$ ). There was no evidence of increased drinking after 3-methylglucose in this hour.

Thereafter, the glucose-intubated condition showed a cumulative food intake consistently below that of both the water- and 3-methylglucose-intubated conditions, reliably so at the third hour after intubation and from 7 hr. to 24 and 48 hr. As in Experiment 1, there was some evidence of overeating seen at 24 and 48 hr. after water intubation. The mean cumulative water intake after 3-methylglucose was consistently 1 ml. above the other conditions from 7 hr. onwards, but this was not statistically reliable.

### Discussion

The present results indicate that 3-methylglucose partially mimics the satiating effect of glucose in the first hour after gastric intubation. There was no evidence of increased or decreased drinking at this time to indicate that this feeding inhibition should be attributed to a colligative effect. It appears therefore that glucose initially activates a chemospecific receptor by a non-metabolic mechanism with which 3-methylglucose has some less effective interaction. Alternatively both solutes satiate by maintaining gastric distension for part of the first hour, but only metabolism of glucose satiates thereafter.

This initial depression of feeding by 3-methylglucose is rapidly compensated. From the second to eighth hours after intubation, cumulative food intakes match or even exceed those seen after water intubation. Also urinary excretion of the analog (Csáky & Glenn, 1957) possibly induces a slight in-

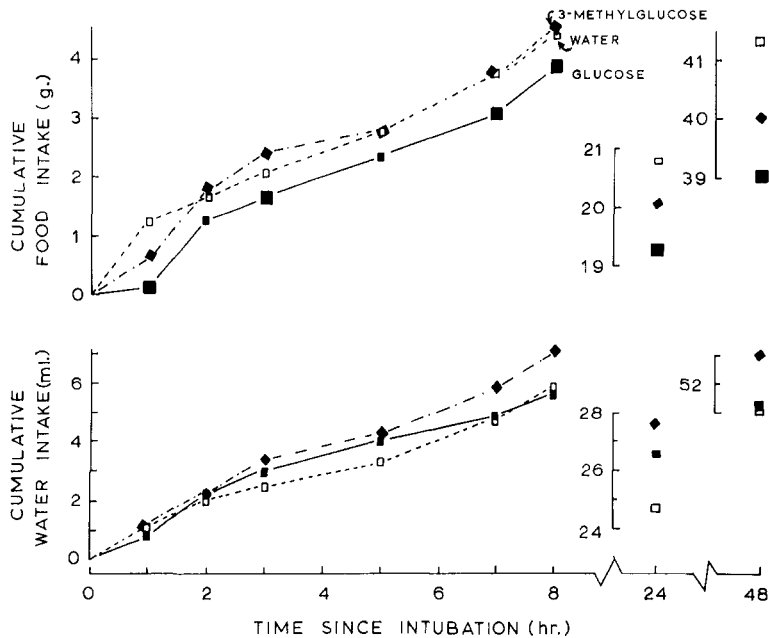


FIG. 3. Cumulative intakes after intubation of 5 ml. of water or of 1 M glucose or 3-methylglucose in the light phase (Experiment 2).

crease in water intake after several hours. The results with 3-methylglucose in this experiment, together with those involving urea and sodium chloride in Experiment 1, establish that the glucose from polysaccharides abundant in most foodstuffs could play a major part in maintaining satiety by noncolligative mechanisms at least from the second hour after ingestion.

The effect of glucose under these conditions of uninterrupted access to food is instructive. Accumulating inhibition at the second and third hour after intubation was not seen, although it had been seen in Experiment 1 in which food was withheld for 1 hr. after intubation. The first hour's satiety was apparently so great that the inhibition of feeding when food is present in that hour is compensated by facilitation of feeding in the subsequent hour, possibly even slightly overcompensated. This suggests the existence of a series of satiety mechanisms—those affected in the first hour under the present conditions being very strongly reactive to glucose, and those affected in the second hour after intubation possibly being somewhat underreactive. This suggests that, in control terms, these

mechanisms may be open loop, and only at 3 hr., or later when glucose absorption has finally been completed, does a closed loop using some measure of energy or energy potential begin to be fully operative.

### EXPERIMENT 3

The final pair of experiments were dose-response studies to determine whether the time course and precision of behavioral caloric compensation varied with the amount of glucose tubed. As the procedure of delaying access to food for an hour after intubation reduced to negligible proportions the effects on food intake of the variations in osmotic effects between sodium chloride, urea, water, air, and glucose, the range of glucose doses was covered in most cases by varying glucose concentration in a constant intubated volume. Different glucose concentrations are liable to produce differing degrees of gastric distension because of variations in gastric secretory response, but this source of variation would also be diminished by stomach emptying during the hour without access to food.

One group was intubated in the light phase. As 10-ml. loads in the dark phase



gave reliable effects on a basal feeding rate three times that seen in the light phase, the volume intubated throughout this experiment was 3 ml. A dose-response study of the effects of urea was incorporated, as it seemed to be the most appropriate inexpensive substance to serve as a colligative control.

Another group, accommodated to a reversed lighting cycle, was intubated in the dark phase. In similar animals, some estimates were made, in addition, of the time course of passage of intubated glucose through and out of the gut, and of the amount lost in the urine.

### Method

#### Light-Phase Group

Each of a fresh group of rats received each of eight types of 3-ml. loads according to a Latin-square design. The extremes of glucose concentration were compared with equimolar urea concentrations. The eight intragastric loads were water; 5%, 10%, 20%, and 40% glucose; and 1.67%, 3.33%, and 13.3% urea. Food was withheld for 1 hr. after intubation as usual and intake measurements at 4 and 6 hr. after intubation were omitted.

#### Dark-Phase Groups

There were seven types of intragastric loads given at the start of the dark phase. Water and 5%, 10%, 30%, and 40% glucose in 10-ml. volumes and 5 ml. of 30% glucose were given in sequences determined by a Latin square, interrupted in the middle for all 12 rats by an intubation of 10 ml. of 18% (1 M) glucose as used in Experiment 1. Food was withheld for 1 hr. after intubation. Intakes were measured hourly until 8 hr. after intubation, and at 25 and 48 hr.

Other rats were intubated under identical conditions with 10 ml. of water or 10%, 20%, or 40% glucose. They were killed by cervical dislocation at intervals up to 6 hr. after intubation. The stomach was rapidly clamped at the esophagus and pylorus, and clamps placed at 36-cm. intervals along the small intestine, taking care to minimize the flow of contents in the jejunum as it was dissected out. These four sections of gut were removed and placed on chilled plates, slit open, and washed free of their contents by a known amount of saline at 0°-2°. The total washings were weighed. Resuspended portions were then deproteinized and their glucose content estimated by the glucose oxidase assay in the Sigma Chemical Co. version, except that 5 M tris was included in the incubation medium to inhibit the disaccharidase activity of the enzyme preparation (Dahlquist, 1964).

Another rat was kept under identical food, water, and lighting conditions in a metabolism cage. It was intubated at intervals of 2 or more days suc-

cessively with 10 ml. of 10%, 40%, and 20% glucose and 10 ml. of water. Urine samples, uncontaminated with feces or food, were collected on NaF over 0-4, 4-8, 8-24, and 24-28 hr. after intubation and stored at -18°. They were assayed for glucose content by the glucose oxidase method (Sigma).

### Caloric Compensation Analysis on Meal-Pattern Individual Data

Grouping intermeal-interval and meal-size data picks out some orderliness in the meal-pattern estimates at the cost of discarding a good deal of parametric information. In the dark-phase group of the present experiment, food-intake measurement every hour for 7 hr. after restored access was coupled with seven dose levels of glucose (including zero). Such data permit an analysis which uses much more of the information in the meal-pattern data, to provide an estimate of the stages in the meal pattern after tubing at which behavioral compensation for the load becomes calorically complete. The plots of Figure 7 were a test of the assumptions in the following derivation.

The rat's caloric input rate, averaged over long time intervals, must equal its caloric output rate plus rate of increase of energy stores and other parts of body mass. First let us assume that, under the conditions of the present experiment, the combined rate of long-term average caloric output and growth is constant. Let  $T_c$  (time for behavioral compensation) be a time period of sufficient length and in appropriate phasing with the meal pattern to allow regulation via adjustment in caloric input to be achieved. Then, on the above assumption:

$$(\text{Input calories during } T_c)/T_c = K, \quad [1]$$

where  $K$  is a constant.

If the undisturbed rat with free access to food gets a fixed number of calories from a given weight of food over the long term, then:

$$k_t F_0 / T_c = K, \quad [2]$$

where  $F_0$  is grams of food taken during  $T_c$  under these conditions, and  $k_t$  is the caloric yield of the food (kcal/gm).

Next assume that a load of glucose does not change this caloric yield of the food (an assumption about which doubts are raised in the General Discussion below). Then, according to Equations 1 and 2:

$$\frac{k_t F + k_g G}{T_c} = K = \frac{k_t F_0}{T_c},$$

where  $F$  is food intake (in grams) from time of tubing over the period  $T_c$ ,  $G$  is dose of glucose (in grams), and  $k_g$  is the caloric yield from glucose.

This linear equation rearranges as follows:

$$\frac{F}{T_c} = - \left( \frac{k_g}{k_t} \right) \left( \frac{G}{T_c} \right) + \frac{F_0}{T_c}.$$

To test the hypothesis that caloric regulation

entirely via behavioral compensation is achieved by some specific number of meals and intermeal intervals, values should be substituted in this equation for each phase in turn of the meal pattern after tubing. The time substituted for  $T_c$  will of course vary from occasion to occasion and from rat to rat, generating a set of data different from either the cumulative-intake dose response or the meal-pattern dose response. On the assumption that variability in the constants  $K_r$ ,  $K_g$ , and  $K$  from rat to rat is small compared with the functional relationship expressed in the above equation, then, at a stage in the meal pattern after tubing which is late enough to allow compensation, a plot of  $F/T$  against  $G/T$ , using the  $F$ s and  $T$ s observed for that meal-pattern stage after each of the intubated  $G$ s, should give a linear function. Its slope would equal the ratio of caloric yields from glucose and food. Its intercept would equal the average uninterrupted feeding rate for that phase of the lighting cycle.

### Results

#### Dose-Response Functions

The mean cumulative food- and water-intake responses to increasing concentrations of glucose or urea in constant volume are given in Figures 4 (light phase) and 5 (dark phase). Least-squares regression lines were calculated for all of these dose-response functions. Those regressions which reliably accounted for intake variance between doses or whose slopes were reliably different from zero are listed in Table 1.

**Food intake.** For the light phase, in the first hour of restored access to food (the second hour after intubation) the regression slope was  $-.9$  gm. of chow per gram of glucose tubed. In the subsequent hour there seemed to be a slight (statistically insignificant) steepening of the slope to  $-1.05$ , which was maintained in the subsequent 2-hr. period, but then decreased again slightly, to  $-.85$ . Thus there was a repetition of the pattern of cumulative inhibition developing a maximum at 3 hr. after intubation and then possibly relapsing slightly, which had been seen for a single dose of 5 ml. of 1 M (18%) glucose relative to liquid control intubations in Experiment 1. Exact caloric compensation in food intake would be 1.09 gm. of chow per gram of glucose, according to the figures given in the Discussion section of Experiment 1. No regression slope deviated reliably from this value.

Dark-phase intubations produced relatively smooth dose-response functions in the cumulative food intakes (Figure 5). This was despite the fact that two points in the middle of the dose range were obtained either out of sequence (1.8 gm.) or in half volume (1.5 gm.)—a result which supports the attribution of the feeding inhibition to amount of glucose administered and not its concentration. Once again, no food-intake regression slope deviated reliably from  $-1.09$ , the value for exact caloric equivalence of load and intake decrement ( $ps > .1$ ). It is evidence from Figure 5 (as indeed in Figure 4, the light-phase dose response) that this reflects a remarkably linear dose-response function in the cumulative food intakes starting 3–4 hr. after intubation through to the eighth hour. An approximation to gram-for-gram compensation remained at 1 and 2 days after intubation. However, it should be noted that, in the case of the earliest observed effects of glucose on feeding, there may be an artifact in the linear regression slope estimate and its increase between 1–2 and 1–4 hr. intakes: There appears to be a “floor effect” in the first and second hours of restored access to food coming into operation at the highest doses, coupled with a considerably steeper than gram-for-gram dose-response line for doses below 2 gm. Indeed a linear regression for the first hour of access to food, excluding the 3-gm. and 4-gm. data, intersects the ordinate well below 4 gm. This fits with the suggestion from the results of Experiments 1 and 2 that there is an initial overcompensatory food-intake inhibition produced by moderate doses of glucose, which is corrected after 2 or 3 hr. or more by a slight acceleration of feeding. As in the light-phase group, regression slopes after these dark-phase intubations tended to decrease, although not reliably, from the fifth hour after intubation.

**Water intake.** After bright-phase intubation, there was a marginally reliable tendency for cumulative water intake over 48 hr. from intubation to increase with dose of glucose. Although this 48-hr. regression line accounted for some variance and differed in slope from some regression estimates at

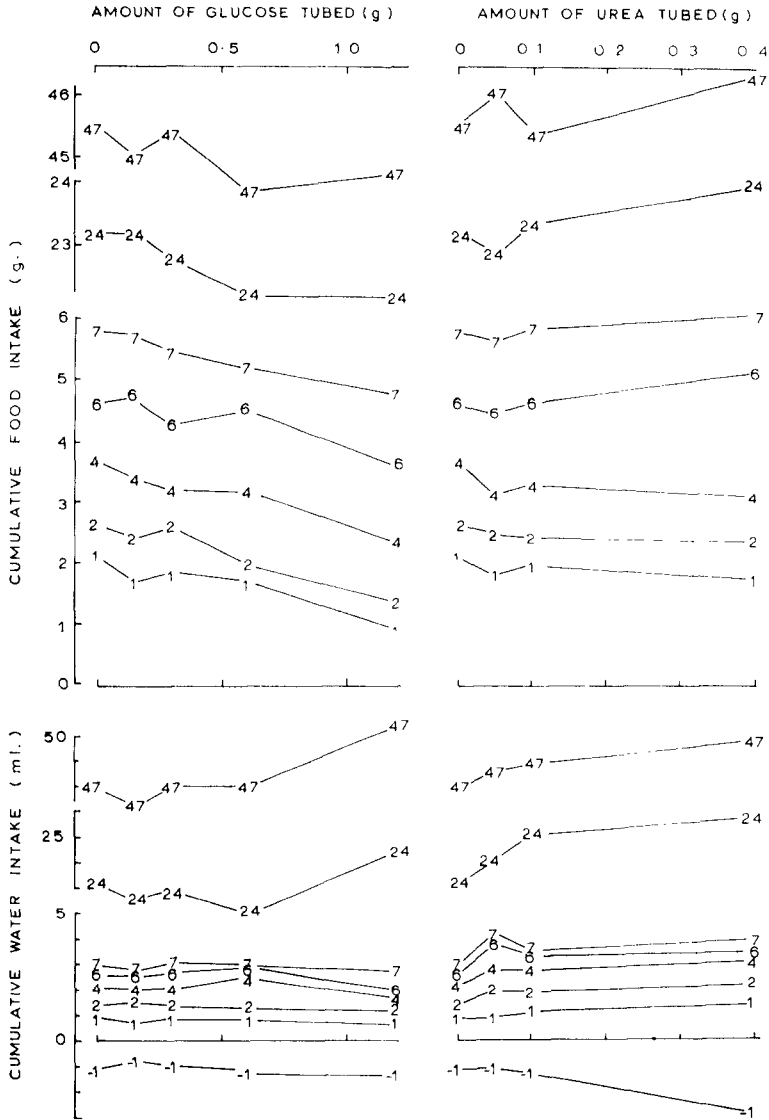


FIG. 4. Cumulative intakes after 3-ml. intubations in the light phase (Experiment 3). (The data point numbers represent the number of hours since restoration of food 1 hr. after intubation. Thus water intakes below the origin occurred in the absence of food. Linear regression statistics are given in Table 1. Glucose and urea doses are drawn on equiosmolar scales. All intubations were given in a single experimental design and so the zero-dose data are identical for glucose and for urea.)

earlier times after tubing, its slope was not reliably different from zero. In the dark, there were no effects of increasing dose of glucose on water intake at the time the major effects on food intake were occurring (lower parts of Figures 4 and 5). At later times some small but reliable decreases in

water intake were seen, but ultimately there were increases, if anything.

Urea, on the other hand, gave a reliable water-intake regression for the hour between intubation and restored access to food. Signs of late effects during access to food were not, however, statistically relia-

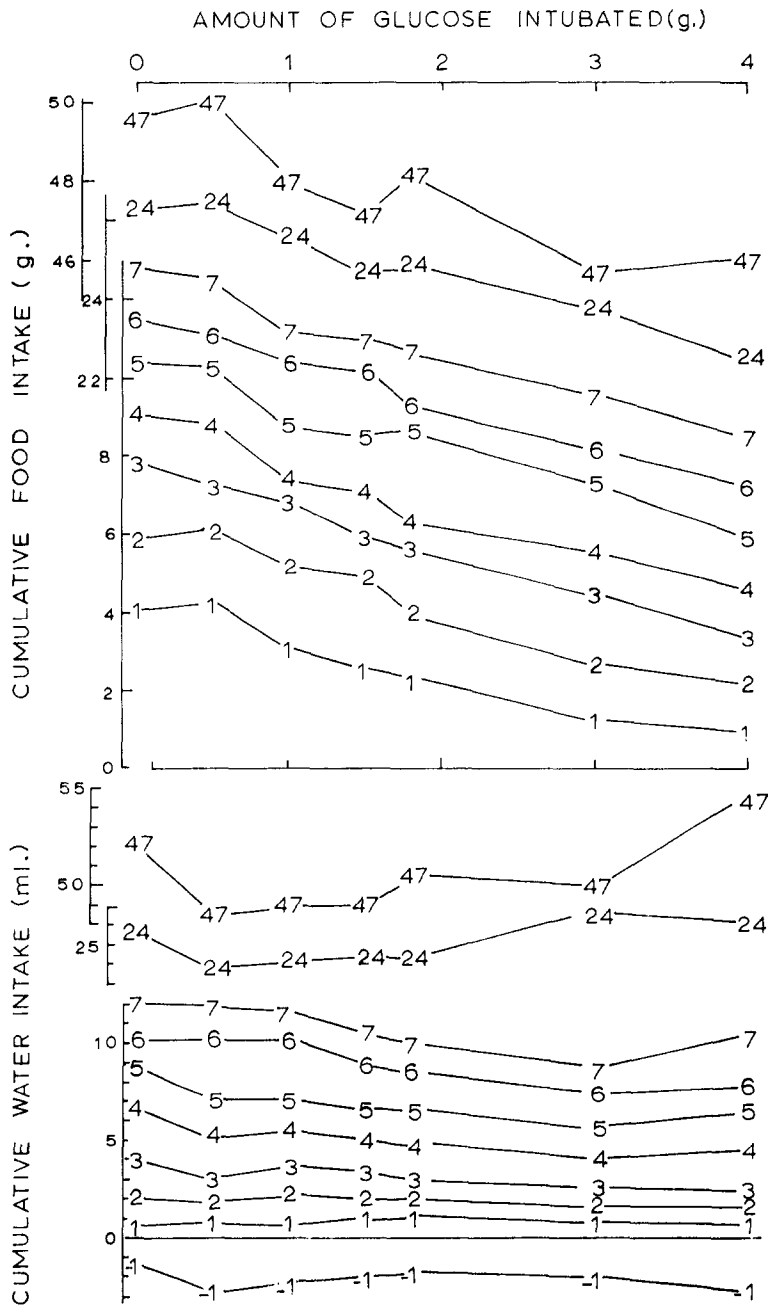


Fig. 5. Cumulative intakes after 10-ml. intubations in the dark phase (Experiment 3). (See Table 1.)

ble, nor were there any systematic effects on food intake. This confirmed over the whole dose range that the present procedure detects satiating effects of glucose which are not simply colligative.

*Meal-Pattern Compensation Functions*  
Estimates of the meal pattern from the hourly intake data after dark-phase intubation were consistent with there being at

TABLE 1  
LINEAR REGRESSION OF CUMULATIVE INTAKE DOSE RESPONSE (FIGURES 4 AND 5)

Condition	Time interval since intubation <sup>a</sup> (in hr.)	Regression parameters				Intervals whose slopes differ from this slope		
		Reliability ( $p$ ) <sup>b</sup>	Intercept (in gm. or ml.)	Slope $\pm$ SE (in gm. or ml/gm load)	Slope = 0 ( $p$ ) <sup>c</sup>	$p < .05$	$p < .01$	$p < .001$
Light phase								
Water intake after urea	0-1	< .01	-.87	-4.76 $\pm$ .57	< .02	7, 8	3, 5	2
Water intake after glucose	0-48	< .05	47.32	2.32 $\pm$ 1.18	<i>ns</i>	2, 3, 5, 8	1, 7	--
Food intake after glucose	1-2	< .01	2.06	-.90 $\pm$ .33	< .1	--	--	--
	1-3	< .01	2.68	-1.05 $\pm$ .29	< .05	--	--	--
	1-5	< .01	3.63	-1.04 $\pm$ .24	< .05	--	--	--
	1-7	< .05	4.72	-.85 $\pm$ .44	<i>ns</i>	--	--	--
	1-8	< .001	5.78	-.85 $\pm$ .11	< .01	--	--	--
Dark phase								
Water intake after glucose	0-4	< .05	3.73	-.30 $\pm$ .19	<i>ns</i>	7, 25	2	--
	0-5	< .05	5.90	-.48 $\pm$ .36	<i>ns</i>	2, 3, 25	--	--
	0-7	< .01	10.31	-.76 $\pm$ .31	< .1	4, 48	1, 3, 25	2
Food intake after glucose	1-2	< .001	4.17	-.89 $\pm$ .23	< .02	4	--	--
	1-3	< .001	6.23	-1.06 $\pm$ .23	< .01	--	--	--
	1-4	< .001	7.81	-1.14 $\pm$ .09	< .001	1	--	--
	1-5	< .001	8.91	-1.14 $\pm$ .25	< .01	--	--	--
	1-6	< .001	10.36	-1.08 $\pm$ .22	< .01	--	--	--
	1-7	< .001	11.56	-1.11 $\pm$ .13	< .001	--	--	--
	1-8	< .001	12.71	-1.07 $\pm$ .16	< .002	--	--	--
	1-25	< .001	26.54	-.98 $\pm$ .19	< .002	--	--	--
	1-48	< .01	49.63	-1.07 $\pm$ .50	< .1	--	--	--

Note.—A regression is listed only if it had some statistically reliable parameter ( $p < .05$ ).

<sup>a</sup> There was no access to food for 1 hr. after intubation.

<sup>b</sup>  $p$  value of  $F$  ratio of regression variance and error variance.

<sup>c</sup>  $p$  value for  $t$  test of difference of regression slope from zero.

the highest doses of glucose an increase in incidence of long feeding latencies, small first meals, and short subsequent intervals (Figure 6), but the variation in distributions approached reliability only in the case of meal sizes ( $p < .1$ , chi-square test). The data from this experiment were sufficiently numerous and varied in doses to provide a more sensitive measure to determine at which stage in the meal pattern subsequent to intubation an asymptotic behavioral compensation had been achieved. According to the derivation given in the Method section for this experiment, a plot of the average rate of food intake to a given stage

in the meal pattern against the dose of glucose divided by the time to that stage should give a straight line, having a slope equal to the ratio of caloric yields from food and glucose, and having an intercept equal to the undisturbed feeding rate (given the assumption that caloric regulation is achieved entirely by depression of food intake in response to the glucose load). Scatterplots of all the available data are given in Figure 7. At the end of the first meal and at all subsequent phases of the meal pattern up to the beginning of the third meal following intubation, there were reliable correlations between feeding rate and dose

per time. However, there appeared to be a floor effect in the function at the end of the first meal: An extrapolation of the lower end of the vertical range of the data points appeared to intersect the abscissa at about 1.2 gm/hr, and the points above that value showed no tendency to a negative slope. This implies that the regression line for data of a dose per time less than 1.2 gm/hr is a better estimate of a truly linear phase of the response elicited by that early stage in the meal pattern subsequent to intubation. Its slope of  $-1.24$  was greater than would be obtained even if all the energy in the glucose load were available and high carbohydrate intake produced no increase in the energy available from chow ( $-1.09$ ). Also the ordinate intercept (2.25) was much greater than the average feeding rate of this group when not tubed (1.3 gm/hr). Thus there was overcompensation up to the end of the first meal after glucose loading. However, by the end of the subsequent inter-meal interval, the slope had flattened to  $-1.03$  and the intercept was down to 1.57 gm/hr. Similar values were obtained at the end of the interval following the second meal, although the data were more sparse and less representative because the hourly intake measurements extended only to 8 hr. from intubation. A similar slope but an incorrectly high intercept were obtained at the end of the second meal.

#### Glucose Disposal

Glucose disappeared from the gastrointestinal tract approximately according to a square-root function after intubation (Hopkins, 1966), not affected by the amount or concentration loaded (Figure 8). A large proportion of the load was still in the stomach when access to food was restored 1 hr. after intubation. Despite clearance of glucose from the stomach in the subsequent 1-2 hr., the weight of stomach contents, and hence presumably their volume, remained relatively constant at high values over that period in the case of the largest dose. This maintenance of stomach distension correlated with the period of marked inhibition of feeding (Figures 2 and 5). At the lowest dose assayed (and therefore with isotonic

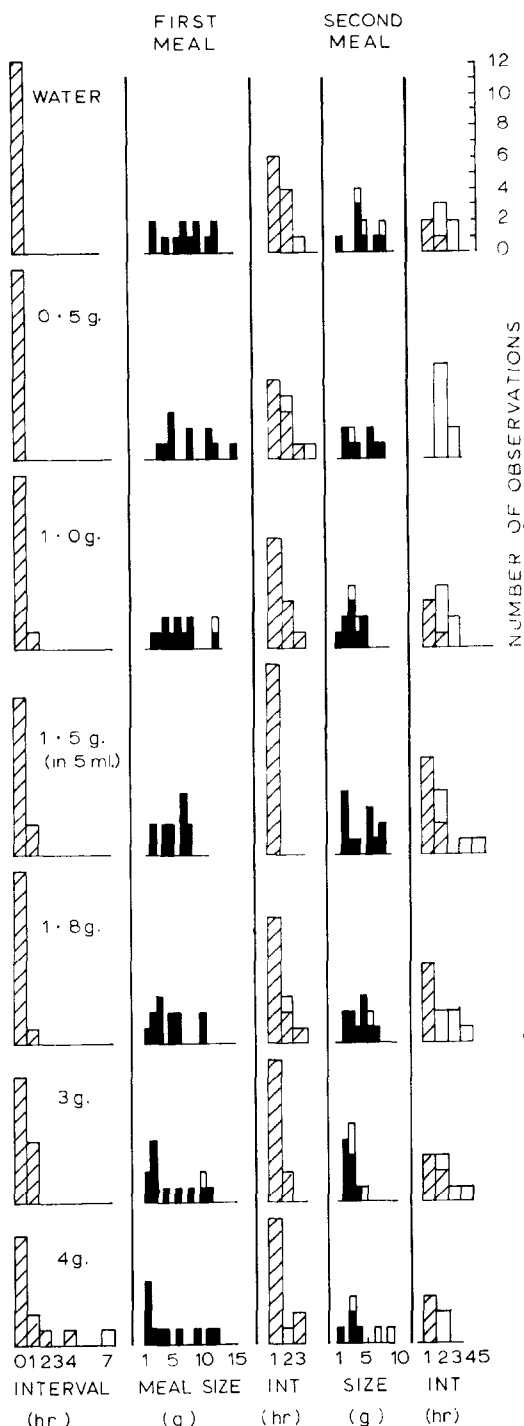


FIG. 6. Meal-pattern analysis for Experiment 3.

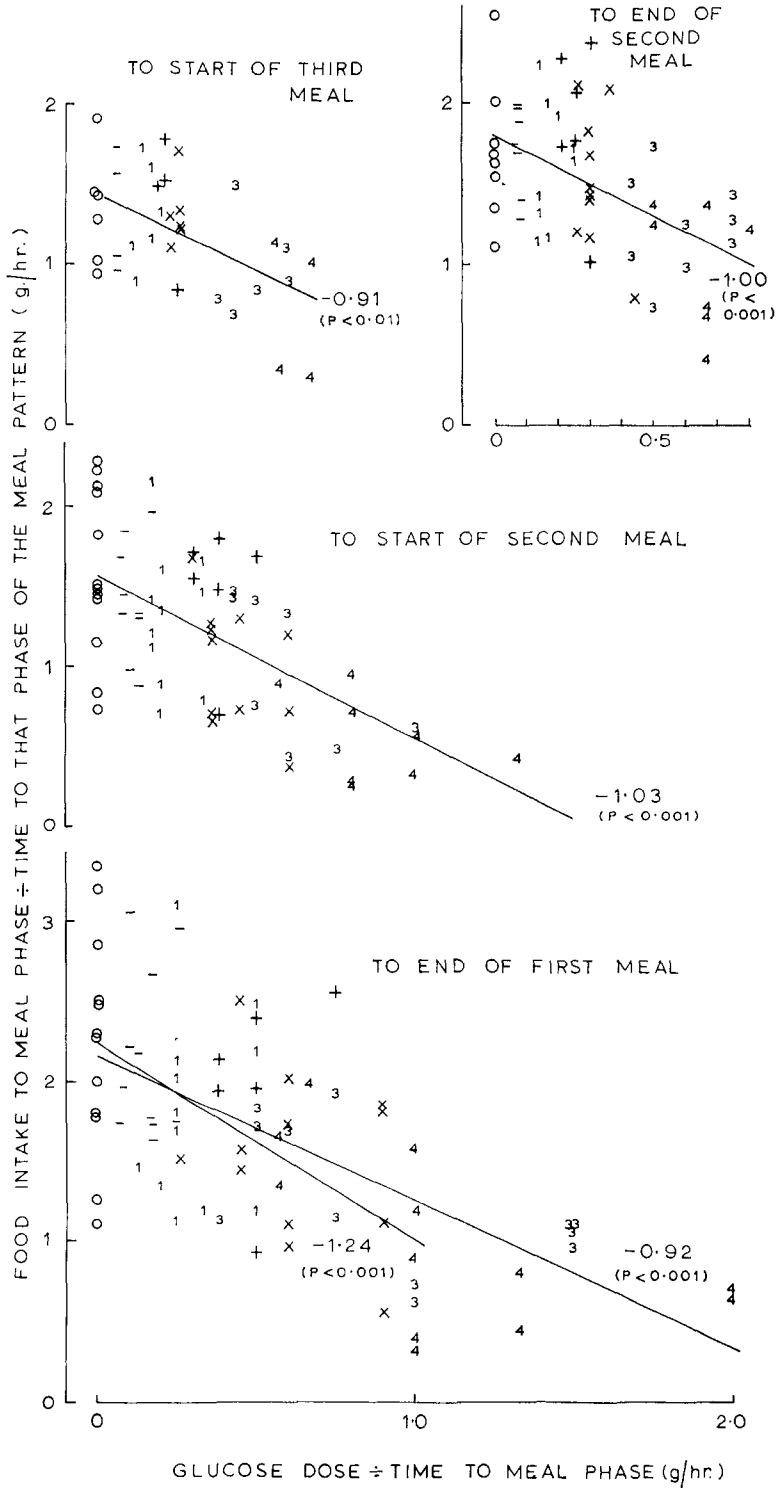


FIG. 7. Compensation functions at various stages in the meal pattern after intubation (Experiment 3). (Each data point represents average food-intake rate up to a given meal phase, plotted against

glucose at the still lower dose of .5 gm.—Figure 5) the inhibition of feeding must be attributed primarily to postabsorptive action. In the case of higher doses of glucose, the final stages of absorption were being completed in the period after 3 hr. from intubation, when cumulative inhibition of intake was slightly decreasing toward asymptote.

Less than 1 mg. of glucose appeared in the urine in the 24 hr. following gastric intubation of 1, 2, or 4 gm. of glucose.

### GENERAL DISCUSSION

The assumptions of the caloric compensation equation were supported by the functions obtained at the starts of the second and third meals after intubation, but not by the functions for the ends of the first or second meals (Figure 7). This suggests two conclusions. First, compensation is complete only by the start of the second meal after intubation, and not with that initial reaction over 2–3 hr. from intubation which was seen in the latency to feed and size of first meal in Experiment 1 and in Figure 6 here. This supports the interpretation of the dose-response regressions of Table 1 as indicating an initial overreaction which takes up to the fifth hour after intubation to be compensated. Second, the failure of the data to meet the assumptions at the ends of meals and its success at the starts of meals support a suggestion based on very different data (Booth, 1970) that caloric regulation according to some measure of caloric reserves is mediated by the timing of meal initiation, not by varying the initiation of satiety that ends a meal. Le Magnen has also argued from a wide variety of results that the main unconditioned mode of feeding regulation is via intermeal intervals not meal sizes (Le Magnen & Devos, 1970). It appeared from Experiment 1 that glucose was acting to prolong the satiety induced by the meal preceding intubation, at least in the light; it remains to be seen whether the degree of prolongation varies with the interval from the previous meal to intubation. However, at least in the dark-phase

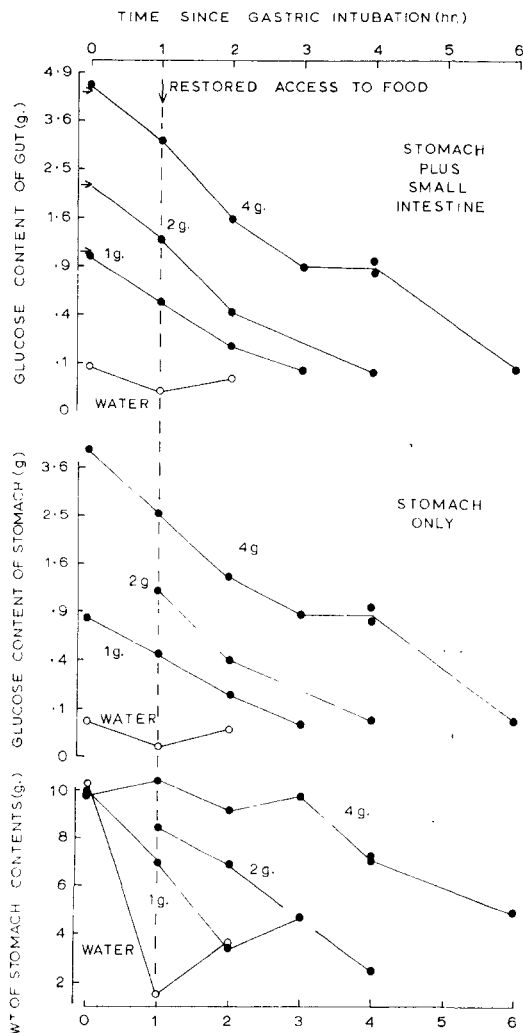


FIG. 8. Gastrointestinal contents after intubation.

group of Experiment 1, and probably in Experiment 3, the glucose load definitely also decreased the size of the meal following intubation. A similar effect has been seen in freely feeding man (Booth, Campbell, & Chase, 1970) and possibly related effects in the daily fed dog (Janowitz & Hollander, 1955; Share, Martyniuk, & Grossman, 1952) and monkey (Baile, Zinn, & Mayer, 1971): Intubated glucose might reduce the acceptability of food (cf. Cabanac, Minaire, & Adair, 1968) or it might lower the threshold

glucose dose divided by the time to that phase. Symbols represent doses in grams [0, 1, 3, or 4 gm.; .5 gm. represented by —; 1.5 gm. represented by +; 1.8 gm. represented by x]. Lines are least-squares linear regression estimates, with slopes and their reliabilities appended.)



for initiation of satiety by acting on central or peripheral responses to gastric distension or other satiety signals.

### *Satiety Mechanisms*

The time course of changes in the distribution of glucose through the gut after dark-phase intubation indicates the type of mechanism by which the earlier satiating or satiety maintaining effects of glucose are produced in this type of experiment. The same mechanisms should be operative in intermeal intervals during feeding on the liquid diet 116EC (General Biochemicals, Ohio) used by Snowdon (1970) and others, for this is 34% glucose plus components similar to glucose in their effect on the gut or of negligible effect. Results using these solutions should not be extrapolated to explain control of intermeal intervals on normal foods which contain unhydrolyzed carbohydrate and protein plus substantial amounts of fat, and so produce viscous non-hypertonic stomach contents and, more importantly, the profound effects of fatty acids on intestinal control of the stomach. A large proportion of the glucose remains in the stomach throughout the interval to the first meal following intubation, for 2 hr. or more. The action of glucose on intestinal receptors which have some chemical specificity inhibits stomach clearance (Reynell & Spray, 1956). The lack of an appreciable satiating effect of urea, in contrast to glucose, is an indication from the present results that more than simple osmoreception is involved. Also, Experiment 2 indicated that even the overall effect in the first hour after glucose intubation may be chemospecific to some extent. However, in addition to inhibiting its own discharge from the stomach, and indeed inhibiting the initial gastric secretory responses (Konturek & Grossman, 1965), hypertonic glucose induces a slow secretion or sequestration (Warren, Karr, Hoffman, & Abbot, 1940) which maintains stomach distension despite continuous clearance of glucose (Figure 8). According to this account, the satiating effect of hypertonic nutrient solutions at 1-3 hr. after administration should not be attributed to simple distension nor to simple

colligative effects. Intestinal chemoreception is a necessary stimulus as well as gastric response to osmotic influence. Furthermore, these intestinal receptors are not necessarily generating satiety via direct afferents, but may well be sending signals indirectly to the brain by causing the stimulation of gastric mechanoreceptors. It should be noted that the dose-response line is straight over the whole dose range at 3 hr. after intubation (Figures 4 and 5), although it has a slope representing inhibition of food intake to a degree greater than calorically appropriate. This suggests that the characteristics of intestinal control of gastric distension could, with a more normal nutrient than free glucose, produce an exact caloric compensation well in advance of complete absorption. The digestion of starch would produce glucose at the intestinal receptor and slow gastric emptying as effectively as glucose (Hunt, 1960) but the gastric secretion to hypotonic polysaccharide would be less than to equivalent free glucose, and thus would distend the stomach less and give a dose-response line at 1 hr. or so after intubation less steep than that given by glucose.

The slight flattening of the dose-response line at 5-8 hr. after intubation occurs after absorption of the loaded glucose. Thus the present experiment shows that some residual adjustment of the meal pattern depends on postabsorptive signals. These could arise from energy production rather than circulating metabolites but it remains to be determined under free-feeding conditions how completely an equivalent to the load has been oxidized by the time that the cumulative inhibition of feeding has reached its final value. It must also be noted that the possibility of a major postabsorptive satiety signal acting even in the first hour after intubation has not been reduced by any of the present data.

There is evidence that glucose has some noncolligative satiating effect, not only under the free-feeding conditions of the present experiments, but also in the starved rat (Jacobs, 1964; Panksepp, 1971; Smith, 1966; Smith et al., 1961). However, a full range of doses and colligative controls with frequent intake measurements has yet to be

examined to see whether the satiating effect after extended deprivation is as great and whether the cumulative inhibition shows the dose-response relation seen under ad-lib conditions. As energy exchange is so different in the starved rat, the glucose-induced satiety and its regulatory role may well be different, as appears to be the case in the dog fed only once daily and given nutrient intragastrically (Share et al., 1952).

### *Behavioral Contribution to Caloric Regulation*

Booth et al. (1970) had found an approximately gram-for-gram reduction in 24-hr. food intakes after administration (in the light phase) of a wide range of doses of glucose at a constant concentration of 50%. The dose-response lines had slopes of  $-0.92$  for administration by drinking ( $p < .05$ ) and  $-1.20$  ( $p < .01$ ) for intragastric administration (least-squares linear regressions recalculated to exclude a datum more than three standard deviations from the mean of the remaining data). The present studies, using the intragastric route exclusively, have shown that this behavioral compensation is achieved within several hours (fewer than two meals) after intubation and reflected in any intake measure thereafter. Asymptotic values of the regression slope varied from  $-0.85$  to  $-1.07$ . No value was reliably different from  $-1.09$ , the slope to be expected if the gross oxidation energy of the glucose was matched by a cutback of chow intake of identical digestible energy. Thus it is evident that control of food intake could in this case be the sole expression of precise long-term energy exchange regulation, without any regulatory control via adjustments of completeness of absorption, heat output, or muscular activity. Nevertheless, a full energy balance determination will be necessary to assess how precisely the asymptotic value of the dose-response slope reflects the energy the rat actually derives from the glucose load. The results of glucose assays indicated that virtually all of the glucose load was utilized at all doses in the dark. A negligible amount was detected in the urine even at the highest dose. Even with load volumes of 10 ml.,

significant amounts of glucose reached no further down the small intestine than the jejunum. The ileum can absorb glucose if any reaches that far (Barry, Matthews, & Smyth, 1961) and so it is unlikely that appreciable amounts were lost in the feces.

Some estimates can be made of the importance of various aspects of the energy exchange in this situation.

Probably all the glucose is absorbed even at high doses: Reynell and Spray (1956) have shown in the rat that the intestine regulates gastric release of glucose to a rate below the maximum intestinal absorption rate. The hyperglycemia after intubation of glucose does not exceed the kidney threshold by a great amount if at all and in Experiment 3 a rat's urine contained negligible amounts of glucose even after the highest dose used.

Another consideration is that the caloric values for glucose and chow used in this paper are based on the assumption that all carbohydrate is completely oxidized to carbon dioxide and water. Now the carbon in the glucose molecules intubated does not have to have been completely converted to  $\text{CO}_2$  for this assumption to be valid. There does not even have to be production of  $\text{CO}_2$  from calorically equivalent molecules—conceivably, regulation could be achieved in advance of generation of the energy loaded. However, even 4 gm. of glucose (the largest amount tubed) is calorically equivalent to only one-sixth of the daily food intake, and so the 5 hr. or so which are necessary to give asymptotic dose responses are presumably sufficient to allow the energy equivalent of the load to be consumed, and precise regulation to be achieved in direct response to an "energostatic" set point (see below). Something that may invalidate the use of gross caloric values does arise, however, from the possible effects of glucose loads on chow utilization. Kekwick and Pawan (1965) have presented evidence that the oxidation of standard maintenance diet in the rat is far from complete, and furthermore that increasing the proportion of carbohydrate in the nutrient input improves the recovery of carbon as  $\text{CO}_2$ . Thus a glucose load could in fact increase the net energy supply to the rat by an amount greater than the maximum energy that could be produced from it directly. However, the conditions of carbohydrate loading in the experiments of Kekwick and Pawan (1965) were quite different from those of the present experiments, in which the manipulations may be sufficiently minor and brief not to produce marked effects of this sort.

The observed behavioral compensation would be inappropriate if stored energy were permanently increased or decreased by the glucose load. A quarter of intragastrically administered glucose is converted to fatty acids (Jansen et al., 1966). At the moment we do not have the body weight or fat content measures to determine whether long-term net storage is induced under the conditions of the present experiments.

Also I have yet to measure heat output to determine whether there is any change (up or down) in net cumulative energy expenditure after the caged rat has received a glucose load. It has been both calculated and observed that 10% of the energy of glucose in the diet must be used for gastrointestinal processing and for storage by synthesis (Baldwin, 1970). However, the same applies to the energy-yielding nutrients in chow. Indeed the chow includes protein, which has a high heat increment ("specific dynamic action"), making the chow caloric equivalent of glucose slightly higher than the value taken in this article. Another factor tending in the same direction is the satiety produced by glucose intubation lessening the usual motor activity and reduced thermal insulation involved in getting food. On the other hand, uncoupling of energy utilization from synthetic and external work may "burn off" excess energy during prolonged overfeeding (Miller, Mumford, & Stock, 1967); there is, however, no evidence for the existence of such an effect after a single caloric load.

So without carcass composition and heat output measures, we cannot be certain of the exact regulatory significance of the observed asymptote of compensatory food-intake inhibition. However, in advance of such physiological data, there is a reasonable coincidence of the value for the asymptotic dose response with the numerical value of gross caloric compensation, to serve as an indication that we do in fact have here precise regulation purely by means of food-intake control.

It should be clear that the present results give no specific indication as to the nature of the measure(s), if any, of whose regulation the observed compensatory inhibition of feeding may be an expression. My belief at the moment is that feeding (and body weight) are entrained by many linking factors to the self-regulating characteristics of intermediary metabolism—an "energo-static" regulation, perhaps, but with no simplistic error signal such as glucose availability or a substance whose circulating concentration is a function of amount of

adipose tissue. Moreover, these results do not indicate the nature of the factor whose operation produces the asymptotic compensation after several hours, if that is not identical with regulatory error signal(s). Glucose was administered, indeed, but neither those molecules nor the other glucose molecules spared by them need be the inhibitory factor. Some more generally informative signal might be used—one deriving from all energy sources such as amino acids, glycerol, and fatty acids as well as glucose, and one closer to the actual use of energy in the cells, e.g., levels of high energy phosphates. Nevertheless, the present data do provide the first direct and parametric behavioral demonstration in support of the longstanding suggestion (Mayer, 1953; Mayer & Thomas, 1967) that glucose utilization can generate a transient effect on feeding according to some measure of caloric input integrated over a few hours ("short-term regulation"). Note, however, that the regulation could be energostatic rather than glucostatic, even if its main link with feeding were through effectors controlled primarily by glucoreceptors.

A final point of interest in the present results is that the regulatory response of the feeding system to overlapping dose ranges of glucose was indistinguishable between night and day. This was despite large differences in average feeding rate and probably in postingestive events, and some indications of a difference in the type of meal-pattern adjustment mediating the caloric compensation. Therefore dark-phase hyperphagia cannot be attributed to a complete lack of sensitivity to metabolic influences. On the contrary, the asymptotic cumulative inhibition of feeding by glucose given at the start of the dark phase is, if different at all, somewhat greater than that induced by light-phase gavage of glucose.

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