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The Pig as a Model for the Study of Obesity and of Control of Food Intake: A Review

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The use of the pig for studies of food intake and obesity is reviewed. Effects of ambient temperature and taste on food intake as well as satiety factors impicating both neural and hormonal mechanisms originating in the gastrointestinal tract are considered; the integration of information in the central nervous system for both internal and external sources is hypothesized. Special concerns of food intake controls in the neonate are discussed, including effects of neonate sweet preference on food intake, gastrointestinal satiety factors, and hypoglycemia as a stimulus for food ingestion.

For obesity studies, pigs offer several advantages, including their general physiological similarity to humans, similar fat cell size, and body fat distribution. Lipogenesis, lipolysis, and lipid mobilization are under intensive study in swine and the information obtained may have important application in studies of human obesity. The voluminous literature on metabolic differences between genetically lean versus obese populations of pigs suggests possibilities for application in humans. Greater characterization of differences and similarities between pigs and humans in important metabolic parameters related to regulation of food intake and obesity should facilitate better understanding and control of human obesity.

INTRODUCTION

The purpose of this review is to present the current evidence validating the use of the pig as a model for studies of control of food intake and of obesity in humans. Although the two phenomena are interrelated, they are discussed separately because of the incomplete knowledge concerning factors affecting them in both species. As additional knowledge accumulates, an integrated discussion will be appropriate.

CONTROL OF FOOD INTAKE

Limitations of Various Animals as Models

Studies of the controls of food intake have been made with a variety of species of animals. By far the greatest number of such studies has been performed on rodents, especially rats. Mice have also been used for investigations of food intake related to obesity, both genetic obesity [1] and obesity after administration of gold thioglucose [2]. Dogs were used in early studies of gastric and oral factors in food intake [3]. For example, some of the early evidence that a fall in plasma glucose secondary to insulin

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administration led to an increase in food intake was also obtained from dogs [4]. In early neurological studies implicating the lateral and ventromedial hypothalamus in the control of food intake, rats [5], cats [6], and monkeys [6] were used as the experimental animals. Recently, gastrointestinal and hepatic factors in satiety have been investigated in a lagomorph, the rabbit [7,8].

There are major drawbacks to the use of each of the species mentioned above as models for the study of human ingestive behavior. In addition to the anatomical and physiological differences between rodents and humans, the small size of rodents precludes many types of surgical and blood sampling procedures that should be used in studies of the physiology of behavior. Rats and mice were, originally at least, granivores. Dogs and cats are carnivores whose natural diet and meal patterns differ from those of humans. The relatively short, simple gastrointestinal tract of carnivores also differs from that of the omnivorous human. Finally, lagomorphs are strict herbivores that meet some of their nutritional needs by a combination of cecal microbial fermentation and coprophagy. The most appropriate model for the human would be an omnivorous primate, preferably an anthropoid ape. Rhesus monkeys have been used for studies involving cross transfusion [9], cholecystokinin-induced satiety [10], and brain lesions that alter body weight [11]. The expense and scarcity of primates have limited their use in studies on controls of food intake. Furthermore, primates are not tractable laboratory animals and must be either chaired, which severely limits their activity to less than that of the most sedentary human, or sedated for many procedures that could be performed on fully conscious members of a more tractable species.

The Pig as a Model

The pig is an excellent model for studies of the control of intake in humans. The pig, like the human, is an omnivore with a digestive tract intermediate between the short, straight tract of the carnivore and the complex, compartmentalized tract of the true herbivore. The use of the pig as a model for human physiology and disease has been documented in several books [12,13,14]. Some of the important similarities are in gastrointestinal physiology, including predisposition to ulcers [15,16]; atherosclerosis [17]; nutrition [18], including malnutrition of the neonate [19,20]; and alcoholism [21]. The adult pig weighs 120–200 kg and the miniature pig, 70 kg. Although feed and housing facilities are relatively expensive, the large size of the pig is an advantage in other respects. Large blood samples may be taken easily and surgical manipulations performed with relative ease. For example, cross circulation can be established and maintained for many days, both because of the size of the pigs and because histocompatible pigs can be identified [22]. Procedures such as the reentrant pancreatic cannulation technique developed by Pekas [23] and the selective vagotomy procedures of Stadaas et al. [24] will no doubt be useful.

Ingestive Behavior

In discussing the role of the pig as a model for human ingestive behavior, we first consider exteroreceptive influences on food intake, namely, thermoregulatory eating and taste. Next, we consider changes in the internal environment including a decrease in energy balance and changes in glucose utilization. The importance of satiety factors in the normal meal to meal control of food intake is stressed and data implicating both neural and hormonal satiety mechanisms originating in the gastrointestinal tract are presented. The integration of information for both internal

(i.e., gastrointestinal, hormonal) and external sources (i.e., skin temperature, sight of food) in the central nervous system is hypothesized. Finally, special concerns of food intake controls in the neonate are discussed.

Thermoregulatory eating. Brobeck [25] has postulated that animals eat to keep warm and stop eating to prevent hyperthermia. It seems evident that homeothermic species do indeed respond to a cold environmental temperature by increasing their food intake and respond to a hot environment by decreasing their intake. Pigs are no exception to this. In a very hot environment (40° C) food intake of pigs falls markedly [26]. More moderate increases from a thermoneutral temperature of 22° to 33° C also result in a sustained depression of food intake [27]. A fall in environmental temperature stimulates food intake. A short exposure of as little as four hours at 5° C results in an increase in food intake of young growing pigs. Figure 1 illustrates the effect of environmental temperature on food intake of pigs [28]. This response is analogous to that of the human. The daily caloric intake of young men is 5,000 Kcal in Arctic temperature of −36° C and 3,000 Kcal at tropical temperatures of 38° C [29].

In contrast to the marked and consistent changes in food intake in response to environmental temperature changes the evidence regarding the influence of brain or spinal cord temperature on food intake is contradictory. If an increase in body or blood temperature depressed intake, the increase in temperature due to the specific dynamic action of a meal might be a physiological satiety factor. However, in the pig and in the rat, warming the hypothalamus increases intake and cooling decreases intake; spinal cord heating and cooling have no effect on intake [30,31,32]. These results do not support the hypothesis that an increase in brain temperature acts as a short-term satiety-inducing factor. The effect of ambient temperature on food intake is presumably mediated through exteroreceptors rather than directly on the central nervous system.

Taste. Four primary tastes have been identified in humans: sweet, salt, sour, and bitter [33]. Sweet taste preferences are believed to have evolved because sweet tastes are usually produced by carbohydrates of high available energy content. Salt preference may have a similar basis because salty taste is associated with sodium salts essential for maintenance of the internal milieu. The aversive properties of sour and bitter tastes may protect the taster from toxic and caustic substances.

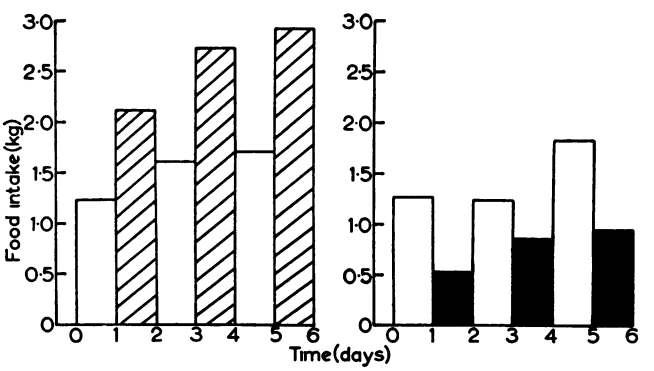

FIG. 1. Daily food intake of pigs fed *ad libitum*. Pig on left was subjected on alternative days to 25° C (*open*) and 10° C (*hatched*). Pig on right was subjected on alternative days to 25° C (*open*) and 35° C (*black*). Reprinted with permission from Ingram and Legge [28].

The earliest of the studies on taste preferences in pigs [34] showed preferences for sucrose, lactose, and fructose. Some, but not all pigs showed a saccharin preference. Later Kennedy and Baldwin [35] studied pig preferences for sucrose, glucose, saccharin, and cyclamate. In both short term (1 hr) and long term (12 hr) tests, the pigs showed marked preferences for the natural sweeteners: glucose and sucrose. The strength of the preference can be deduced from the *increase* in fluid intake from a value of 13 liters/12 hr when 0.001M sucrose and water were available to a value of 17 liters/12 hr when 0.23 M sucrose and water were available. Saccharin was also preferred but sodium cyclamate was neither preferred nor rejected. Operant conditioning techniques in which the pig pushed a panel for a sucrose reward indicated that the stronger the sucrose solution, the greater the number of responses the pigs would make. Using electrophysiological techniques on pigs, Hellekant [36] recorded neural responses to sucrose, sodium chloride, and citric acid, but not to two proteins (monellin and thaumatin) that taste sweet to humans and produce an electrophysiological response in monkeys. The results with three of four artificial sweeteners show that the pig may not be an appropriate model for testing artificial sweeteners and further raise the interesting possibility that there may not be a single common type of sweet receptor in mammals. Pigs are similar to humans in their response to bitter solutions; both species reject quinine [34].

Energy balance. If body weight or rate of growth is regulated in the developing animal, then energy intake must equal energy output, or energy in the form of fat will accumulate and the animal will become obese. As the classical experiments of Adolph [37] indicated, young animals, including young pigs, possess this ability. Pigs (38–105 kg) increased their food intake as the caloric value of their diet fell from 3,910 to 2,970 Kcal/kg to maintain a constant caloric intake (575 Kcal/kg weight) [38]. In other recent experiments [39], responses to dietary dilution are similar. Humans also have this ability as shown by Spiegel [40]. Pigs are able to control their food intake by responding in an unknown manner to the caloric content rather than to the bulk of the diet.

Perhaps the most interesting phenomenon is that in which food intake appears to be independent of body weight. Miller and Payne [41] restricted the growth of two young pigs and although the exact composition of the diets was not given, growth was retarded by limiting protein. Although one pig consumed twice as many calories as the other, the body weights remained the same. The pig on the higher calorie diet was apparently losing more energy as heat—a form of "luxus consumption" [42]. Similar results were reported by Pond et al. [43] who found that equal body weights were maintained by protein-deficient pigs fed high or low calorie diets. Efficiency of food energy conversion falls from 40 percent on a 15 percent protein diet to 27 percent on a protein-free diet [44]. Pigs given a free choice of diets differing in protein content and amino acid balance choose a nitrogen-free diet over an imbalanced amino acid mixture [45,46]. These experiments suggest an innate "nutritional wisdom," but more likely, pigs and other animals learn not to eat those foods that make them sick [47]. The ability to learn to avoid a taste associated with acute illness is well developed in pigs. Suckling pigs showed a marked preference for glucose solutions, but when the pigs' first exposure to glucose was followed by illness induced by injections of 10 ml/kg of 0.3 LiCl, they showed a preference for water over glucose when presented with both fluids several days later. Saline-injected controls continued to show a large preference for glucose over water [48]. Suckling piglets also could learn to form an aversion to their dam's flavored milk if the nipple was painted with

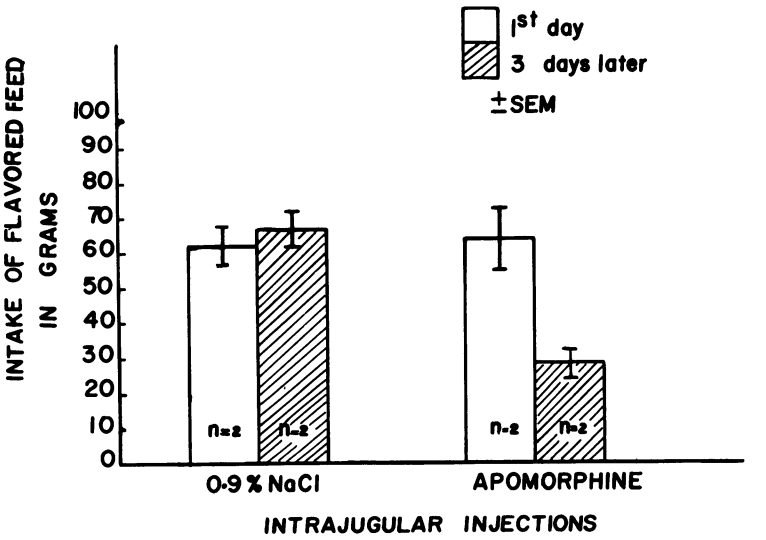

FIG. 2. Formation of a taste aversion to a novel flavor when that flavor is associated with illness. For each pair of columns, the open column on the left represents the intake of flavored (honey) food in a 5-minute period just before injection of either .05mg/kg of apmorphine or an equivalent volume of 0.9 percent NaCl intravenously. The hatched columns are intake of the same flavored food when against presented 3–4 days later. *n* = number of animals.

maple syrup and illness had been induced after the piglets suckled from the maple-flavored nipple. Apomorphine may also be used to produce an aversion to sweet solutions in older pigs (Fig. 2).

One of the most popular corollaries to the theory that animals eat in order to regulate body energy is the glucostatic hypothesis, as advanced by Mayer [49], which states that animals eat when the level of glucose utilization, particularly in the brain, falls. The hypothesis that hunger varies not with absolute levels of plasma glucose, but with rate of glucose utilization, explains the otherwise paradoxical hyperphagia of the diabetic as well as the simpler case of the hunger that accompanies hypoglycemia.

Eating in response to a fall in glucose utilization produced by either insulin hypoglycemia or by administration of the glucose analog 2-deoxy D-glucose that actively blocks intracellular glucose utilization has been shown in a wide variety of animals including rats [50], monkeys [50], and pigs [49,51]. Figure 3 illustrates the hyperphagic response of weanling pigs to 1 unit/kg of regular insulin. The pigs respond within six hours of injection and the early response explains the earlier failure to show an increase in food intake in response to insulin when intake was measured weekly rather than at shorter intervals [52]. It is believed that insulin stimulates intake secondarily. Glucose utilization within cells should initially be increased by insulin administration; but as glucose leaves the blood for the intracellular, predominantly intramuscular space, plasma glucose falls, and less glucose is available for utilization in the central nervous system. This effect of insulin may be pharmacological rather than physiological because: (1) insulin in smaller doses appears to act not as a stimulant of intake, but rather as a depressant, and (2) plasma levels of glucose do not fall to the levels seen after insulin administration during normal *ad libitum* feeding nor even following fasts of moderate length in the weanling pig. Plasma glucose, approximately 30–40 mg/dl or less following doses of

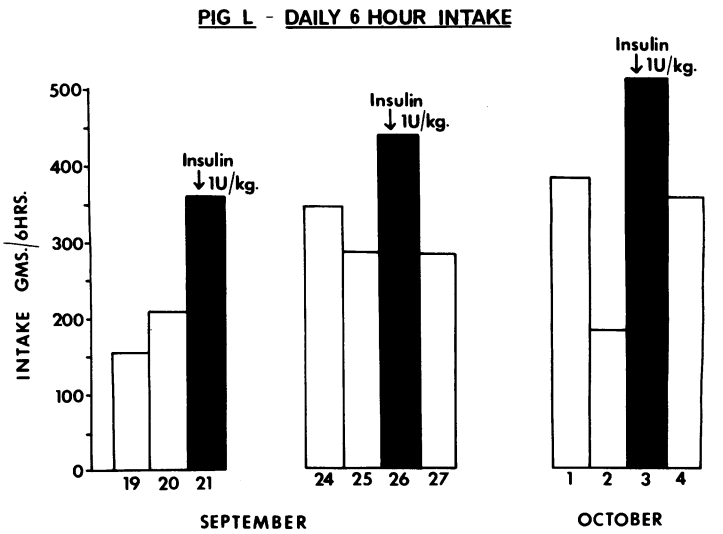

FIG. 3. Individual record of a pig showing intake during the six hours immediately following intraperitoneal injection of 0.9 percent NaCl (*open*) or 1.0 unit/kg regular insulin (*black*). Reprinted with permission from Taste and Development (edited by JM Weffenbach), Washington, U.S. Government Printing Office, 1977, p 94.

insulin, is sufficient to stimulate feeding. This and similar evidence [53] obtained in primates shows that glucostatic eating (1) may be an emergency mechanism that serves to increase energy intake when readily available energy stores have been acutely depleted, and (2) probably does not function in the meal to meal control of food intake.

Satiety. Food intake ceases before all or even a substantial part of a meal has been absorbed. If intake continued until enough food was digested and absorbed to correct the body's energy deficit, energy regulation systems would overshoot the amount necessary for energy balance by the amount eaten but not yet absorbed. Apparently, therefore, a meal is probably brought to an end by some preabsorptive mechanism(s). Other candidates for satiety sensors might be located in the portal vein or the liver, the tissues first encountered by newly absorbed nutrients.

To induce satiety, the brain must be appraised of the presence of food in the gastrointestinal tract. Two alternative mechanisms seem likely, hormonal or neural. The presence of food in the upper gastrointestinal tract may release a hormone or may stimulate a receptor that in turn sends afferent impulses toward the central nervous system. Cannon and Wasburne [54] first implicated the stomach as being the focus of hunger which was signaled by gastric contractions or hunger pangs. The findings that gastrectomized persons still perceived hunger and that gastric contractions were not always correlated with hunger turned attention from the gastrointestinal tract for many decades; recently interest has returned to gastrointestinal factors in satiety. One of these factors is the hormone cholecystokinin-pancreozymin (CCK-PZ).

CCK-PZ was first identified in 1928 by Ivy and Oldberg [55] as a substance that caused gall bladder contraction. In 1943, Harper and Raper [56] identified a substance in the duodenal mucosa which stimulated the release of pancreatic enzymes. Eventually, it became clear that the two substances were of the same structure [57]. The hormone has a number of actions on gastrointestinal motility,

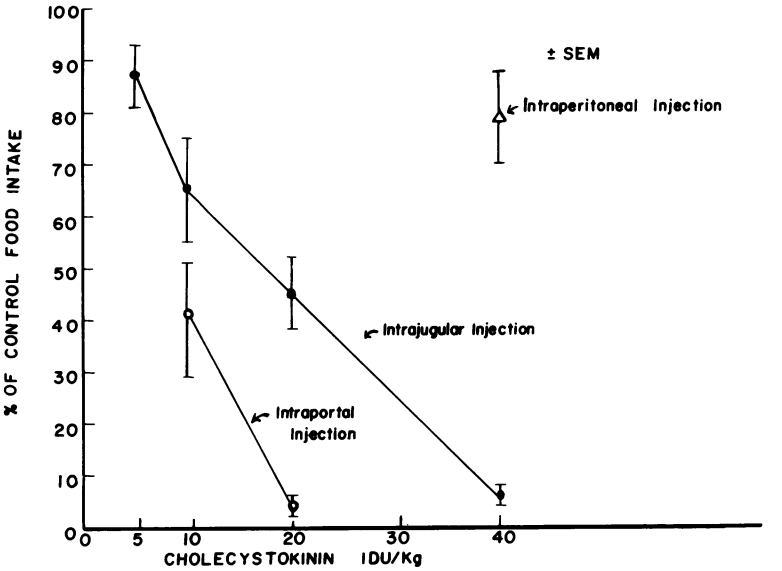

FIG. 4. Effect of cholecystokinin-pancreozymin (CCK-PZ) on subsequent food intake of pigs. The pigs were fasted for four hours before treatment. Intake was measured for 10 minutes after infusion of CCK-PZ into the jugular vein. Each point represents a mean value of tests on 10 pigs. The control or 0 dose was 0.9 percent NaCl.

insulin release, and mesenteric blood flow [58]. It was first implicated as a satiety hormone by Gibbs [59]. In humans, CCK-PZ suppresses intake under some conditions and increases it under others [60]. The hormone is available in a 20 percent pure form extracted from intestinal tissue of hogs, so the pig was the natural species in which to test the hypothesis that CCK-PZ is involved in satiety. A radioimmune assay for CCK-PZ has been developed [61] and the hormone and its COOH-terminal octapeptide have been identified in pig brain [62].

When given intravenously to pigs at doses of from 10 to 40 Ivy dog units (IDU)/kg of body weight, CCK-PZ depressed intake in a dose-related manner in four-hour-fasted pigs (Fig. 4). The lowest dose to produce a significant depression of intake was 5 IDU/kg. This dose is to be compared with a level of 3 ng/ml or approximately 10 IDU/kg found in the serum of postprandial pigs [61]. After CCK-PZ administration to pigs (40 IDU/kg), plasma insulin levels increase [58] and plasma glucose falls from preinjection levels of 109 mg/dl to 87 mg/dl [58]. When low levels of insulin (.05 U/kg) are administered intravenously to fasted pigs, plasma glucose falls similarly and food intake is depressed.

These findings indicate that CCK-PZ induced satiety may be mediated by insulin release, although the presence of CCK-PZ in pig brain [62] raises the interesting possibility of central actions of gastrointestinal hormones on ingestive and other behaviors. In support of such a possibility, genetically obese mice recently have been shown to have a lower cerebral cortical content of CCK than their lean littermates and other normal mice, suggesting a causal relationship between appetite and brain CCK content [63]. Insulin in higher doses stimulates food intake in a variety of species including pigs. The dual action of insulin on food intake may explain the effect of CCK-PZ on human food intake where injection of a bolus dose of CCK-PZ suppresses intake, but an infusion slightly elevates intake over that of saline-infused controls [60].

Foods high in protein and fat release CCK-PZ, the putative satiety hormone, but

carbohydrate diets also produce satiety. Isotonic gastric or duodenal loads of glucose suppress subsequent three-hour intake of previously fasted pigs. This response to glucose is probably postabsorptive because intake is not suppressed until 10–20 minutes after infusion; however, most normal solid food is not isotonic, and the process of digestion itself increases the osmotic pressure of the intestinal contents. Osmotic pressure appears to be at least one of the factors responsible for preabsorptive satiety because intraduodenal, but not intrajugular or intraportal infusion of glucose and saline of equal osmolarity produced equal suppression of food intake in fasted pigs (Fig. 5). These hypertonic loads did not produce illness in the pigs, for aversions to novel food associated with hypertonic duodenal infusion were not produced (Fig. 6). There appears to be neural mediation of osmotic stimuli because intrathoracic vagotomy attenuated the suppression of intake after hypertonic duodenal loads (Fig. 5) as did intraduodenal infusion of a local anesthetic (Fig. 7). Figure 8 is a schematic diagram of the factors involved in short-term satiety produced by hypertonic duodenal contents. The osmoreceptors postulated by Hunt and Pathak [64] to be involved in gastric emptying may also play a part in satiety. These hypothetical osmoreceptors may lie within the intestinal mucosa because nonabsorbed sugars such as sorbitol are far less effective in suppressing intake than absorbable compounds (Fig. 9). Also, the fact that the moderate (20 percent) suppression produced by these absorbable compounds cannot be blocked by local anesthetic, shows that some other mechanisms such as fluid shifts between the intestine and the blood stream may be involved in satiety produced by nonabsorbable compounds.

The gastrointestinal hormones are not the only ones to affect food intake. The ovarian hormones also affect food intake. Estrogen suppresses food intake in sows. The sow is in estrus every three weeks and during that week, food intake is 4 kg lower than during other weeks [65] (Fig. 10). Although food intake is depressed during estrus in a variety of animals and although administration of exogenous estrogen suppresses intake, the mechanism of the depression is not clear. The variation in

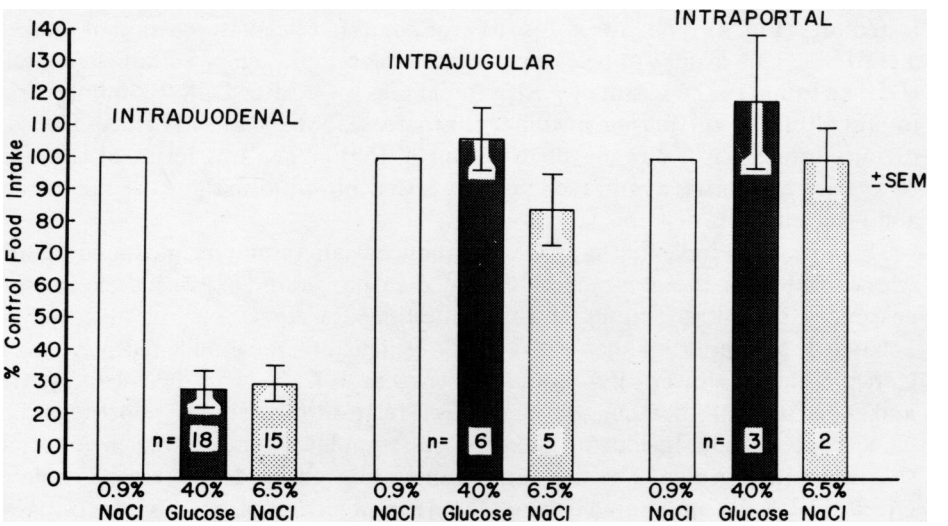

FIG. 5. Lack of significant effect on food intake of glucose and NaCl solutions injected into jugular or portal veins and effects of duodenal preloads. The intravenous injections were given continuously over the 10-minute test period so as to deliver the same amount (5 ml/kg body wt) as the duodenal preloads. *n* = number of animals.

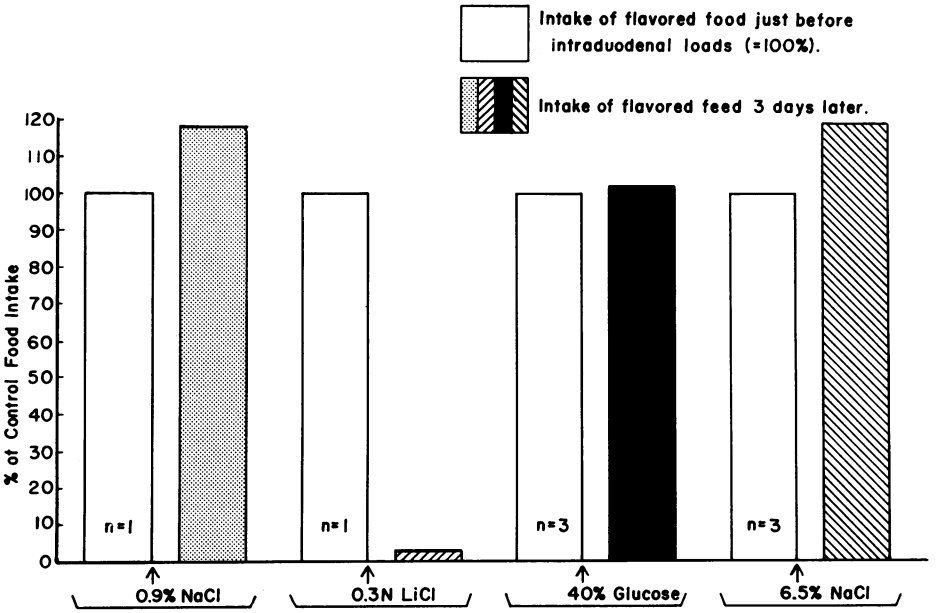

FIG. 6. Failure to form a taste aversion to a novel flavor temporally associated with hypertonic duodenal loads of glucose, NaCl, and sorbitol and demonstration of such taste aversion to a LiCl load. For each pair of columns, the clear column on the left represents intake of flavored food in a 5-minute period just before intraduodenal load is given (= 100 percent). Shaded columns are intake of the same flavored food when again presented 3-4 days later. Dose of duodenal load was 5 ml/kg body weight. *n* = number of animals.

caloric intake of women during the menstrual cycle has not been carefully studied, but the incidence of obesity rises in post-menopausal women [66].

Central nervous system. Many areas of the central nervous system are, no doubt, involved in integration of sensory information from the gastrointestinal tract, fat depots, and exteroreceptors and in the initiation and coordination of the motor

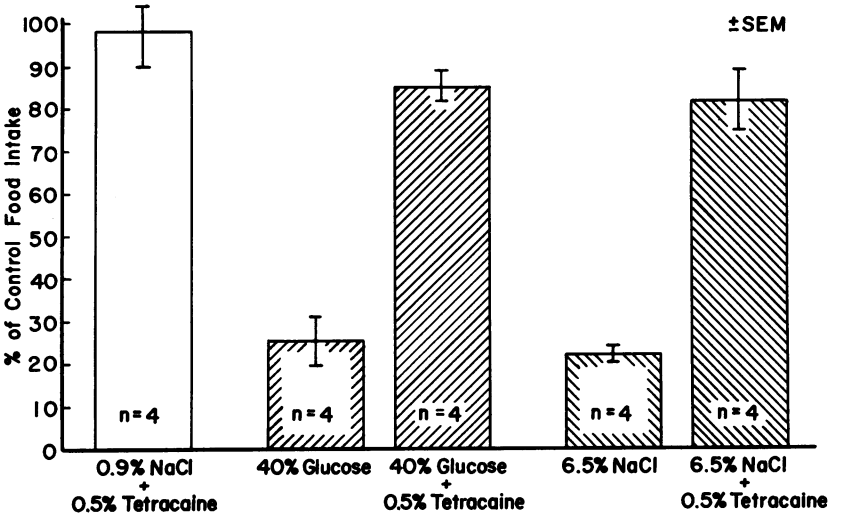

FIG. 7. Effects on 10-minute food intake of inclusion of tetracaine HCl in duodenal preloads. Measurements after 40 percent glucose and 6.5 percent NaCl duodenal loads were paired tests on the same 4 pigs. *n* = number of animals.

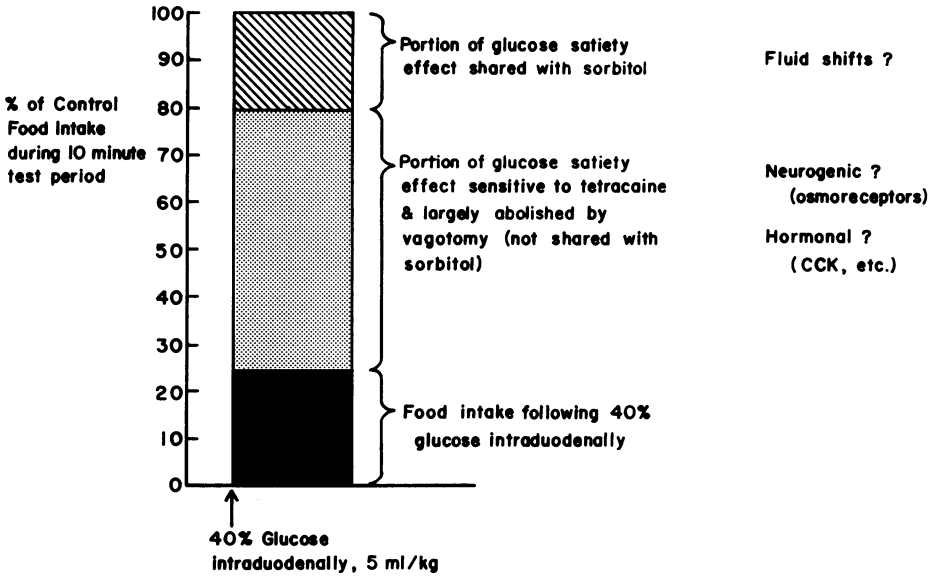

FIG. 8. Partition of satiety effect of intraduodenal glucose. Upper two sections of the column together represent the satiety effect (i.e., food not eaten) after 40 percent glucose intraduodenally. Top section represents satiety effect of 40 percent sorbitol or 40 percent glucose + 0.5 percent tetracaine. After vagotomy, a part of the satiety effect of 40 percent glucose is abolished, and this vagally sensitive portion is equal to about 4/5 of that sensitive to tetracaine (*middle section of column*).

activities involved in searching for, prehending, and ingesting food. Research interest has focused on the hypothalamus because of the clinical reports [67] that trauma or tumors in that area caused abnormalities of body weight and food intake in humans.

In addition to stereotaxic techniques, placement of intracranial electrodes and cannulas must be radiographically confirmed in the pig because of individual variation in skull conformation and because the animals operated upon are usually

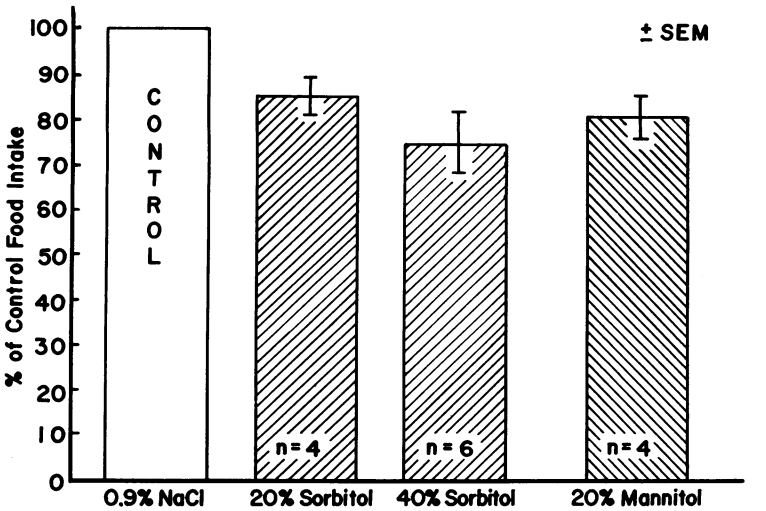

FIG. 9. Food intake during 10-minute test period following control preloads (0.9 percent NaCl = 100 percent) and duodenal preloads of sorbitol or mannitol solutions (5 ml/kg body wt). *n* = number of animals.

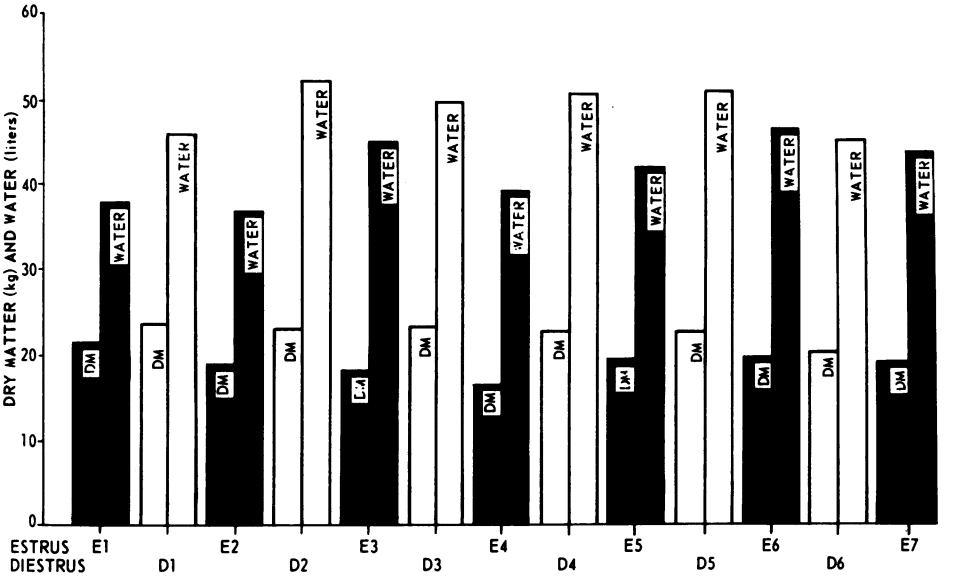

FIG. 10. Variation of food and water intake with the stage of the estrus cycle. Black columns represent intake of gilts (young female pigs) in estrus; open columns represent intake when in diestrus. Reprinted with permission from Friend [65].

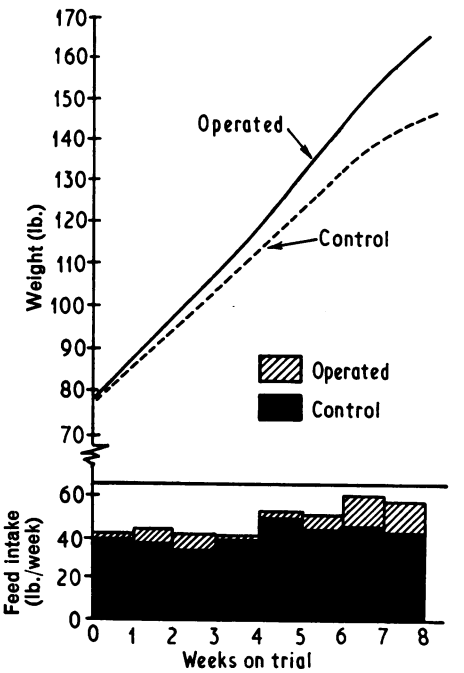

FIG. 11. Weight gain and food intake of pigs with ventromedial hypothalamic lesions. Food intake (*hatched columns*) and body weight (*solid lines*) of lesion pigs; food intake (*black columns*) and body weight (*dashed lines*) of control pigs. Reprinted with permission from Auffray [68].

young growing pigs. Electrolytic lesions of the ventromedial hypothalamus in pigs result in hyperphagia and an increase in body weight [68,69] (Fig. 11). Application of sodium pentobarbital, a central nervous system depressant, results in a resumption of food intake in the satiated pig [70]. Depression of the ventromedial hypothalamus temporarily with an anesthetic or permanently by destroying part of the tissue results in increased food intake. A few cases of human obesity do have as their basis this hypothalamic damage, but a far greater number have different etiologies. These other etiologies may be classified as developmental, genetic, or psychosomatic, but the pathogenesis is unclear. Other areas of the brain must be explored, and the elusive feedback signal from fat depots identified before our knowledge of central nervous system satiety mechanisms is complete.

Lesions in the lateral hypothalamus cause aphagia and adipsia in swine [71], rats, cats, and primates [72]. Infusion of sodium pentobarbital into the lateral hypothalamus of pigs depresses intake; infusion into the ventromedial hypothalamus stimulates intake [70].

These two findings indicate that the lateral hypothalamus is involved in the initiation of ingestive behavior in the pig. Calcium and magnesium ions, when infused into the cerebral ventricles, also stimulate food intake in pigs [73], but shifts in the cerebrospinal concentration of these ions of the magnitude necessary to stimulate feeding are not seen under physiological conditions. The role of ionic shifts in the initiation and termination of normal feeding is uncertain.

Baldwin et al. [73] noted that food intake rose from 61 g/30 min when 0.9 percent KCl was injected to 433 g/30 min when 16 μmoles of sodium pentobarbital was injected. It is assumed that intraventricular injections of a depressant may act by inhibiting a depression of food intake, presumably by way of the ventral hypothalamus. The ventral hypothalamus lies closer to the ventricles than does the lateral hypothalamus, depression of which should lead to an inhibition of food intake. In addition to barbiturates, another type of depressant stimulates food intake in pigs: the benzodiazepine class of minor tranquilizers. Both diazepam [74] and the closely related compound, elfazepam [75], stimulate food intake in pigs. The benzodiazepine tranquilizers serve as useful tools for investigations of the control of food intake. They may also be used to treat anorexia in humans, but their use might be contraindicated in obese or potentially obese patients.

Controls of ingestive behavior in the neonate. Most of the experiments reviewed in the preceding section dealt with controls of food intake in the weanling or young adult pig. Several groups of investigators have studied the ontogeny of taste preferences and gastrointestinal controls of food intake. These studies may be applicable to human infants because the neonatal pig is similar to the human in its brain development [76]. Piglets have been used to develop and evaluate human infant formulas [77,78,79].

Saccharin preferences reported in piglets that had not yet nursed [80], indicate that the preference for sweets is not learned, but is innate. Studies by Houpt and Houpt [48] on one- to three-week-old pigs indicated that pigs have strong preferences for sucrose, lactose, fructose, and glucose (Fig. 12). However, the threshold concentration at which glucose was preferred to water was 10 times that reported for older pigs (0.3M versus 0.03M) [35]. A similar early and, apparently, innate sweet preference also has been shown in human infants [81] and, like young pigs, preadolescent children show preferences at higher concentrations than do adults [82]. An increase in palatability, especially sweetness, of the diet may increase intake in the young child

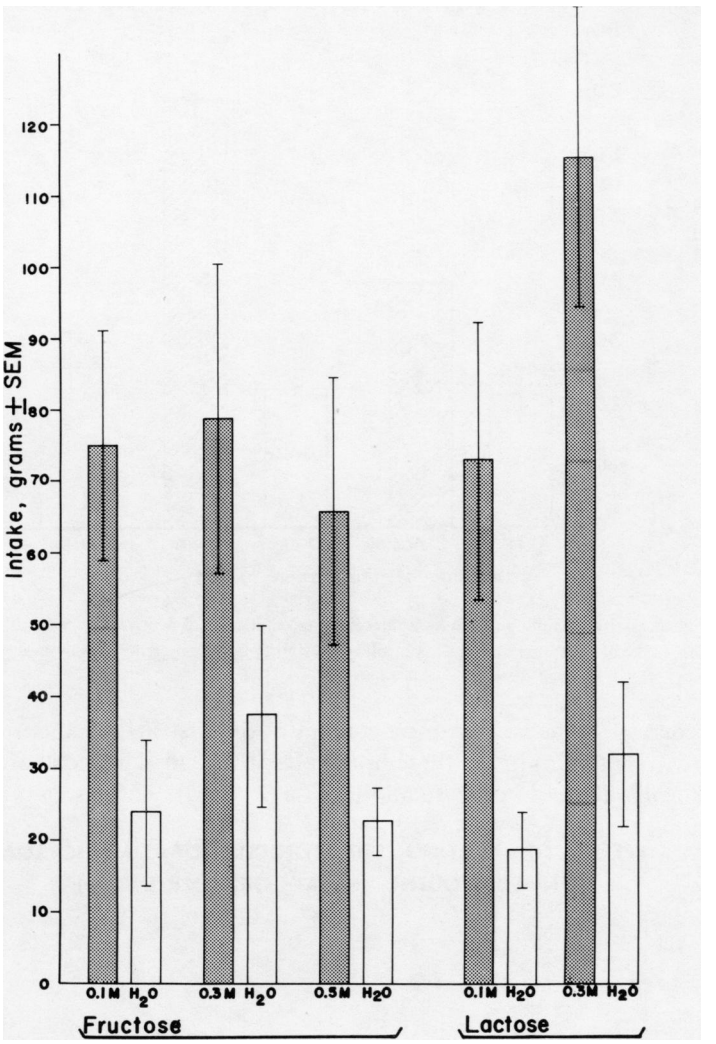

FIG. 12. Intake of water or sugar solutions during a 1-hour, two-bottle preference test. Mean values ± the standard error of the mean are shown. The open columns represent water intake. Shaded columns represent intake of the glucose or sucrose solutions. The molar concentration of the sugar solutions is given beneath each column. Reprinted with permission of Houpt and Houpt [48].

or animal; thus, sugar-coated cereals are prepared for children, and sweeteners are added to the diets of weanling pigs [83].

Neonatal pigs are capable of the most basic of controls of food intake: the adjustment of intake in response to an energy deficit. Piglets fasted for 2–4 hours increase their intake relative to non-fasted controls when given the opportunity (Fig. 13). Gastrointestinal satiety mechanisms also appear to be functional in the suckling pig. Intake was not affected by gastric loads of 0.9 percent NaCl approximately equal to the volume of milk (40 ml) ingested by a three-hour fasted pig [84] although larger volumes equal to stomach capacity do depress intake [85]. Moderate gastric loads of hypertonic solutions of NaCl or of water depress intake (Fig. 14), but isotonic NaCl does not. When caloric loads are given, intake is depressed; however,

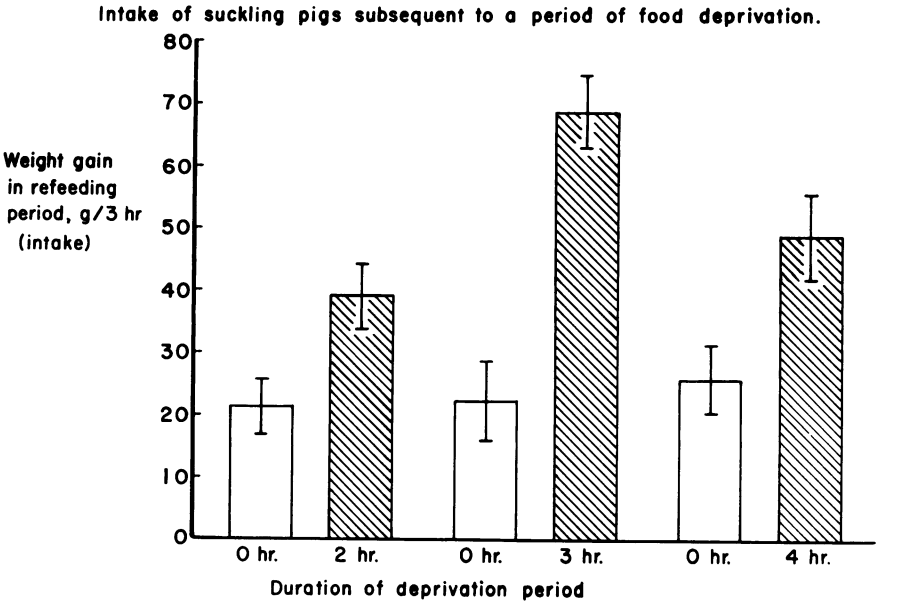

FIG. 13. Milk intake by suckling pigs during a refeeding period after food deprivation of varying duration. Open columns are mean intake of nonfasted littermate controls to previously fasted pigs whose mean intake is represented by hatched columns (± SE). Reprinted with permission of Houpt et al. [84].

there is no correlation between caloric content of the gastric load and food intake (as measured by weight gain) in the three hours after the load. The most effective gastric loads are isotonic loads of glucose and lactose (Fig. 15). These sugars may depress

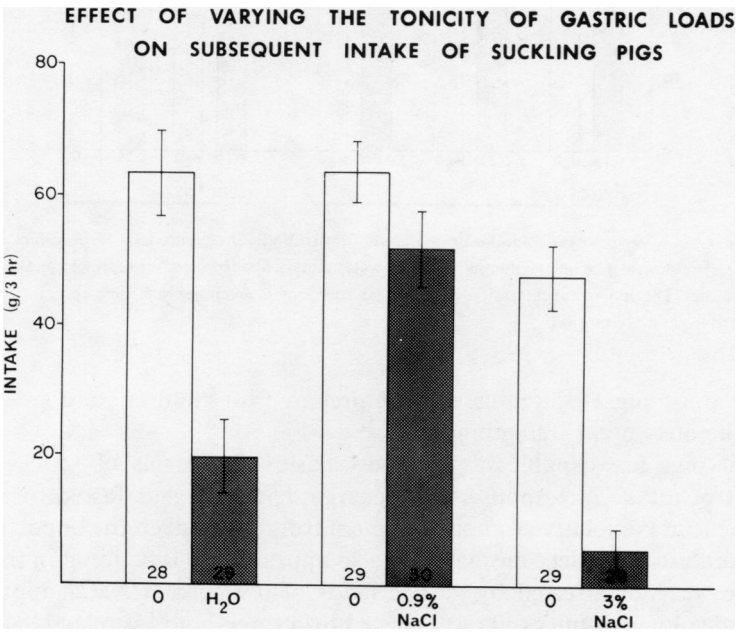

FIG. 14. Milk intake by fasted suckling pigs during a refeeding period immediately after a noncaloric gastric load delivered by stomach tube. Open columns are mean intake of pigs that received no gastric preload and were littermates to preloaded pigs whose mean intake is shown by crosshatched columns (±SE). Numbers within columns are numbers of pigs. Reprinted with permission from Houpt et al. [84].

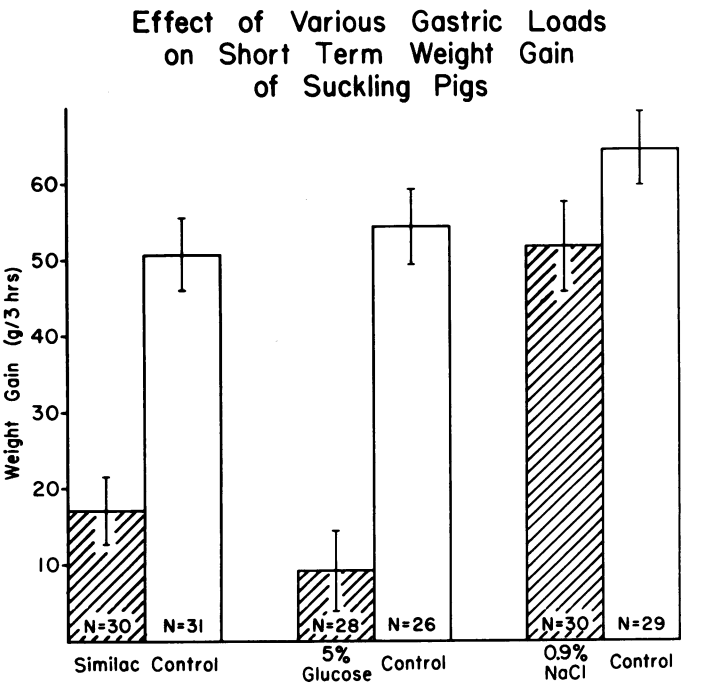

FIG. 15. Milk intake by fasted suckling pigs during a refeeding period immediately after a gastric load delivered by stomach tube. Open columns are mean intake of pigs that received no gastric preload and were littermates to preloaded pigs whose mean intake is shown by hatched columns (±SE). Reprinted with permission from Houpt et al. [84]. *n* = number of pigs.

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intake by stimulating intestinal chemoreceptors, but because the depression occurs over a long (3 hr) period, postabsorptive effects may be involved. The satiety effect of intragastric caloric loads measured indirectly by weighing piglets before and after weaning has been confirmed in piglets taught to nurse from artificial nipples in a situation where intake could be measured directly [85].

Despite the mature response of neonatal pigs to food deprivation and gastric loads, they do not respond to glucoprivation induced by insulin as older animals do. Although plasma glucose falls as in the weanling pig, food intake is not increased in the suckling pig less than one week old [84]. This failure to increase intake in the face of falling plasma glucose and decreased glucose utilization may indicate a lack of development of the diencephalic structures involved in integration of feeding responses. Hypoglycemia is a common abnormality of human neonates especially those of low birth weight [86] and is associated with the failure of the infant to increase its food intake. Hypoglycemia as well as failure to respond with epinephrine release [87] may exacerbate the condition.

OBESITY

Pigs have been used intensively in studies of obesity. In addition to their general physiological similarity to humans, obese pigs are similar to obese humans in that the major contribution to fat mass is the subcutaneous adipose tissue. The mean fat cell size (2 μg fat per cell) and fat cell number (2 to 10 $\times$ 10^{10}) are similar in the two species [88]. One difference between the the species is the layering of subcutaneous fat into

inner, middle, and outer layers in the pig but not in the human; another is that in the pig the primary site of the fatty acid synthesis is the adipose tissue while in the human, it is the liver [89]. Sims [90] reviewed experimental obesity in humans and concluded that "all of the endocrine and metabolic changes studied to date which are noted in spontaneous obesity, including the increased resistance of adipose tissue and of muscle to insulin, may be reproduced in direction if not in magnitude by experimental obesity." He cited his own and other evidence that body heat production varies adaptively in response to over- and under-feeding. This phenomenon has not been studied in the adult pig, although evidence [43] exists for its occurrence in the protein-malnourished baby pig. The research to date on obesity in pigs has been focused on the propensity for fattening during the growing period. Opportunity exists for studies in adult pigs paralleling those in humans cited by Sims [90]. Such adult animal studies could provide valuable information on tissue metabolism and composition not easily obtained from human subjects. This brief review of recent research in lipid metabolism in pigs should provide a basis for parallel studies in humans aimed at understanding and controlling obesity.

Fat Cell Number and Lipid Deposition

Lipogenesis and lipid mobilization in swine are currently receiving intensive study in several laboratories [88,89,91,92,93,94,95]. Gurr et al. [88] suggested that the apparent increase in fat cell number observed in pigs fed a high caloric intake was more likely to result from expansion of "empty" cells than from new cell formation. This suggestion was based on the observation that, because cells with diameters less than about 17 μm are not detected by the methods used, "empty" cells, containing little or no fat, may be present from birth and may be filled subsequently, and thereby become visible when energy intake is appropriate. The concept of a complete complement of adipocytes in the subcutaneous depot fat of pigs at birth is supported by the work of Lee et al. [96,97] who were unable to show an increase in subcutaneous fat cell number above that present at birth in pigs. Mersmann et al. [98] also observed no change in fat cell number per gram of tissue with increasing age. This characteristic appears to be in contrast to that of rat subcutaneous adipose tissue whose cell numbers are significantly responsive to nutritional levels in postnatal life [99]. The work of Lee et al. [96] indicates that early nutritional experience effects permanent changes in the fat cell number of pigs only in specific anatomical locations; although subcutaneous depot fat cell number appears to be constant after birth, the number of intramuscular adipocytes is affected by nutritional level in young, growing pigs. Lee et al. [96] postulated that intramuscular adipocytes may be developed after birth and are under the influence of nutritional manipulation, and change the cell population in intramuscular fat of the adult pigs. Faust et al. [100] have suggested that increases in adipocyte numbers can be induced in fat depots of adult rats. It is not known whether adipocyte proliferation can be induced in adult human beings or in adult pigs. Studies on cellularity of adipose tissue of pigs [98,101,102,103,104] indicate that preadipocytes in subcutaneous back fat (all of which are present around the time of birth) do not develop uniformly as one population, but rather accumulate lipid at different rates. The pig appears to be a good model for the study of the ontogeny of adipose tissue cellularity in humans in relation to adult obesity [104]. Further characterization of these differences and quantitative determinations of important metabolic parameters should be of great value in explaining and controlling human obesity.

Genetic Variation

There is no evidence for homozygous recessive genotypes for obesity in pigs or humans, in contrast to the case in mice and rats [105]. Also, obesity controlled by several gene loci occurs in mice [106,107] and rats [108] but apparently not in pigs or humans.

There are, however, genetic differences in obesity among populations of pigs. For example, a feral population found on the Ossabaw Island of Georgia has an excessive propensity for obesity [109]. The responsiveness of the pig to genetic selection for fattening has resulted in development of lean and obese genetic lines within a breed [110,111,112,113]. The subcutaneous backfat thickness is closely correlated with total body fat so that the application of tools to accurately estimate backfat thickness [114,115] has proved an effective measure of changes in body fat content within selected populations. Several investigators [116,117,118] have determined the rate of fat deposition in early post-natal growth of pigs of various genetic backgrounds. The availability of these diverse types of pigs provides a unique approach to the study of the causes of human obesity.

Voluminous literature is accumulating on metabolic differences between genetically lean versus obese populations of pigs [91,92,112,113,119,120,121,122,123]. Rate of glucose clearance and plasma insulin and growth hormone levels of fasted, genetically lean or obese pigs revealed differences related to genotype [123]. Fasting glucose was similar in lean and obese pigs, but glucose clearance rate was more rapid in lean pigs. Obese pigs were not hyperinsulinemic but had lower plasma growth hormone than lean pigs. Provocative stimulation with glucose or with arginine infusion which showed different responses in the two genotypes, suggested that mild insulin insensitivity and a reduced growth hormone secretory potential may be present in obese pigs during the growing phase of the life cycle. In contrast, observations on swine from a different genetic pool selected for 18 generations for leanness or fatness, showed no difference in metabolic clearance rate or secretion rate of growth hormone at either 15 or 30 weeks of age [122]. The clearance rate of growth hormone per unit mass was greater in younger animals than in older animals of both genetic groups. The role of genetic differences in the human population with respect to these parameters of the endocrine system in relation to obesity is unknown but appears to be worthy of study.

Results in other studies also suggest that genetic differences are important in lipid metabolism of pigs. Lewis and Page [119] found higher concentrations of cholesterol and lipoproteins in the plasma of short, fat miniature pigs than in long, lean pigs and suggested that some of the wide variation in blood lipids in humans is due to genetic factors. More recently [124], plasma cholesterol level in swine has been estimated to have a heritability of 25 percent. Differences between breeds have been detected in cholesterol content of liver and muscle [125] indicating that lipid composition of pork can be affected by genetic means.

Lipogenesis and Lipolysis

Epinephrine-induced as well as pituitary lipotropin-induced release of nonesterified fatty acids from subcutaneous fat pads of pigs selected for thick backfat is less than that of lean pigs [121,122]. Mersmann et al. [126,127] studied factors influencing the lipolytic response in swine adipose tissue and suggested that maximum release of fatty acids and glycerol induced by epinephrine increases fourfold between 12 hours postpartum and day 2, and remains elevated for several weeks before declining.

Activity was maximal at day 25 postpartum when expressed on a tissue or a cell volume basis and at day 80 when expressed on a cell basis; cells from younger animals were more sensitive to epinephrine than cells from older animals [128].

Mersmann et al. have studied lipogenesis in neonatal [129] and growing swine [130]. Growing swine fed equal amounts of isoenergetic-isonitrogenous diets show suppressed fatty acid synthesis from glucose in adipose tissue when dietary fat is increased [95], but there is no effect on adipose tissue enzymes associated with glyceride synthesis. Starvation suppresses activities of enzymes associated with both fatty acid and glyceride synthesis in adipose tissue [95]. Body weight gain is similar regardless of the fat content of the diet [95,127]. Plasma free fatty acids, but not cholesterol, are increased and adipocyte size is increased in pigs fed high-fat compared to low-fat diets at equalized daily energy intake [95,127]. Steffen et al. [95] pointed out that discrepancies between the rat and pig in response to diet may be related to the divergent tissue sites for fatty acid synthesis in the two species. Fatty acid synthesis occurs mainly in adipose tissue in the meal-fed rat but the distribution between the liver and adipose tissue is more nearly equal in the nibbling rat [131]. These species differences in response to diet must be taken into account in selecting a model for studying human obesity.

Clearing-factor lipase, believed to control the extent to which tissues take up plasma triglycerides, has been measured in muscle and adipose tissue of pigs [132]. Activity is higher in the heart than in adipose tissue, and outer subcutaneous fat has greater activity than inner subcutaneous fat and perirenal fat. Starvation for 24 hours causes a rapid decline in activity of the enzyme in adipose tissue, but activity in heart muscle does not decline until 48 hours of starvation. The importance of clearing-factor lipase in regulating fat metabolism in pigs should be studied in more detail to determine its relevance to obesity in humans. Metabolic abnormalities associated with the obese syndrome [103] include the elevation of lipogenic adipose tissue enzymes without a change in activities of liver lipogenic enzymes. Adipose tissue enzymes significantly elevated included glucose-6-P-dehydrogenase, 6-P gluconate dehydrogenase, and malic enzyme. Lipogenesis and enzyme activity in pigs have also been studied in detail by others [91,104,133,134,135,136,137,138,139,140,141]. Rate of adipose tissue lipogenesis appears to be more closely correlated with acetyl CoA carboxylase activity than with any other enzyme measured [130]. Changes in body composition resulting from selection may be associated more with altered age at which lipogenesis ability is manifested than with differences in lipogenic activity [91]. Glycerokinase activity increases rapidly with age in liver, but the increase is more gradual and of 100-fold lower activity in adipose tissue [140].

OTHER COMPARISONS BETWEEN THE PIG AND HUMAN

Davis et al. [142] compared and contrasted the high density lipoproteins (HDL) of porcine and other species and concluded that there is a high degree of compositional and structural similarity between porcine and human HDL. Additional comparative studies are needed to characterize similarities and differences between the pig and the human in normal and abnormal states of fat metabolism. Data recently reviewed [143] from human studies [144] suggest that adipose tissue may be the site for generating signals to control fat storage in adipose tissue, but central and peripheral receptors that recognize the signals must be an important part of the system. Such relationships would lend themselves to study in the pig as a model. The current knowledge of fat metabolism in humans as reviewed by Masoro [145] can serve as a

basis for filling gaps in the network of information needed to more adequately use the pig as a model for human studies. Further characterization of differences and similarities between the two species in important metabolic parameters should be of great value in explaining and controlling human obesity.

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