TOTAL SELF REGULATORY FUNCTIONS IN ANIMALS AND HUMAN BEINGS[1]

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IN 1859 Claude Bernard (1) first described what he called the internal environment of the body, consisting largely of the body fluids, and showed that in mammals the properties of this internal environment ordinarily vary within fixed limits, variation outside of these ranges endangering life. He described many of the physiological mechanisms by means of which the body keeps these properties at fixed levels, and pointed out that it is by virtue of the existence of these mechanisms that mammals are able to live and thrive under widely varying external conditions.

Cannon (2), in a long series of remarkable experiments, collected in 1932 in his book "The Wisdom of the Body," not only confirmed Bernard's concept but greatly extended it. Largely through his efforts this concept has become almost an axiom of modern medicine. Cannon speaks of a constant state or homeostasis. Thus he states: "The constant conditions which are maintained in the body might be termed equilibria. That word, however, has come to have a fairly exact meaning as applied to relatively simple physico-chemical states, in closed systems, where known forces are balanced. The coordinated physiological processes which maintain most of the steady states in the organism are so complex and so peculiar to living beings—involving, as they may, the brain and nerves, the heart, lungs, kidney, and spleen, all working cooperatively—that I have suggested a special designation for these states, homeostasis. The word does not imply something set and immobile, a stagnation. It means a

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[2] This work was carried out with the following collaborators: Doctors Bruno Barelare, John E. Eckert, D. Clarence Hawkes, L. Emmett Holt, Elaine Kinder, Katherine Rice, Edward C. H. Schmidt, Jr., and Mr. John Birmingham, Miss Alice MacLean and Mrs. Kathryn H. (Campbell) Clisby.

condition—a condition which may vary, but which is relatively constant."

Both Bernard and Cannon concerned themselves almost entirely with the physiological and chemical regulators of the internal environment. They showed, for instance, that when an animal is placed in a cold external environment and is consequently threatened with a decrease in body temperature, loss of heat is minimized by decreased activity of the sweat glands and constriction of the peripheral blood vessels, and more heat is produced by increased burning of stored fat and by shivering. These are all physiological or chemical regulators.

The results of our own experiments have shown that behavior or total organism regulators also contribute to the maintenance of a constant internal environment. The existence of such behavior regulators was first established by the results of experiments in which it was found that after elimination of the physiological regulators the animals themselves made an effort to maintain a constant internal environment or homeostasis. I will give you a few examples which are taken mainly from experiments on the endocrine glands. Thus, operative removal of the adrenal glands from animals eliminates their physiological control of sodium metabolism, and as a result large amounts of sodium are excreted as salt in the urine and the internal environment is greatly disturbed (3). If given access only to a stock diet, such animals die in 8–15 days. However, if given access to salt in a container separate from their food they will take adequate amounts to keep themselves alive and free from symptoms of insufficiency. Figure 1 shows a photograph of the cages used for these experiments. Each cage contained a food cup and two graduated inverted bottles. One bottle was filled with tap water, the other with a 3 per cent solution of sodium chloride. The special stock food was made without added sodium chloride. In order to establish base lines, daily records of the intake from each bottle were taken for several weeks before the adrenals were removed. Figure 2 gives two typical records. The first graph gives the water intake and body weight records of a control rat

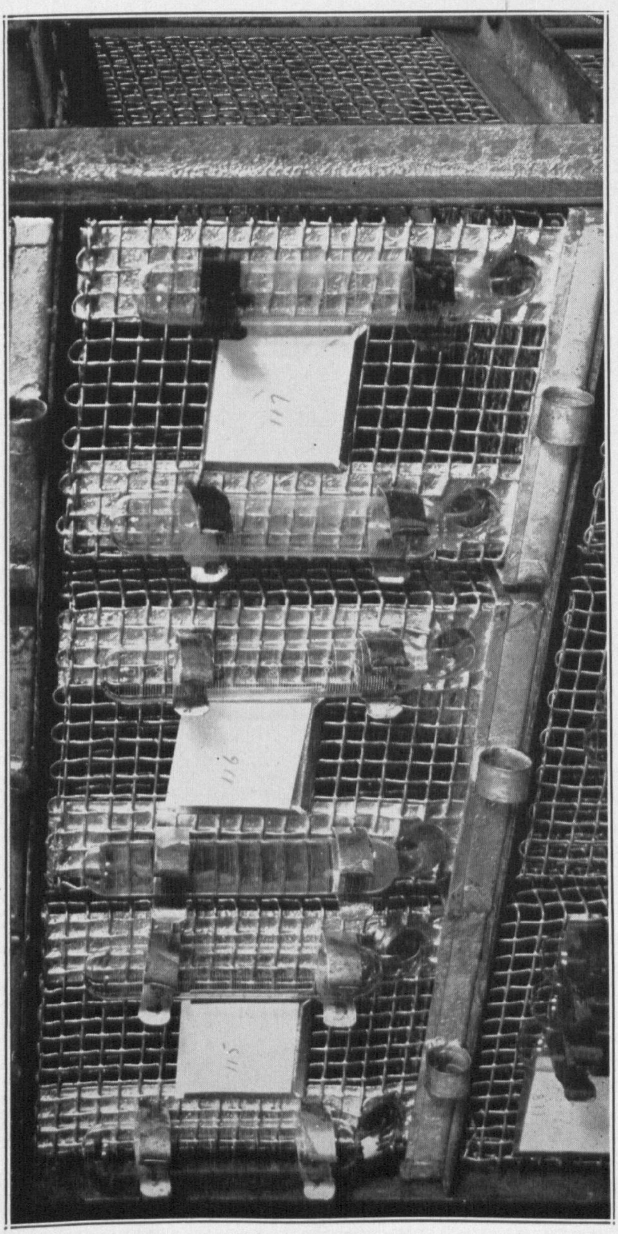

FIG. 1. Three individual cages of the types used for mineral appetite and taste threshold experiments. Each cage is equipped with one food-cup and two inverted graduated 100-cc. bottles.

which had access only to tap water and not to any sodium chloride solution. After adrenalectomy the water intake and body weight dropped sharply and it died in 7 days. The second graph shows the record of one of the experimental animals. Before adrenalectomy the intake of water averaged 22 cc., that of salt solution, 2 cc. Almost at once following adrenalectomy the intake of salt solution increased and after 12 days reached a level near 13 cc. Body weight continued to increase at its normal rate and the rat

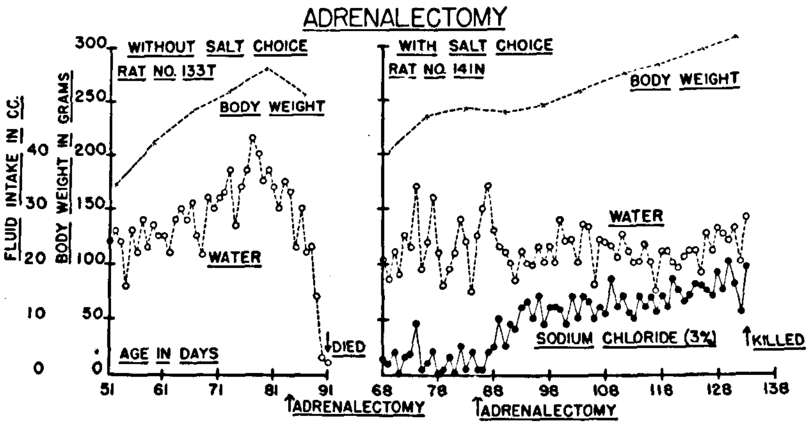

FIG. 2. Increased sodium chloride appetite after adrenalectomy: a. Control rat without access to sodium chloride. b. Experimental rat with choice of water or sodium chloride solution.

was in good health when it was killed 48 days after operation. Similar observations have been made on several hundred adrenalectomized animals. We have found that, when offered a variety of mineral solutions at the same time, the adrenalectomized rats increased their intake of all the sodium salts, and did not show an appetite for other chlorides (4).

We found further that parathyroidectomized rats, which on a regular diet develop tetany and usually die within a few days, will, when given access to a calcium solution, take sufficiently large amounts to keep themselves alive and free from tetany (5). Figure 3 gives a typical record of a rat which had access to two bottles, one filled with tap water and the other with a 2.4 per cent solution of calcium lactate. Almost immediately after parathyroidectomy the rat began to drink more of the calcium lactate solution and less of the water. In 15 days its calcium lactate intake had increased from a preoperative average of 3 cc. to 17 cc. Parathyroid implants made to the anterior chamber of the eye after 45 days reduced the calcium appetite to its normal level

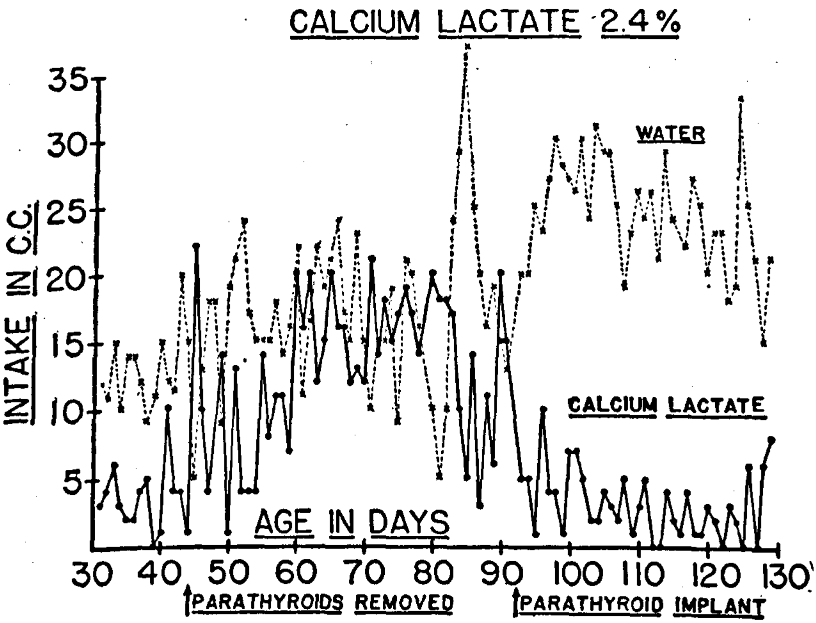

FIG. 3. Increased appetite for calcium lactate following parathyroidectomy and its decrease following successful grafting of parathyroid tissue.

almost at once. It was found further that the parathyroidectomized rats had an increased appetite for other calcium solutions, the acetate, the gluconate, the nitrate, and for the chemically closely related metals strontium and magnesium, but not for other metals. It is noteworthy also that the parathyroidectomized rats manifested a reduced appetite for phosphorus solutions, which is in keeping with the well-known decreased rate of excretion of phosphorus in hypoparathyroidism (6).

In the same way, pancreatectomized rats, which have lost their physiological means of regulating carbohydrate metabolism, ingest large amounts of water, presumably to assist in eliminating the unoxidized glucose. Further, when kept on a regular mixed diet with a high carbohydrate content, they manifest a marked polyphagia, apparently in an effort to obtain needed amounts of substances that can be utilized. They have a high blood sugar and do not gain weight at a normal rate. We have found that when pancreatectomized rats with marked diabetes were offered a carbohydrate, a fat, and a protein in separate containers, in place of the mixed diet, they refused the carbohydrate and ate large amounts of fat and protein (7). As a result they lost their symptoms of diabetes, i.e., their blood sugar fell to its normal level, they gained weight, ate less food, and drank only normal amounts of water.

Similarly, removal of the posterior lobe of the pituitary gland eliminates one of the chief physiological regulators of water metabolism. Without the antidiuretic hormone from this gland animals excrete large amounts of urine and as a result become dehydrated and soon die. When not given access to water some of the experimental rats lost as much as one sixth of their body weight in urine during the first eight hours after the gland was removed. However, when given access to unlimited amounts of water such animals began to drink large amounts soon after the diuresis had become well established (8). They continued to show a high water intake, in some instances taking almost twice the body weight in water per day, and kept themselves not only alive but in good health. We must regard the great thirst of animals with diabetes insipidus not as a primary symptom produced by an injury to a so-called thirst center in the brain stem, but as a secondary symptom, an effort made by the total organism to compensate for the abnormal fluid loss (9, 10).

One more example should suffice for the present purpose. It is taken from the field of body temperature regulation and is concerned with the rat's effort to maintain a constant body temperature after the physiological heat regulating mechanisms have been seriously disturbed (11, 12). The individual cages used for these experiments were each equipped with a roll of soft paper ½ inch wide and 500 feet long, with the free end readily accessible to the rat within the cage. Figure 4 shows a cross-sectional view of one of these cages. By means of a cyclometer and a scale to compensate for the progressively decreasing diameter of the roll, the amount of paper used each day was measured, and interpreted as an effort made by the rat to conserve heat by covering itself.

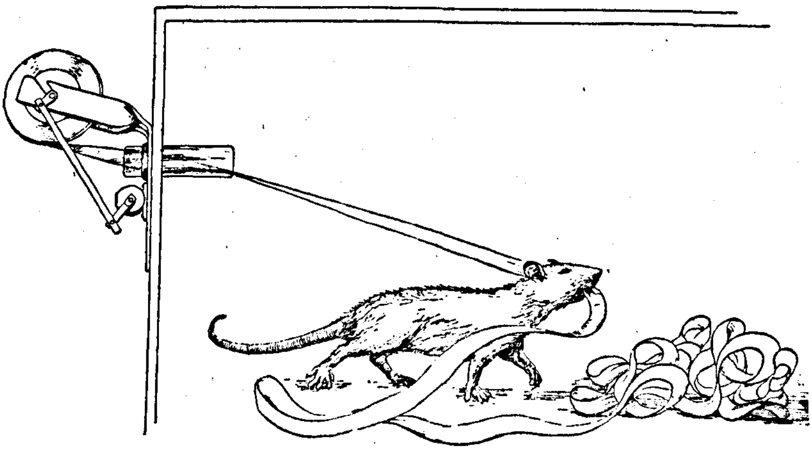

FIG. 4. Side view of nest building cage, showing paper roll and cyclometer.

All used paper was removed each day at noon. It was found that normal male and female rats used approximately equal amounts of paper to build nests which varied in size with changing external temperatures, for example, a drop in room temperature from 80 to 45 degrees increased the amount of paper used daily from 500 to 6000 centimeters. With this method we were also able to show that hypophysectomized rats built much larger nests than normal animals, as a result of their inability to produce adequate amounts of heat, which consequently threatened them with a fatal reduction in body temperature. Figure 5 shows the effect produced on nest building activity of a rat by hypophysectomy. The length of paper used daily increased from 700 to 3500 centimeters. When nest building paper was no longer made available, the rat died after 35 days, with a body temperature more than 15 degrees below normal. Thyroidectomized rats, which likewise have lost their ability to produce adequate amounts of heat, also built very large nests in an effort to cover themselves and thus to conserve heat. Both thyroidectomized and normal rats treated

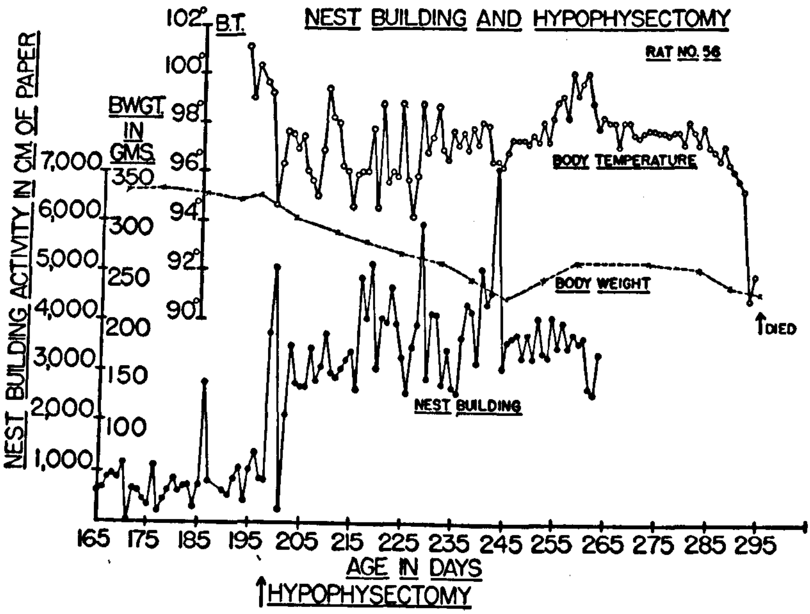

FIG. 5. Increased nest building activity after hypophysectomy, and fall in body temperature with consequent death, after removing nesting paper.

with large amounts of thyroid extract stopped building nests altogether. Some of the hypophysectomized and thyroidectomized rats used the entire roll of 15,000 centimeters (500 feet) of paper in 24 hours. Thus we have another instance in which, after removal of the physiological regulators, homeostasis was maintained by a total organism response.

On the basis of the results of these different experiments, it would seem very likely that in the normal, intact animal the maintenance of a constant internal environment depends not only on the physiological or chemical regulators, but also on the behavior or total organism regulators. We do not yet know, however, the relative parts played by each: whether, for instance, the physiological responses take care of most of the regulation, or whether they function only when the behavior mechanisms have failed or broken down, or whether both are constantly and simultaneously in action. We may discuss as an example the regulation of sodium metabolism. When an animal lives in a region in which the available food does not contain an adequate amount of salt, it may either seek salt by migrating to a salt lick, or its adrenal cortex may become more active and as a consequence less salt will be lost in the urine. On the other hand, an animal may be forced to take a high amount of salt in its food: in this case it may either decrease its food intake, or increase the excretion of salt by drinking large amounts of water, or its adrenal cortex may become less active and as a consequence more salt will be lost in the urine. I will return later to the problem of the relation of these processes.

The question of the basis of these self regulatory abilities has undoubtedly already come to your minds. Does experience determine the dietary choice? Do rats eat certain substances because the ingestion of these substances makes them feel better, and avoid others because their ingestion produces discomfort or pain? Or does the taste of the substance determine the choice? In other words does appetite serve as a guide to the selection of a beneficial diet? It is not possible to give definite answers to these questions at the present time. Certainly the selections may depend on both factors. The evidence at hand, however, indicates that taste plays a very important part. In the first place, section of the taste nerves (glossopharyngeal, chorda tympani and lingual) apparently abolishes the ability of rats to make beneficial dietary selections. In one series of experiments it was found that after combined section of all three pairs of nerves, thus eliminating taste sensation from the entire surface of the tongue, adrenalectomized rats no longer increased their salt intake and as a consequence died just as they would have done had they not had access to any salt at all (13).

Further evidence for the significance of taste sensation in making dietary choices comes from experiments on the taste thresholds of rats. In order to determine the concentration at

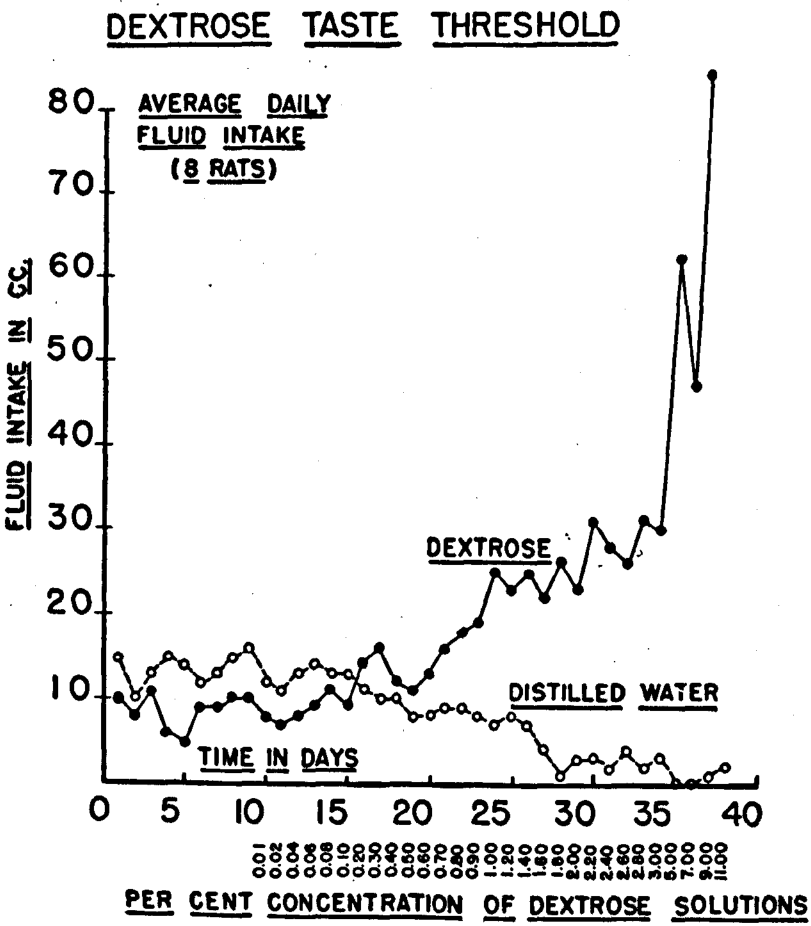

FIG. 6. Curves showing average dextrose taste threshold for 10 rats.

which rats could first distinguish between water and a given solution we again used the small cages containing a food cup and two graduated inverted bottles shown in Figure 1. Base lines were obtained with both bottles filled with distilled water. After 8–16 days, when the intake from each bottle had become relatively constant, one bottle was filled with a solution of subliminal concentration of the substance to be examined, and each day thereafter the concentration was increased in small steps. Such determinations have now been made with various substances (14, 15, 16). Figure 6 gives the average dextrose intake curve for 8 rats under these conditions. Over a period of 29 days the concentration of the dextrose solutions was increased from 0.01 to 11.0 per cent. It will be noted that the rats first indicated a definite preference for the dextrose solution when the concentration reached 0.2 per cent. With increasing concentrations up to 11 per cent the preference constantly became more marked. All of the other substances tested so far, such as sucrose, maltose, sodium chloride, potassium chloride, calcium lactate, etc., which gave this same type of record, are known to have nutritional value. Since the amounts of the substances obtained by the rats at the threshold concentrations were certainly not sufficient to have any physiological value, the preference must have depended entirely on taste.

With poisons, or any harmful substances, the type of curve is quite different (17). In such cases the first indication the rats gave of the recognition of the substance was a preference for water over the solution. This may be seen in Figure 7 which gives a typical record of a rat which received increasing concentrations of mercuric chloride. This rat suddenly decreased its intake from the mercuric chloride bottle when the concentration reached 0.003 per cent, or 3 parts in 100,000 parts of water. At this level the total amount of the drug ingested was too small to have any detectable physiological effect.

Using the same technique, we have found that adrenalectomized rats, which have a greatly increased need for salt, have a much lower salt taste threshold than normal rats (18). For 12 normal rats the average taste threshold was 0.055 per cent, and for 4 adrenalectomized rats it was 0.0037 per cent, about 15 times lower. Here again the minute amount of salt obtained from the solutions for which the adrenalectomized rats first manifested a preference for salt solution over water could not have had a physiological effect.

At present, then, the processes involved in the selective activity of the rat can be formulated as follows, using the salt appetite of adrenalectomized rats as an example. In such animals there is a sodium deficiency in all the tissues of the body, including the

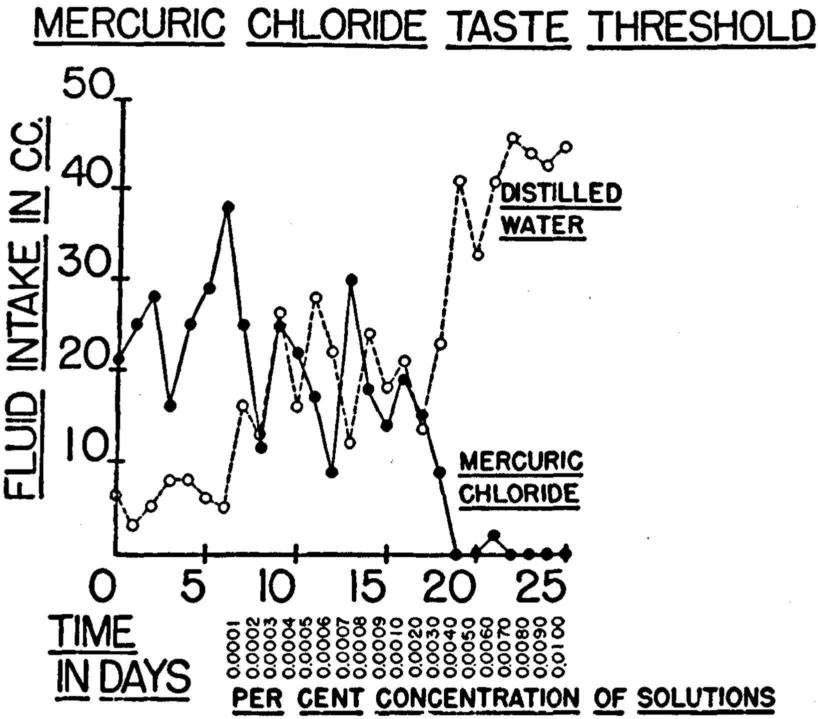

FIG. 7. Typical individual curves showing mercuric chloride taste threshold.

taste buds of the tongue; consequently a salt solution of a given concentration brought into contact with the taste buds in such an animal would encounter a different situation from that found in the normal rat, with the higher salt content. In particular, the sodium ion would be expected to diffuse through the membrane more readily and thus stimulate the taste buds at a lower concentration. More detailed studies are necessary before the mechanism of taste recognition can be more fully understood: osmotic pressure relationships must be investigated, as well as the rôle of the amount and composition of the saliva, and more knowledge is required of both taste bud and central nervous system processes.

I would like now to point out that knowledge of the behavior regulators offers us a new method of attacking a great many different problems, especially those concerned with the relationships between the endocrine glands and nutrition. Thus we can often determine the function of a gland by observing the adjustment that the animal makes to its removal. Had this method been available we could have determined the sodium regulatory function of the adrenal glands many years ago, long before the advent of modern biochemical methods, in particular the excellent studies of Loeb and others (19, 20). It would only have been necessary to give some adrenalectomized rats access to a variety of mineral solutions, and by their selections they would have indicated at

TABLE I

A	B
1. Sucrose	1. Dextrose
2. Casein (vitamin-free)	2. Casein (vitamin-free)
3. Olive oil	3. Olive oil
4. Sodium chloride—3%	4. Sodium chloride—3%
5. Potassium chloride—1%	5. Potassium chloride—1%
6. Calcium lactate—2.4%	6. Calcium lactate—2%
7. Dibasic sodium phosphate—8%	7. Dibasic sodium phosphate—4%
8. Cod liver oil	8. Magnesium chloride—0.5%
9. Wheat germ oil	9. Cod liver oil
10. Baker's yeast (dried)	10. Thiamine hydrochloride—0.02%
11. Water (tap)	11. Riboflavin—0.00125%
	12. Nicotinamide—0.01%
	13. Calcium pantothenate—0.01%
	14. Choline chloride—0.3%
	15. Pyridoxine hydrochloride—0.02%
	16. Biotin—0.05% (= 5γ/cc.)
	17. Water (tap)

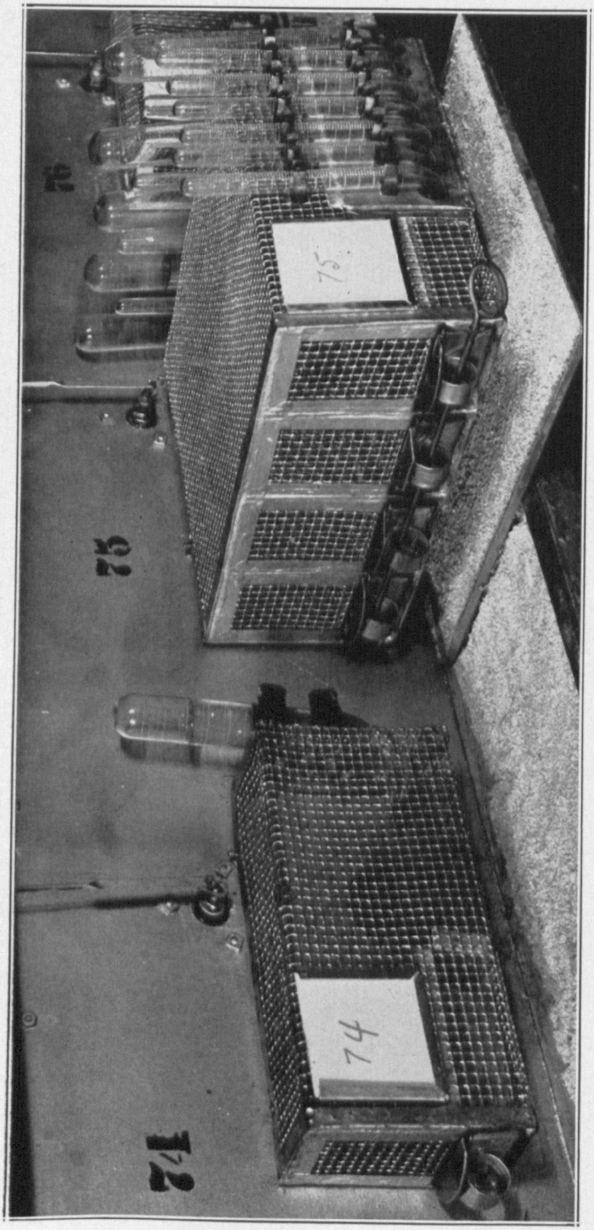

FIG. 8. Cages used for single food choice and self selection experiments showing graduated inverted bottles for fluids and food-cups for solids.

once that removal of the adrenals produces primarily a change in sodium metabolism. In the same way we might have determined the calcium regulatory function of the parathyroids long before the biochemical studies of MacCallum (21) and others.

I will give you a few illustrations of the different uses which have been made of this method. We have applied this technique

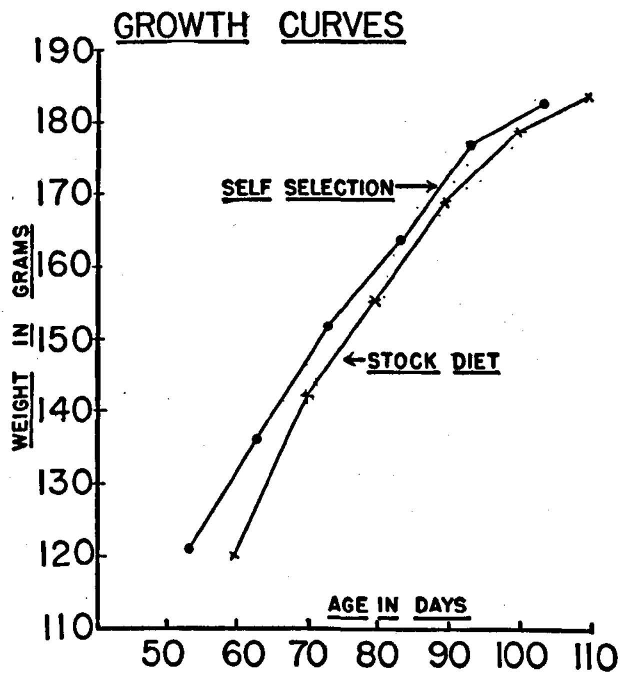

Fig. 9. Average growth curves for 8 rats on self selection diet and 19 rats on stock diet.

to the determination of the normal dietary requirements of the rat (22). For this purpose the rats were given access to an assortment of 11 substances, one source of each of the substances known to play an important part in nutrition, as listed in Table I, A. Large cages of the type shown in the photograph in Figure 8 (cage 75) were used in these experiments. The cages contained several food cups for solids and from 8–20 graduated inverted water bottles with capacities of either 30 or 100 cc. for fluids.

On the selections made from these substances the rats grew at a normal rate, were normally active, reproduced, and showed no signs of deficiency, actually thriving for as long as 500 days, at which time the experiment was discontinued. Figure 9 gives the average growth curves for 8 rats on the stock diet[3] and for 19 rats on this self selection diet. That the rats actually made very efficient choices from this assortment is shown by the fact that, although they grew at the same rate, their total food intake as measured in grams was 36 per cent less than that of the control rats kept on our stock diet. The difference in total caloric intake was less great, 46 and 56 calories on the self selection and stock diets respectively, by virtue of the higher fat content of the self selection diet. In terms of the total caloric intake the self selection diet consisted of 64 per cent fat, 16 per cent protein, and 20 per cent carbohydrate.[4]

In later experiments, the yeast was omitted from the list of substances offered for choice, and replaced by the various components of the vitamin B complex, singly and in different combinations, thus offering a means of determining metabolic interrelationships between these and other constituents of the diet. (See Table I, B.) When given access to all of the substances, without either yeast or any of the members of the vitamin B complex, the rats took high amounts of fat, little or no carbohydrate, and no protein (23, 24). They thus indicated that without any vitamin B they could use fat, but not carbohydrate or protein. When given access to thiamine hydrochloride as the only member of the vitamin B complex the rats reversed their fat and carbohydrate appetites, taking more carbohydrate and less fat, but still no protein. The appetite for fat was greatest in the group receiving riboflavin as the only representative of the B complex. This

[3] The stock diet used contained graham flour 725, skim milk powder (Breadlac) 100, casein (No. 30, Labco) 100, calcium carbonate 15, sodium chloride 10, and butter 50.

[4] Small amounts of magnesium and trace elements such as iron, copper, iodine, were undoubtedly contained in the tap water, casein, and yeast.

observation is in agreement with the work of Mannering, Lipton, and Elvehjem, who demonstrated that the growth of young rats on a riboflavin low ration was increasingly stunted as the fat content of the ration was increased, and that the deleterious effect of the high fat rations was entirely overcome by the addition of riboflavin to the diet (25). Progressively as each member of the vitamin B complex was added in our experiments, riboflavin, nicotinamide, pyridoxine, calcium pantothenate, biotin and choline chloride, in addition to the thiamine (Table I, B, gives the full list of all the substances offered for choice), the rats took more carbohydrate and protein and less fat; also, the number of rats which made successful choices increased, as was evidenced by more nearly normal growth curves, more regular oestrous cycles, and more normal endocrine weights. Almost without exception, however, the success of the selections depended on whether the rats showed an active appetite for protein: unless they ate protein freely they did not thrive. By controlling the individual components of the vitamin B complex offered for choice we could almost at will make an animal eat large amounts of fat or little or no fat, similarly we could influence the appetite for carbohydrate and protein. From such experiments we have learned that rats are able to make beneficial selections from purified foods quite as well as from natural foods. Further, since all of the substances are offered in purified form, it becomes possible with only one or two exceptions, by removing any one bottle or food cup to eliminate all of any one substance from the diet. For instance, removal of one bottle eliminates all thiamine chloride from the diet, or the removal of one food cup all carbohydrate.

We have used this method also to study the nutritional needs of the rat during pregnancy and lactation (26). The rats were given access to the 11 substances listed in Table I, A, with yeast as the source of the vitamin B complex. The daily intake of each substance was recorded for several weeks before mating, during pregnancy, for 25 days of lactation, and for several weeks after the litters were weaned. A special cage was devised to prevent the young from eating and drinking from the mother's food cups and bottles. The rats showed quite definite and consistent changes in appetite for each of the different substances offered, especially during the lactation period. Figure 10 gives the average daily intake of the four mineral solutions in 5-day periods for 20 days before mating, 20 days of pregnancy, 25 days of lactation, and 10 days after the litters were weaned. Figure 10, A, shows

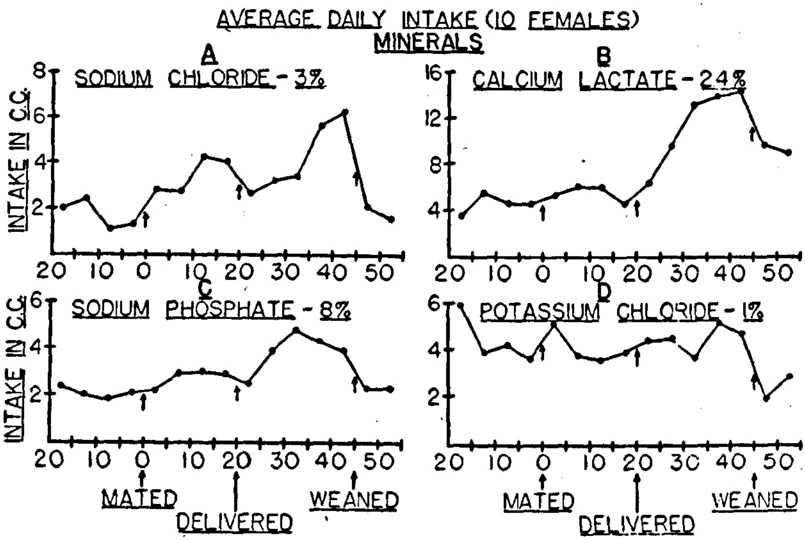

Fig. 10. Average daily intake curves for 10 rats showing changes in mineral appetite during pregnancy and lactation.

that the ingestion of sodium chloride increased during the first five days of pregnancy to a definitely higher level, and increased still more during the second half of the lactation period, dropping to its original level almost at once after weaning. The sharp increase in salt appetite during the first 3–5 days of pregnancy was one of the most constant of all the changes in appetite. Figure 10, B, shows that the calcium lactate intake increased slightly during pregnancy, but very markedly during lactation, at the height of which it reached peaks which were 30–40 times as high as the average daily intake present before mating. After the litters were weaned the calcium intake did not decrease at once to its original level but only after several weeks. Figure 10, C, shows that the sodium phosphate appetite increased slightly during pregnancy and very definitely during lactation, dropping to normal at once after the litters were weaned. Figure 10, D, shows that no changes in potassium chloride intake occurred during pregnancy and lactation. However the intake decreased sharply after the litters were weaned.

Figure 11 summarizes the observations made on the changes in appetite for fat (olive oil), protein (casein), and carbohydrate (sucrose). The fat intake showed a small but definite increase during pregnancy and a very large increase during lactation. It

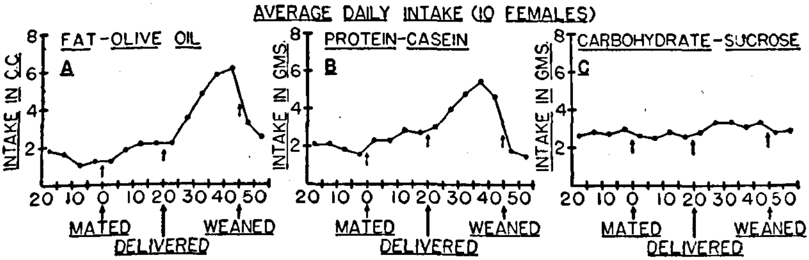

FIG. 11. Average daily intake curves for 10 rats showing changes in fat, protein, and carbohydrate appetites during pregnancy and lactation.

decreased fairly rapidly after the litters were weaned. The protein intake gave much the same record. In marked contrast the intake of carbohydrate remained essentially unchanged throughout all of the periods. That the rats made very efficient selections is shown by the records in Figure 12, which gives the average daily food intake in grams, in 5-day intervals, for 10 rats on the self selection diet and for 10 rats on the stock diet, both groups of mothers nursing the same number of babies. In spite of the fact that the babies produced on the self selection diet weighed as much as those of stock rats and were apparently in as good health, the food intake, measured in grams, was about 20 per cent lower during pregnancy and almost 50 per cent lower at the height of lactation. The smaller intake of the self selection rats must be explained by the fact that they could satisfy their increased appetite for minerals without ingesting a large amount of other, unneeded, foodstuffs. On the stock diet, for instance, the rats that wanted a high amount of calcium had to take a large amount of the entire diet along with the calcium.

Thus, in these self selection experiments the pregnant and lactating rats have indicated with their appetites that they need increased amounts of fat and protein, as well as of sodium, calcium, phosphorus, and possibly potassium. These results are closely in agreement with knowledge derived from biochemical

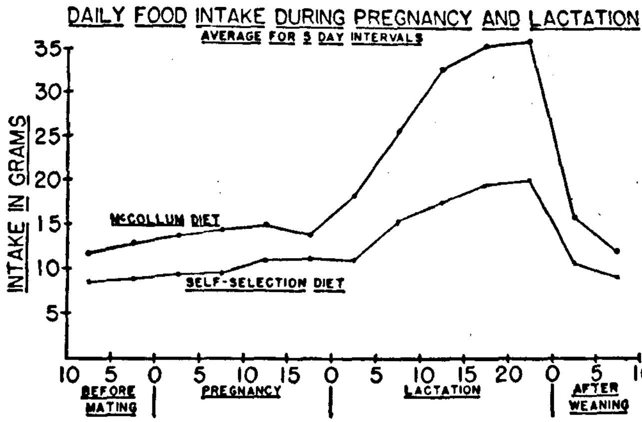

FIG. 12. Average daily intake in grams for 10 rats on the self selection diet and for 10 rats on our stock diet (modified McCollum diet).

studies regarding the needs present during these conditions, except for the sharp increase in salt appetite which occurs during the first few days of pregnancy. With this method we may determine not only the substances that are needed by the animals under special conditions, but also the relative amounts of each.

These and similar experiments have brought out one of the most important self selection principles, namely the inverse relationship between the appetite for carbohydrate and fat. Invariably, when a rat eats high amounts of fat it eats little or no carbohydrate, and the reverse is also true. One example will suffice for the present purpose. Figure 13 shows the olive oil, sucrose, and casein intake curves of a rat placed on the self selection diet listed in Table I, A, but without yeast and wheat germ oil, that is, entirely lacking in all vitamin B. For the first 11 days large amounts of sucrose were taken and only a small amount of olive oil. Then, when the vitamin B deficiency began to manifest itself, the intake of sucrose decreased and that of olive oil in-

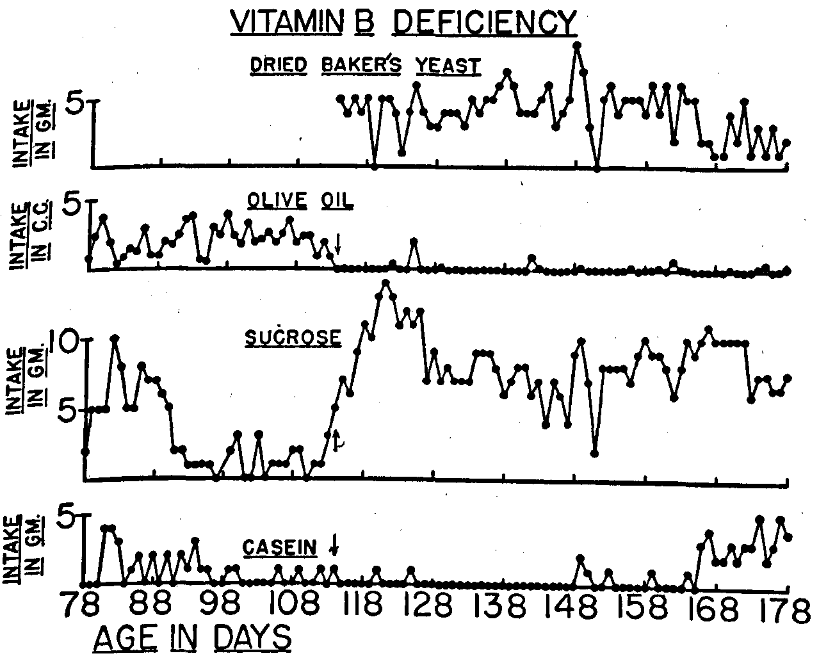

FIG. 13. Typical individual record showing inverse relationship between carbohydrate and fat appetites, and their dependence on the vitamin B complex content of the diet.

creased. After 2 weeks the rat showed almost no appetite at all for the sucrose. Thirty-six days after the start of the diet dried baker's yeast was offered; large amounts were eaten at once, with the result that the animal immediately manifested a great appetite for sucrose and stopped taking olive oil. It may be noted incidentally to the present purposes that progressively as the vitamin B deficiency developed the rat took less casein and after several weeks refused it almost entirely. After yeast was made available its appetite for casein did not return for over 45 days. Presumably in the meantime the protein obtained from the large amounts of yeast ingested satisfied the animal's requirements for this foodstuff.

Another self selection principle brought out by these experiments is that rats will make every effort to maintain their daily caloric intake at a fixed level. Thus, when rats are kept on the stock diet and are forced to take additional fat by stomach tube, or additional sugar or alcohol in their drinking water, they will reduce their intake of the stock diet almost exactly by the equivalent caloric value received from the additional substances. For instance, three groups of rats which could satisfy their thirst only from 8, 16, and 24 per cent solutions of alcohol respectively, reduced their food intake directly in proportion to the caloric value of the ingested alcohol, so that the total caloric intake still remained the same as when the rats received the stock diet (27). In some of the rats on the 24 per cent solution of alcohol, the daily intake of alcohol averaged from 45 to 50 per cent of the total caloric intake. In spite of their high intake of alcohol and the consequent great reduction in the intake of vitamins and minerals, the rats were in excellent shape when they were killed and autopsied after nine months on the experimental diets.

We have also used the self selection technique for a further study of the functions of the adrenal gland. In one series we offered rats access to a 40 per cent solution of dextrose, and a 3 per cent solution of sodium chloride, in addition to a salt-poor stock diet and tap water (28). As shown in the typical record in Figure 14, after adrenalectomy the rats started at once to drink more of the salt solution and less of the sugar solution; however, their food and water intake remained essentially unchanged. Thus these rats indicated that they needed, or could use, the salt but not the carbohydrate. Parenteral administration of percorten (desoxycorticosterone) quickly reduced the salt appetite to its normal level, and increased the dextrose intake very markedly.

In another series of experiments we studied the changes in appetite for dextrose of normal rats produced by daily injections of protamine zinc insulin (29). In these experiments the rats had access to the stock diet, a 40 per cent solution of dextrose, and tap water. The initial dosage of 2 units was increased by increments of 0.4 unit each day either until the rats died or a level of 16 units was reached. As shown in a typical record in Figure 15

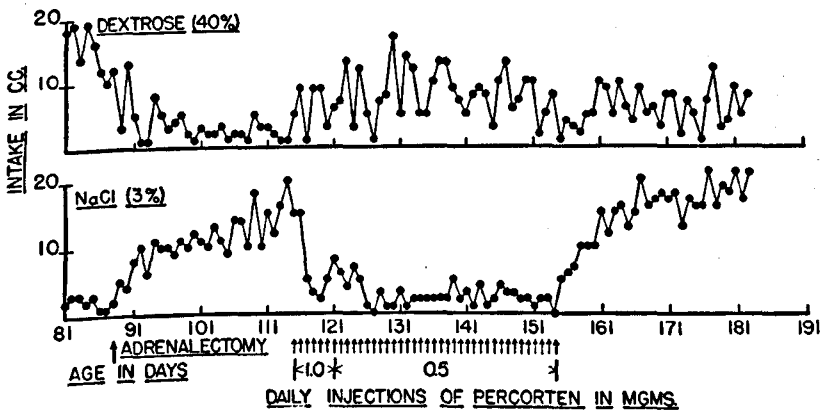

FIG. 14. Typical individual record demonstrating effects of adrenalectomy and of subsequent percorten injections on the daily intake of dextrose and sodium chloride.

the dextrose intake increased steadily, more than doubling during treatment, while the intake of the stock diet increased only very slightly, thus indicating that the increased appetite of insulin treated rats is specifically directed toward carbohydrate. Of special interest was the precipitous drop in dextrose appetite which occurred immediately after cessation of the insulin injections. For about a week the rats scarcely touched the dextrose solution. Thereafter the dextrose intake increased again, first reaching the pre-experimental level, and finally surpassing it. The maintenance of the abnormally high level must indicate changes of some sort in the carbohydrate-insulin balance, the nature of which we cannot explain at the present time.

Preliminary results of some of our experiments indicate that the appetite method may also be used to bioassay various biological preparations. For example, it was found that substances which influence calcium metabolism all affect the calcium lactate intake of parathyroidectomized rats (30). For such an experiment the substances to be tested were incorporated in the food, which was a modification of our usual stock diet made without the

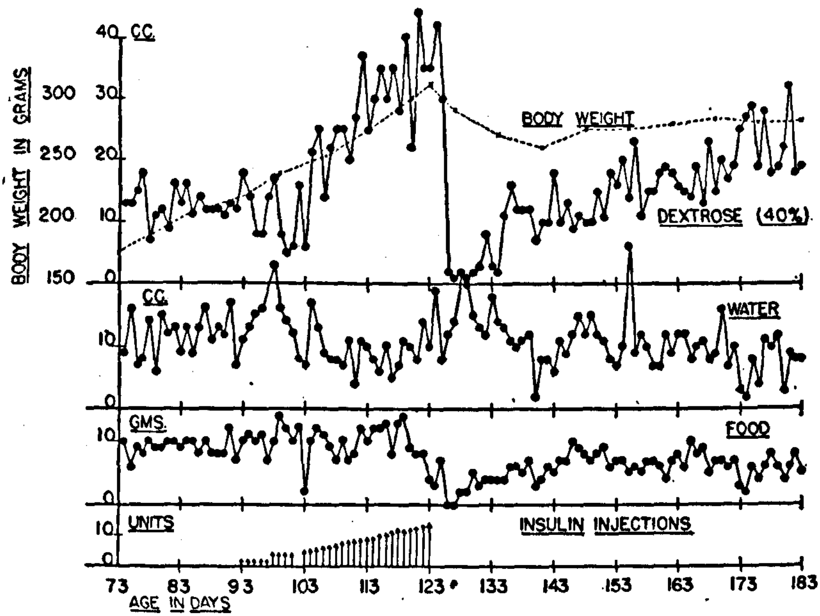

Fig. 15. Typical individual record of the daily dextrose, food, and water intake of a normal rat treated with increasing doses of insulin.

skim milk powder and calcium carbonate. It was found that the presence of even very small amounts of the various vitamin D preparations or of dihydrotachysterol (A.T. 10) placed in the food could be detected by an immediate decrease in the intake of the calcium solution. For assay studies the amounts of the test substances mixed with the food were increased or decreased until the calcium lactate intake returned to its normal preoperative level. Figure 16 shows an assay record for A.T. 10. In this ani-

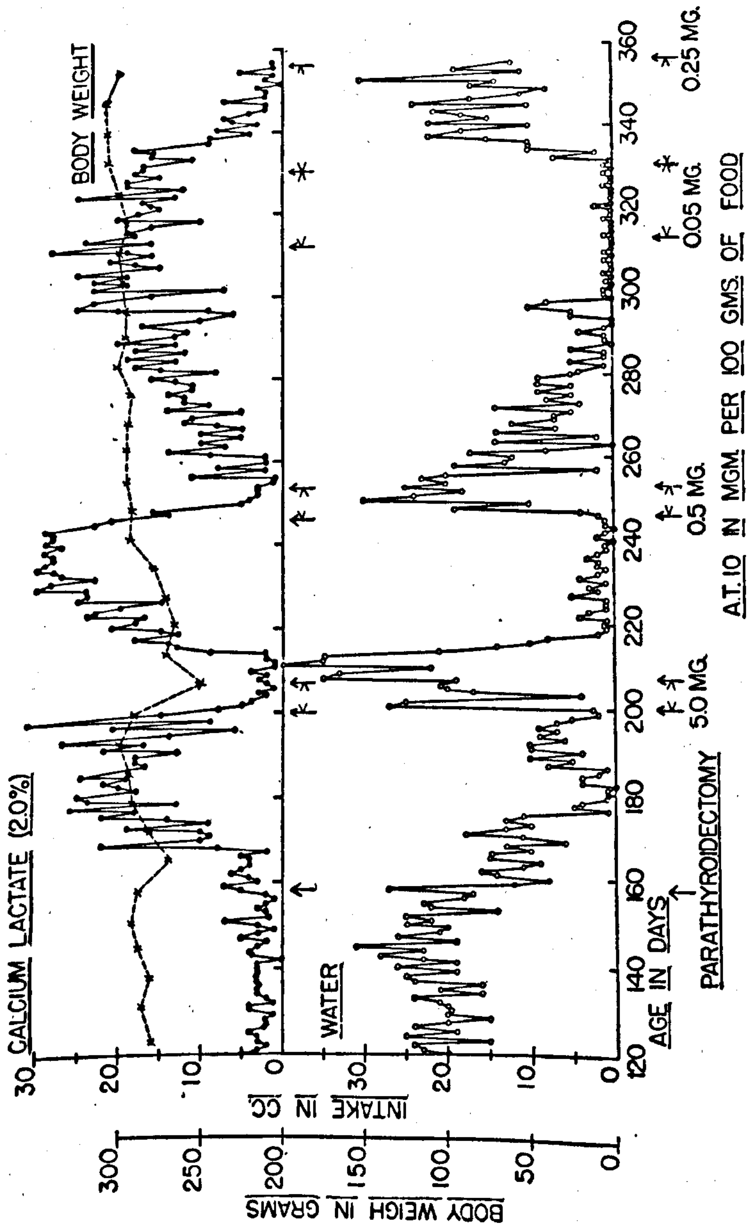

FIG. 16. Typical individual record showing the effects produced on increased calcium lactate appetite by varying doses of dihydrotachysterol (A.T. 10) added to the food.

mal parathyroidectomy had increased the intake of 2 per cent calcium lactate from 3 cc. to a fairly constant level near 16 cc. Forty days after parathyroidectomy the drug was first added to the diet at the rate of 5 mgm. per 100 grams of food. As can be seen this amount had an immediate effect on the calcium intake, but was toxic, as indicated by the prompt weight drop. In successive periods, 0.5 and 0.05 mgm. per 100 grams of food were tried, allowing intervening time for recovery; the larger dose had a marked effect while the smaller dose had none at all. Finally, a dose of 0.25 mgm. per 100 grams of food was tried and was found to bring the calcium lactate intake gradually down to its preoperative level. Thus the minimum effective dose of A.T. 10 for a parathyroidectomized rat must lie between 0.05 and 0.25 mgm. per 100 grams of food, or between 5 and 25 micrograms per day when measured in terms of actual intake. Using the same technique we have assayed vitamins D_2 and D_3, as well as irradiated ergosterol and irradiated cholesterol. It was further found that parathormone, which is known to act primarily on phosphorus metabolism, had only a slight effect on the calcium lactate intake of parathyroidectomized rats, even when given in toxic amounts.

Some of the most fruitful applications of the study of the rat's appetites have been made in so-called single food choice experiments, in which the rats have access to only one purified food, a fat, carbohydrate or protein, or to a single whole food such as corn, graham flour, peanuts, etc., either alone or with access also to one or more of the different vitamins, enzymes or minerals (31). Figure 8 (cage 74) shows one of the small cages used for these experiments. Each cage contains a food cup and either one or two graduated inverted bottles. Under the conditions of such an experiment specific dietary interrelationships can often be more clearly brought out than when mixtures of foodstuffs are fed. I will give you only a few examples. It was found in confirmation of some preliminary observations made by Holt and Kajdi (32) that, while young adult rats kept on no food at all, but with free access to water, survived only 4–6 days, when kept exclusively on dextrose and water they survived 36 days, and when given access also to a 0.02 per cent solution of thiamine hydrochloride they lived more than twice as long, 76 days (33). Thus, under the simplest conditions, these experiments showed the marked effect which thiamine hydrochloride has on the metabolism of dextrose. Of special interest from the point of view of the possible use of these data in planning emergency rations, was the extreme activity for more than 20 days of the rats on dextrose alone, some animals running as much as 15 miles on the 25th day, while on dextrose and thiamine hydrochloride a high level of activity persisted as long as 60 days.

Applying this method to the study of the nutritional value of various single whole foods we have found that on an exclusive diet of yellow or white corn rats maintained their original weights for more than 3 months (34). However, after approximately 60 days on the diet they became inactive, and the yellow corn-fed rats showed only dioestrous vaginal smears, while the white corn group began to show a vitamin A deficiency, as evidenced by constantly cornified smears, after about 50 days. The voluntary ingestion of cod liver oil produced remarkable results on the yellow corn-fed rats. Within only 4 days they all again showed regular 4-day oestrous cycles; almost at once they ate more corn, gained weight, and became much more active. After 15 days they reached approximately their pre-experimental levels of running activity, averaging 10–15 miles per day. Figure 17 shows a typical record of the activity, food intake, body weight, and vaginal smears of a rat kept on the single food yellow corn diet, and later given access to cod liver oil. The results of these experiments indicate that, under the conditions of this experiment, yellow corn when supplemented with cod liver oil becomes an excellent food. In marked contrast, the rats on white corn failed to respond to the ingestion of the cod liver oil, except with an immediate change of their vaginal smears from a condition of constant cornification to a persistent dioestrous condition. They remained inactive and did not show an increased appetite, or gain weight. These results demonstrate that white corn must lack some essen-

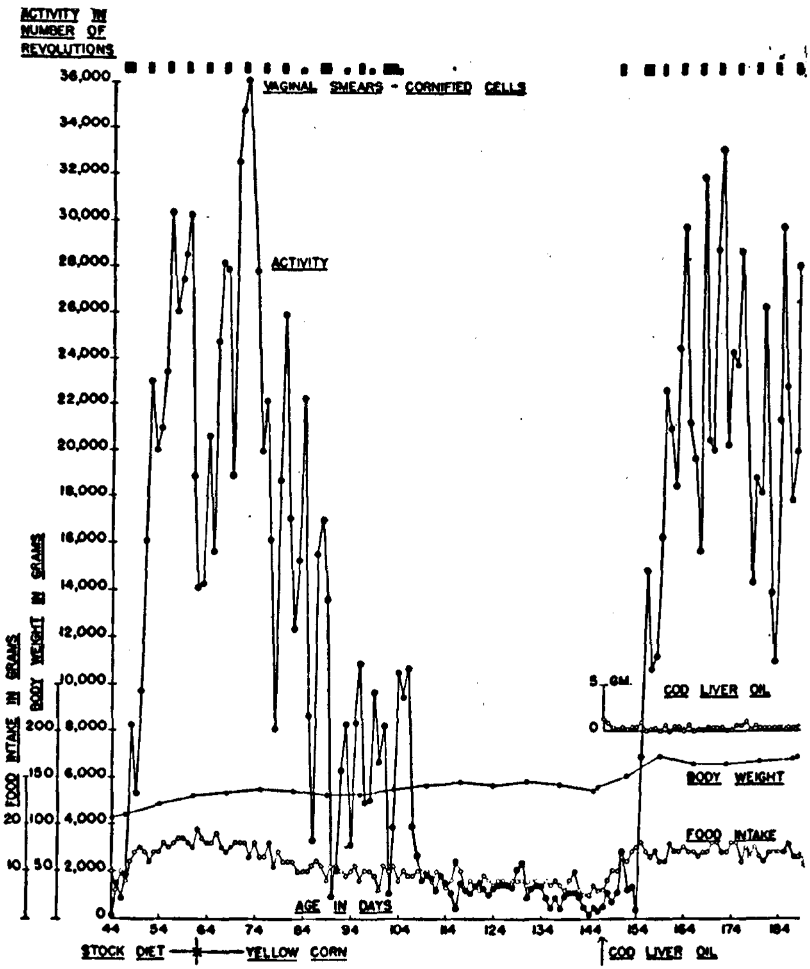

Fig. 17. Typical individual graph showing daily activity, food intake, body weight, and vaginal smears of a rat kept on an exclusive diet of yellow corn and the effects produced by the ingestion of cod liver oil.

tial nutriment that is present in yellow corn, and not supplied by cod liver oil.

Other animals besides the rat have also been reported to make beneficial selections of diets from natural and semi-natural foodstuffs. In 1914 Evvard tried a "free choice" system of feeding pigs, and concluded that "the appetite of the pig appears to be a very good guide as to its bodily needs" (35–38). One such experimental animal grew to be the largest hog ever raised at the Iowa Agricultural Experiment Station. Nevins found that dairy cows made beneficial selections of diet, as evidenced both by milk output and weight gains (39). Godden stated that sheep grazing in hill pastures in which some areas were deficient in minerals, consistently left the deficient herbage untouched (40). Orr has reported numerous further instances of beneficial selections of diet made by livestock (41). Similarly, Price reported that chickens given a choice between three varieties of butter, one with a high content of vitamin A and D, another high in the A factor but poor in D, and a third variety poor in both factors, unerringly selected the first sample, though neither taste nor odor indicated any differences to the human observer (42). Pearl and Fairchild also found that chickens made more efficient choices of food on self selection diets than on mixed diets (43). Similarly, Stearns and Hollander successfully used a "cafeteria" system of feeding for pigeons (44). We have found that monkeys, given access to the same selection of foods as the rats, with the single exception that vitamin C was also available to them, thrived throughout the three months of the experiment. Guinea pigs, ferrets, and mink did less well, perhaps owing to a deficiency of vitamin K, which was not offered for choice; these species consistently showed intestinal hemorrhages at autopsy after several months on the diet, though there was never any gross bleeding from the gastro-intestinal tract.

If it is true that rats have such a remarkable ability to select beneficial foods and to avoid harmful foods, it may be asked how it is possible to poison them. In our experiments it was found that when poisons such as arsenic trioxide, mercuric chloride, or morphine sulphate were offered separately in solution the rats avoided them in extremely low concentrations, far below the level at which they might have had any physiological effect. Franke and Potter found that rats made clear cut differentiations between diets which contained varying amounts of selenium (45). It has been our experience that rats can be made to take poisons only under two conditions: (1) when the poisons are sufficiently thoroughly mixed with their food to mask most of the taste, and then usually only when the rats are very hungry; or (2) when the poisons are too highly insoluble in the saliva to be tasted. In this connection it may be pointed out that the inability to vomit may explain the great caution with which rats approach their food. Dogs and many other animals that are able to vomit are usually less cautious. We have found, however, that monkeys and chimpanzees, despite active vomiting responses, can be made to take soporifics orally only with the greatest difficulty. They detect the presence of the drugs even when very thoroughly mixed with their food or powdered and hidden in bananas.

I would like to call your attention also to the possibility that various phenomena, ordinarily spoken of as perverted appetites, such as coprophagy, infantophagia, autophagia, placenta eating, and bone eating, may be regarded as instances of self regulatory activities. We are now making special studies of some of these phenomena, determining how they fit into the picture of the total nutrition of animals. Coprophagy, or feces eating, is frequently observed, especially among animals on deficient diets. That it serves a useful purpose, and is actually a form of self regulatory activity, is evidenced by the fact that rats on a single food dextrose diet lived more than half again as long (54 as compared with 34 days) when given access to their feces (33). Similarly, it may well be that urine drinking, or ouronodypsia, is of comparable significance with coprophagy. Thus, Orent-Keiles and McCollum have reported a pica exhibited by rats on diets low in potassium (46). The animals showed a marked tendency to lick their genitals, especially after urinating, while coprophagy was not observed. Since potassium is excreted almost entirely through the kidneys, it seems likely that the rats were attempting to recover this deficient element from the urine. It may be of interest that we have found that rats have an active appetite for cancer tissue (47). Recently, for example, 3 almost moribund tumor-bearing rats were kept in one cage, each rat carrying more than 100 grams—very nearly half the body weight—of neoplastic tissue. After the first rat died, the other two were observed avidly eating the tumor off its body and by the following morning not a trace of tumor remained on the dead rat. On occasion the rats will even eat large portions of the tumors off their own bodies. This appetite may not be as extraordinary as it seems at first glance when we consider that the tumors are constituted of young, extremely rapidly growing tissue. Nash has reported the autophagia of wounded paws or tails in 50 per cent of starved traumatized rats (48). Since neither injury nor hunger alone were sufficiently strong stimuli to induce self eating, it was concluded that the mouthing of wounds practiced almost universally among animals only leads to actual autophagia in the presence of a very strong hunger drive.

There are many reported instances in which animals manifest special appetites as a result of dietary deficiencies. Theiler, Green, and Viljoen found that the osteomalacia so prevalent in South African cattle was associated with a phosphorus deficiency in the soil and vegetation of the regions in which the disease was prevalent, and that such animals were confirmed bone eaters (49). When the bones were infected with the bacillus para botulinus, the cattle developed acute botulism, so-called Midland Disease or Lamsiekta, with its consequent high mortality. An adequate supply of phosphorus eliminated the disease. Similarly, Jones found that the sheep at Burrowa, in New South Wales, cured themselves of "weakness" by eating the earth in certain paddocks (50). On analysis, the earth from these natural lick holes proved to be unusually rich in iron (7.1 per cent Fe_2O_3). Orr also mentions a disease of oxen in Kenya known as Nakuruitis, characterized by emaciation, anemia, "running at the eyes," and in the advanced stages by loss of power and coordination of the limbs, which was cured when the animals were allowed to lick ad libitum a mixture of equal parts of common salt and ferric oxide (51). According to Orr, horses in Victoria, Australia, circumvent the natural consequences of grazing on inferior pasturage by eating the bark of "grey-box" trees, which on analysis is shown to be exceedingly rich in lime, containing 53.7 per cent as compared with 2.7 per cent in native grasses (41).

McCollum has observed that hens on experimental diets designed to determine whether birds could synthesize lecithin, developed such a strong habit of egg eating that they had to be carefully watched in order to secure the eggs immediately after they were laid (52). Since egg yolk is an unusually rich source of this phospholipin it seems very likely, at least, that the animals were making an effort to correct the deficiency.

Before I give you the results of observations that have been made on self selection ability in humans, I would like to point out the astonishingly close relationship that exists between the dietary requirements of rats and human beings. With the exception of the needs for vitamin C their requirements have proved to be almost identical. It is of interest, then, that actual measurements of the taste ability have shown that rats and human beings have almost exactly the same taste thresholds for all of the substances so far tested, with the difference that human beings show a wider range of individual variation. The methods used for determining taste thresholds were essentially the same in both cases, with the exception that the human subjects used words to describe their taste reactions. It is not astonishing that humans recognize a difference in taste between distilled water and the solution being tested at a consistently lower concentration than that at which they can definitely characterize the taste of the solution. Thus, the average concentration at which adult humans first recognized a difference between salt solution and distilled water was 0.010 per cent, while the average concentration at which they first definitely recognized the salty taste was 0.065 per cent (53). This latter figure agrees very well with the 0.055 per cent taste threshold of rats for sodium chloride. Similarly, the human sweet taste threshold for sucrose solutions falls at an average of 0.41 per cent, while the average taste threshold of rats for sucrose is 0.50 per cent (54). In the case of the bitter tasting toxic compound, phenylthiocarbamide, there is even closer agreement, as seen in

Figure 18. The taste difference threshold and the bitter taste threshold of human beings both averaged 0.0003 per cent, while the average taste threshold for rats also fell at this same concentration (55).

We may now discuss self regulatory functions in human beings. To what extent do behavior regulators manifest themselves in

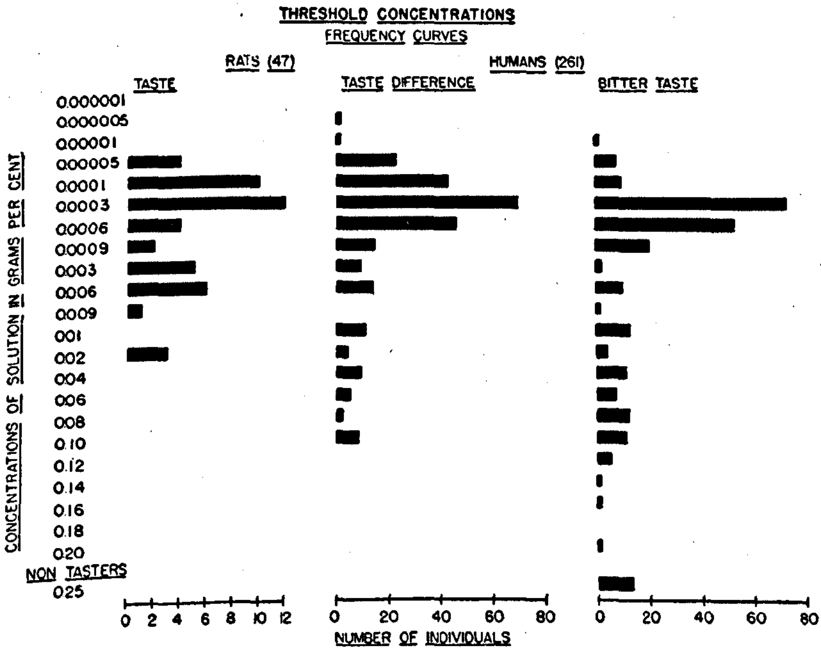

FIG. 18. Maximum frequency curves for phenylthiocarbamide taste thresholds for rats and human beings.

human beings? That we must have essentially the same ability as animals to make beneficial dietary selections is attested by our very existence. Certainly in the wild state, when man was dependent for his food on selections made from a great variety of nutritious, harmless, and poisonous substances, he did not have the guiding hand of the modern nutritionist to help him select his diet. Appetite must have been his chief guide then, and today appetite must still play a far more important rôle than many nutritionists seem willing to admit.

Davis has reported many interesting examples of infants who thrived and grew on diets which they selected from a wide assortment of natural foods, even citing one child who overcame the symptoms of a marked vitamin D deficiency by voluntarily drinking large amounts of cod liver oil (56–60). In Davis' experiments with children, when natural foods were offered for choice, there was a wide fluctuation in appetite for the different foods from day to day and from week to week. This seems readily understandable in view of the fact that each food may be used to satisfy any one of several appetites at different times. However, when rats are kept on a full self selection diet of purified substances, their appetites remain surprisingly constant over long periods of time. Sweet has also adduced evidence to show that children thrive better when allowed to select their own food and meal times, than on a fixed regime (61).

Along this same line I would like to mention the results of some preliminary observations that we have made on the cod liver oil appetite of children at different ages (62). We have now tested over a thousand children from 5 to 14 years of age simply by letting them taste a small spoonful of the unadulterated oil. At 5 years almost all of the children liked cod liver oil; progressively with increasing age more and more of them manifested a dislike for it. This was found to be true regardless of whether or not they had had cod liver oil before. Thus, as shown in Figure 19, of 328 children tested in one of the schools near the Johns Hopkins Hospital, in the 5-year-old group, 100 per cent of the girls and 92 per cent of the boys liked cod liver oil, while in the 14-year-old group only 36 per cent of the girls and 28 per cent of the boys still liked it. Some children at 14 years had an almost insatiable appetite for cod liver oil. When allowed to satisfy their craving they took as much as 16 tablespoonsful in one day, and continued to take high amounts for 5–10 days. After that they took only small amounts, and finally stated that they no longer liked it. Rats kept on diets deficient in vitamins A or D responded in much the same way when offered cod liver oil. Our results thus suggest the possibility of using the cod liver oil appetite as a means of detecting deficiencies of vitamin A or D or some of the fatty acids.

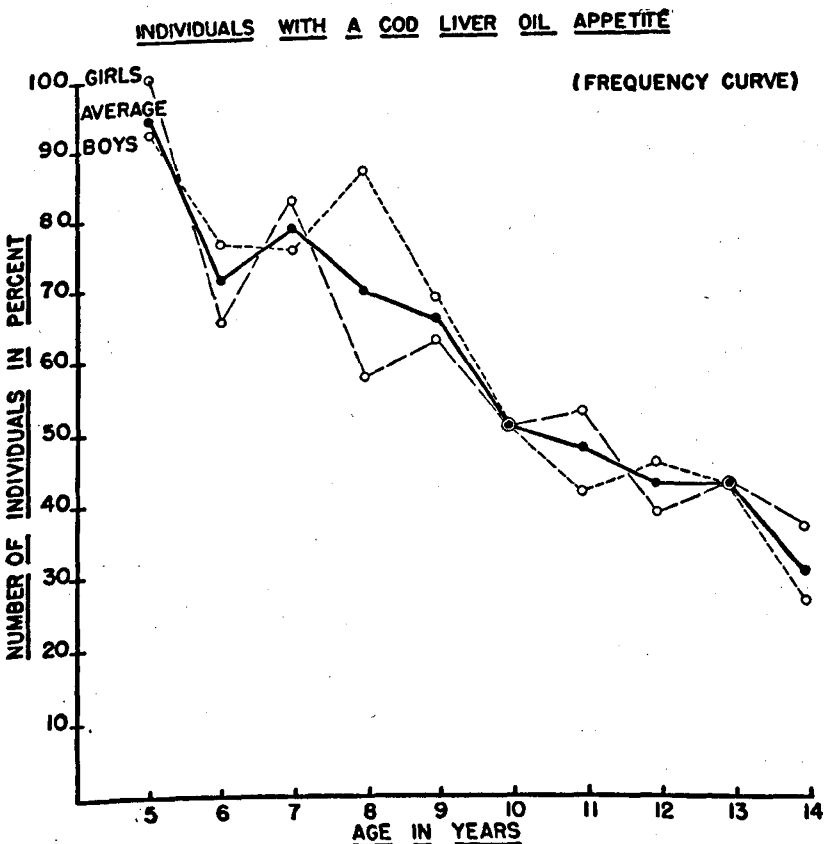

FIG. 19. Chart showing decreasing appetite for cod liver oil with increasing age in 328 school children.

We do have a few instances in which in human beings just as in the rats, the physiological regulators have been either completely or partially eliminated. Thus, in Addison's disease, in which there is a destruction of the adrenal cortex, we have found many patients who manifested a marked craving for salt—either for salt itself or food with a high salt content, such as ham, sauerkraut, etc. In the latter instances the patients themselves did not in any way associate the craving for these foods with their high salt content. All they knew was that the food had an unusually pleasant taste to them. Doctor Lawson Wilkins and I have described a 3½-year-old boy with destruction of adrenal cortical cells by hyperplasia of the androgenic zones of the glands, who kept himself alive for more than two years by eating large amounts of salt, literally by the handful (63). When his salt intake was restricted to the amounts present in a regular hospital diet he promptly developed symptoms of insufficiency and died. Another patient, a 34-year-old man with marked Addison's disease, put approximately ⅛-inch layer of salt on his steak, used nearly ½ a glass of salt for his tomato juice, used salt on oranges and grapefruit, and even made lemonade with salt. As a matter of fact, a salt craving is so often an early manifestation of Addison's disease that it is of considerable diagnostic significance.

Similarly, children with parathyroid deficiency have been reported to show a craving for chalk, plaster, and other substances with a high calcium content. Instances have also been reported in which patients with pernicious anemia have kept themselves in good health as a result of the satisfaction of a strong craving for liver. Similarly, dietary anemias may be at the root of the clay-eating habits commonly practiced in the poorer sections of the South (64). The high water intake of patients with diabetes insipidus may also be regarded as an effort to prevent dehydration, which is threatened by the loss of physiological regulation of the posterior lobe of the pituitary gland. In the same way, we may regard the high water intake of the diabetes mellitus patient as a means of diluting the urinary sugar and avoiding a consequent dehydration. The high food intake may also be regarded as an effort to supply the necessary calories, the ability to utilize sugar having been lost. Similarly, the voracious appetite of the hyperthyroid patient is presumably the direct result of the increased metabolic rate, which would soon produce cachexia if the food intake were limited to normal amounts.

Other instances of self regulatory functions not in the field of nutrition might also be cited. We may regard the great physical activity of many normal individuals, the play activity of children, and perhaps even the excessive activity of many manic patients, as efforts to maintain a constant internal balance by expending excessive amounts of energy. On the other hand, the low level of activity seen in some apparently normal people, the almost total inactivity seen in depressed patients, again may be regarded as an effort to conserve enough energy to maintain a constant internal balance.

Those who do not believe that self regulatory ability still exists in man cite various instances of individuals who failed to make advantageous selections, instances in which individuals have eaten the wrong foods, or too much or too little food. We can offer several points which must be taken into account in considering these failures. In the first place, the use of natural foods instead of purified chemical substances will certainly frequently confuse the choices, since the selections depend so largely on taste; and in order to get adequate amounts of needed substances it may be necessary to take other harmful or unneeded substances. In the second place, with the present prevalence of highly refined foods, the necessary vitamins, minerals, etc., may not be available in sufficient amounts, so that no matter how adequate the self regulatory ability, the individuals could not make satisfactory selections. In the third place, inherited and acquired defects of the sensory mechanisms may also account for some of the poor dietary selections. Thus, from the work of Blakeslee and Fox and of Snyder and others, it is known that a small percentage of individuals are unable to taste the bitter-tasting substance, phenylthiocarbamide, and that this inability is inherited as a Mendelian recessive (65, 66). Likewise, we have found some individuals who are unable to taste other bitter substances, and some who are unable to taste sweet substances. We have found further that, although most children dislike alcohol solutions above 10–15 per cent, about 8 per cent of a large group of children were either indifferent to, or actually liked, solutions of alcohol in concentrations as high as 50 per cent (27). This observation may perhaps account for the excessive drinking of some individuals. However, cultural influences probably account for most failures to make beneficial dietary selections. Most children are brought up by their parents to distrust their own appetites. Often when they like a food they are told not to eat it, and when they dislike it they are equally often told that it is nourishing and good for them. In later life such persons are much more apt to depend on food faddists than on their own taste sensations.

Finally in this connection I want to draw your attention to the possibility that self regulatory functions may undergo a partial or total breakdown. Some of the instances of dietary failures just mentioned may be instances of such a breakdown. The total regulators may wear down or age just as Cannon has reported that the physiological regulators do (2). A breakdown of the total self regulators would depend in the first place on disturbances in the sense organs—the heat, cold, pain, taste receptors, etc.—or in the parts of the brain involved in the ability to observe sensations of fatigue, pain, taste, etc., and to react to them. Thus, Ruch, Brobeck, and Blum have shown that monkeys with lesions of the arcuate nuclei are no longer able to make advantageous taste differentiations (67). The fact that animals deprived of the frontal poles of their brains may become so active that they literally run themselves to death would indicate that this part of the brain also plays an important part in the total self regulatory functions (68–71). The great overactivity seen in some psychiatric patients may result from a breakdown of the self regulatory systems. Further instances would be seen in catatonic patients who no longer react to external or internal stimuli and unless cared for by tube feeding, etc., would not live; and in anorexia nervosa patients who when left to their own devices would gradually let themselves starve to death. Many other instances might be explained on this basis.

Thus, in summary, I have tried to show that the maintenance of a constant internal environment depends not only on the physiological or chemical regulators, but as well on behavior or total organism regulators. Proof of the existence of the behavior regulators was taken from experiments in the field of endocrinology and nutrition. It was shown that disturbances created in the internal environment by removal of one or the other of the endocrine glands were corrected by the animals themselves. It was demonstrated that the ability to select diets with relation to internal needs seems to depend more upon taste sensations than on experience, and it was pointed out that this knowledge of the ability of animals to make beneficial selections can be used to study a variety of problems in the fields of endocrinology and nutrition. Evidence was further presented for the existence and successful operation of similar behavior regulators in human beings. Thus, we believe that the results of our experiments indicate that in human beings and animals the effort to maintain a constant internal environment or homeostasis constitutes one of the most universal and powerful of all behavior urges or drives.

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