CONTROL SYSTEMS AND BEHAVIOR

KARL PRIBRAM
Department of Psychiatry
Stanford University School of Medicine
Palo Alto

THIS, AS YOU KNOW, is not my field, and I took upon myself this task because I wanted to see whether the models that we and others have been playing with have any power.

I think a model has power in two senses; one: that it leads a sophisticated investigator to make his problems more precise and allows him to test against this precision; and two: that it enables someone who is naive to work his way through problems of extraordinary complexity. It is in the latter sense that I want to present a model tonight.

The way in which I have organized this presentation is to take the homeostat notion of Cannon seriously; to look into a model of the homeostat, and to modify the model according to what we know today. The model that I am going to use is the thermostat and its control of a heating system.

I will proceed by posing a few questions. The first of these is a rather obvious one. In order to obtain regulation of anything, one must have some influence on it. In the central nervous system this would be the efferent influence on some peripheral mechanisms. The kind of efferent influence that is exerted led to the notion of the constancy of the milieu intérieur and to the notion of homeostasis.

Efferent influence on peripheral structures certainly exists, but the question arises: how independent are the peripheral mechanisms from this efferent influence?

When I look at a thermostat in my own home and study the peripheral mechanisms, the feature that is most striking is that the furnace, besides providing heat, also has a blower connected with it. This blower is rigged in a very special manner in that, when heat is first turned on, the blower is not on, but after the heat has been on for a little while the blower starts up; and then from time to time it turns off and on. On investigating this operation, I find another

gadget on the furnace which has a needle and two pointers. When that needle is between those two pointers, the blower is on; when it swings to either side of the two pointers, the blower goes off. So, there is a control mechanism in the heating system which operates quite independently of the central regulation by the thermostat itself, but not quite as independently as would at first seem.

The analogy here is to the autonomic control; and it is very disappointing that our Russian colleagues could not be here, because I am sure they would have presented material to fill out this picture of the relation between central control and autonomic activity.

As I listened to our discussions, there was only one example of this kind of autonomic on-off mechanism that came to my attention. This example seemed to perform within the limits of the central regulation. Dr. Andersson described shivering in the centrally cooled animal. Shivering occurs, he said, only when peripheral cold receptors are also stimulated; that is, when the environment is sufficiently cooled. This reminded me very much of what happens when the blower goes on in the heating system, namely that the peripheral mechanism works only between two temperatures yet is under the broader control of the central regulating device.

The next thing to look for in our model, the thermostat, is that it must have a detector in order to do its job; it must be fitted with a sensitive element. In the thermostat, this is usually a thermocouple made of two kinds of metal, one of which expands when the temperature in the room reaches a certain point and, when expanded, it closes the switch.

The question that arose over and over again in the discussions with regard to the glucostat and osmoreceptors, temperature control and other visceral regulations, was whether there were such detectors in the central nervous system. And from the examples given, it seemed that there is, indeed, evidence for such detectors spatially distributed in and around the midline ventricular system, certainly as far forward as the pre-optic region, and at least as far posteriorly as the respiratory centers.

The next question that immediately arises, of course, is: to what physical and chemical events are the detectors sensitive? Some of the answers given, again as examples, were blood temperature change and osmotic differences across the blood-brain barrier. In addition, there is the work of Michael, on sensitivity to estrogen (7) and the work of Meyer on the sensitivity of the respiratory mechanism to partial pressure of CO_2 (6).

There is also some evidence that the entire region in and around the midline ventricular system shows some less discretely localizable sensitivity, namely to histamine, acetylcholine, and some adrenergic substance. These data make one remember last year's conference on receptors and sensitive elements, especially Weddell's presentation on this problem: in the case of the skin, although there are specific neural, anatomical, histological elements that are selectively sensitive to one or another physical or chemical event, there also seem to be sensitivities of a more general nature (9).

There is another point about these midline locations in the central nervous system that intrigues me. During ontogeny the midline ventricular system forms by the invagination of the ectoderm. It should, therefore, not be too surprising—though it is hardly proof—that these portions of the nervous system show sensitivities similar to those shown by the skin. Neurosurgeons are routinely faced with the phenomenon. As an illustration, in operating we often say, "Let's have some water" when we want to rinse the field with saline solution. I remember a particular patient in whom the fourth ventricle was exposed. In this instance, the scrub nurse took us literally and gave us water instead of saline. The patient was under a local anesthetic and, when the water touched the brain, there was nausea and retching—no vomiting, but severe pain lasting for a few minutes. This pain was an immediate effect, before the water spilled from the fourth ventricle down to the bottom. When we realized what had happened, we immediately got some saline and quickly rinsed the water out. I do not know how long the effects would have lasted otherwise. In addition to this experience, the observation is often made that pulling the tissues around the third and fourth ventricle causes severe discomfort, whereas the rest of the brain is apparently insensitive to this sort of manipulation.

Another question that concerns the detector element is: how does it work? For instance, what is the glucostat doing that is analogous to the thermocouple in the thermostat? What we have heard somehow does not make sense. How can a satiety-sensitive mechanism control feeding? For the problem is not the control of satiety, but of feeding.

Could it be that we have been asking the question backwards? Perhaps satiety is the *normal* state of events. Just as temperature in this room is a comfortable one now, satiety is the comfortable situation. In this state the glucostat is sending out impulses closing a circuit, much as does the thermocouple in the closed condition—

both the furnace and the feeding mechanism are shut down as a result. Dr. Anand gave us the evidence that indeed the firing of the medial hypothalamic tissues serves to inhibit the feeding mechanism. So, by thinking of satiety as the normal situation, a drop in metabolizing glucose would be conceived to result in a decrease in activity of the ventromedial hypothalamus, thus decreasing its inhibitory control over the feeding mechanism, much as opening the normally closed thermocouple switch on the furnace sets it going.

For me, the power of the analogy is that a precise, answerable question was posed, a question which allowed systematization of the data presented.

Miller: Does this not run counter to the data Dr. Anand reported, namely that he got increased firing when he put glucose into the region if the animal was satiated? He got firing from the ventral medial region, which is the inhibitory one. I think you could just as well say the circuit is normally open and, when the signal comes, it turns it over and starts firing.

Anand: All it means is that, in the physiological arrangement of equilibrium, this situation may be taken as the baseline rather than as the activity line. It is a concept that applies to any response, as for example, whether you take as normal the heart rate of 150, which you would have were there no vagal inhibition, or whether you take 70 as the normal, which is actually the heart rate as a result of vagal inhibition. I think that is what Dr. Pribram means.

Pribram: That is right. The reason I called it 'closed' is because that is the way it looks. But it does not matter what you call it; what is important is that firing of the receptor inhibits the mechanism for action (feeding in this instance).

Mayer: I am afraid that there are more serious objections to this picture than just the definition of what is open and what is closed. I personally think this is an erroneous picture of the mechanism of satiety. The mechanism of satiety is very much more like a brake which is progressively released as the state of the animal gets farther and farther away from satiety and approaches more and more the fasting state. For example, the same psychological stimulus, such as presentation of an appetizing meal, will have very different results if it is given near or far from the point of satiety. It will be more likely to elicit gastric hunger contractions, salivation and the sensation of hunger when the organism is more depleted. This is the weakness of this particular sort of all-or-nothing model. From that

viewpoint you would do better, I think, with a brake than you would with a thermostat.

Pribram: We are using this particular model of the homeostat because it is one with which people are familiar. For conceptual reasons, it is easier to talk about on-and-off digital mechanisms, whereas actually, for many purposes, one can convert into an analog mechanism fairly easily without losing the essence of the process. What I want to say next will show one possibility for the graded changes we must account for. But now we have almost got ourselves into a trap, a trap that I especially wanted to avoid. We have *all* of us begun to talk as if our model corresponded to the events that we are trying to describe.

I began by saying that a thermostat on the wall is a model which allows me to ask questions. I wanted to know in what respects the model is applicable and in what respects it is not. We have not really fallen into the trap yet; at least we caught ourselves in time. The hypothalamus is not a thermostat on the wall; it is something in the brain, and we must keep the distinction clear.

Anand: When we deal with the living, biologically active organism, I think the baseline of the model, whatever the model may be, is an equilibrium between many forces acting in different directions. That would apply whether you are talking of the thermostat or glucose receptor model. In the example of the thermostat on the wall, the similarity would be whether the room is occupied or whether the room is empty. If the room is empty, you want the thermostat turned down.

Mayer: Could I also suggest this: it seems to me that we are all in agreement that, at a given time, the degree to which the brake is to be released is going to be the result of a summation of a number of factors by a computer. When we speak about regulation, however, we are wondering where the *memory* of this computer is. In other words, we are singling out the particular factor which is dependent on modification of homeostasis (be it of carbohydrates, depot fats, etc.). The *regulating* factor differs from other factors which help to determine whether or not the brake is released by being dependent on the physiological state of the organism.

Fremont-Smith: What Dr. Pribram is trying to do is show one way in which you can use a model to ask questions. I think everybody else who has intervened so far has simply been objecting to the model itself. But this is not the issue at all.

Pribram: A thermostat on the wall is not sitting in the third

ventricle, and I have not confused the two. I am merely asking whether the generalized homeostat model leads to some questions that are relevant to our discussion. To me, some of them are and some of them are not.

Let us tackle the next step in the model (the one which is hanging on the wall, not the one in the brain). There is a most neglected part of the gadget on the wall. This is the little "bias" wheel on the top of the thermostat by which the mechanism is set or tuned. At this point many of your questions become relevant. The particular questions brought to mind by this biasing function are the following: first of all, anatomically the biasing mechanism must be near the sensitive element if the brain homeostats are to look like the wall thermostat. If so, what does the biasing mechanism look like? Dr. Morgane showed us that for the so-called feeding center it is very hard to decide whether fiber tracts or cells are primarily involved. Is not this the problem that confronts us everywhere in the brain stem core—the problem that has given rise to the concept of the reticular system? Just to anticipate some questions and comments: I hope later to show that this does not mean that the biasing mechanism, the reticular system, is a mishmash of diffuse, unorganized tissue which can do nothing more than raise or lower the level of excitability. Again, in anticipation: just as the wheel on a thermostat has numbers on it, the reticular system could perform quantifiably and even specifically. We will get to that later.

What questions does this little gadget, the tuning or biasing mechanism, raise? A very interesting and direct question concerns Dr. Lilly's rising train of excitation and the effects—really the differential effects—that are obtained with a constantly rising train of excitation (5). The effects of electrical self-stimulation in the brain have been interpreted to mean that there are reward and punishment systems within the brain. An alternative would be to apply Lilly's demonstration to the self-stimulation results. By gradually and continually turning the bias wheel on a thermostat, the furnace can be kept going all the time.

In the experiments on reward and punishment reported by Delgado, Roberts and Miller (4) it was very difficult to dissociate the reward and punishment regions anatomically. In fact, in one experiment self-stimulation of the same location would be used by the animal to turn the stimulus on, and once on, would then result in the pressing of another lever which would shut the electric current off.

A biasing mechanism could push a homeostat in either direction.

Also, if you pushed too rapidly, the apparatus would go into oscillation. Drs. Brobeck and Andersson described the effects of continuous central cooling, to produce just such oscillations in peripheral vascular phenomena.

Leake: This is interesting in connection with your model, because some thermostats will operate to maintain, as it were, an optimum which is the neutral or equilibrium basis, by either heating on the one hand or cooling on the other. And it can go either way. This was the background for the idea I was trying to express by reciprocal innervation. It will depend on what the optimum condition is for the organism.

Pribram: If, therefore, in addition to efferent influences and a detector mechanism, a bias or setting device is present, the gadget can do all the things it is supposed to do, which is all that you really ask of a mechanism.

The next question is whether the addition of a biasing mechanism can fully account for the controls, internal and external, placed on the homeostatic mechanism. Changing the bias on a system will change its level, e.g., the organism's appetite: after six hours of deprivation, steak looks good; after Thanksgiving dinner, the same steak would be nauseating.

Dr. Morgane's demonstration showed that the input to the bias (the feeding "center" in this instance) must be from several locations in the central nervous system as well as from the periphery, e.g., the stomach. These inputs can actually reset the bias and thus function in lieu of the glucostat's input from the ventromedial nucleus. By our thermostat analogy, when the room is cold, the furnace has gone out. So, you turn the setting wheel to start the furnace. Since you live in this house you get to know your thermostat, actually learn to preset the thermostat at the appropriate moment. The bias mechanism allows the effects of experience to become effective in controlling the homeostat.

A final question that is really a development of Cannon's ideas on homeostasis: we have been shown data that strongly suggest that the various statically regulated mechanisms, whether they be of temperature, food intake, water consumption, or activity production, do not operate independently of one another. Dr. Brobeck's work over a ten or fifteen-year period has certainly pointed to such interdependence. The question is, where does the interaction of variables that leads to interdependence take place? Some of it is peripheral. The eating of bulk results in dehydration through water transfer

into the gut. But there is also a *central* mechanism that is ideally suited to "join" these various homeostats, to use the term developed by Ashby, who has ably explored the consequences of applying the homeostat model to the problem of biological adaptation in his *Design for a Brain* (1)—a book that is not easy reading.

This central mechanism is, I believe, the limbic system of the forebrain. You are well acquainted with the multiple interconnections of this system with the midline parts of the brain. To unravel what it is that this central "interconnectedness" does, it is helpful to have a model in mind while interpreting data.

Ashby speaks of interconnectedness in homeostatic mechanisms as leading to ultrastability. By "ultrastability" he means that a perturbation of one of the homeostats will be balanced out and thus not lead to general disorganization of the behavior of the organism. An example can be taken from Dr. Brobeck's experiments (2): when the temperature of a warm-blooded animal drops slightly, either the organism eats or it becomes active and thus generates heat, depending on the availability of food and of opportunity for exercise. Should the animal be prevented from using one of these two avenues of meeting the drop in basal temperature, it uses the other. In any case, the interrelatedness of the alternatives assures stability to the organism.

When one minimally disrupts central interconnectedness by making limbic system lesions, one disrupts this ultrastability. This should show up as a temporary disturbance of those functions that are homeostatically controlled. And indeed, one finds that one does obtain effects similar in some respects to those reported when hypothalamic lesions are made. For instance, a monkey who has been on an ad libitum food intake will, after bilateral amygdalectomy, double its food intake (Figure 133). If one does more than just an amygdalectomy, i.e., removes the orbital, insular and temporal cortex as well, one then sees a much more dramatic effect. But hyperphagia is not always produced. One can also see the opposite, i.e., aphagia, which may last for ten days or two weeks. Usually, though not invariably, the organism recovers at this time, but recovery may be slow and needs support by external care—tube-feeding, clysis, etc. When a glucose tolerance test is made, one occasionally finds that the blood sugar level will stay up around 200 to 250 mg per cent for as long as a week during the period of aphagia.

During the period of hyperphagia the effects of bilateral amygda-

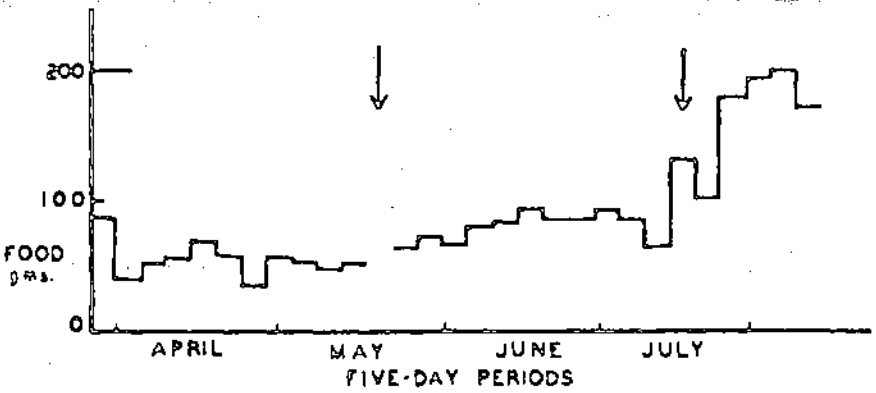

FIGURE 133. The effect of bilateral amygdalectomy on the food intake of a monkey on an ad libitum diet.

lectomy also resemble those of hypothalamic lesions. For instance, in a lever-pressing situation, where the animal has to work for its food, results are obtained similar to those reported by Miller, Bailey and Stevenson for rats with lesions of the ventromedial nucleus (8). Amygdalectomized monkeys eat more but work less for food.

Figure 134 shows that the rate of response changes with deprivation, though note that the distribution of responses made to the fixed interval schedule does not. The normal animal increases both food intake and rate of work (response) when food-deprived. On the other hand, animals after amygdalectomy show no such increase in rate of work (Figure 135), despite the increase in food intake shown in Figure 133. This difference in effect, similar to that obtained by Miller and his co-workers with hypothalamic lesions on a consummatory and on a work response (8), is, however, not limited here to deprivation variables.

If one changes the size of the reward by giving a smaller food pellet in the bar-press situation, then again, as shown in Figure 136, one finds that normal animals react by changing markedly their rate of response. Animals after amygdalectomy do not make nearly as marked a change.

Figure 137 shows what happens when the size of the reward is increased. Again, a very characteristic satiety curve describes the behavior of the normal monkey. On the other hand, animals with lesions of the amygdaloid complex do not become satiated in this

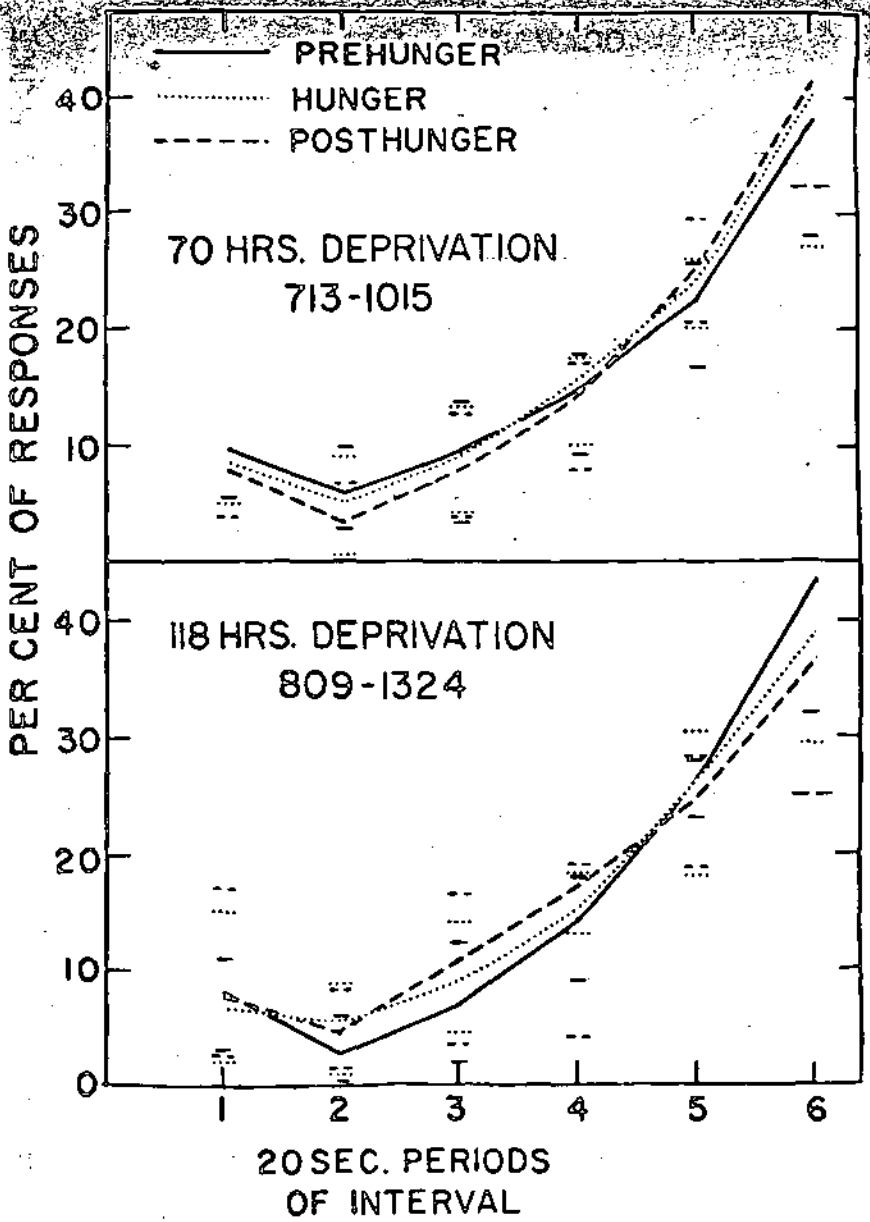

FIGURE 134. The effect of food deprivation on food intake and rate of work (response) in normal animals.

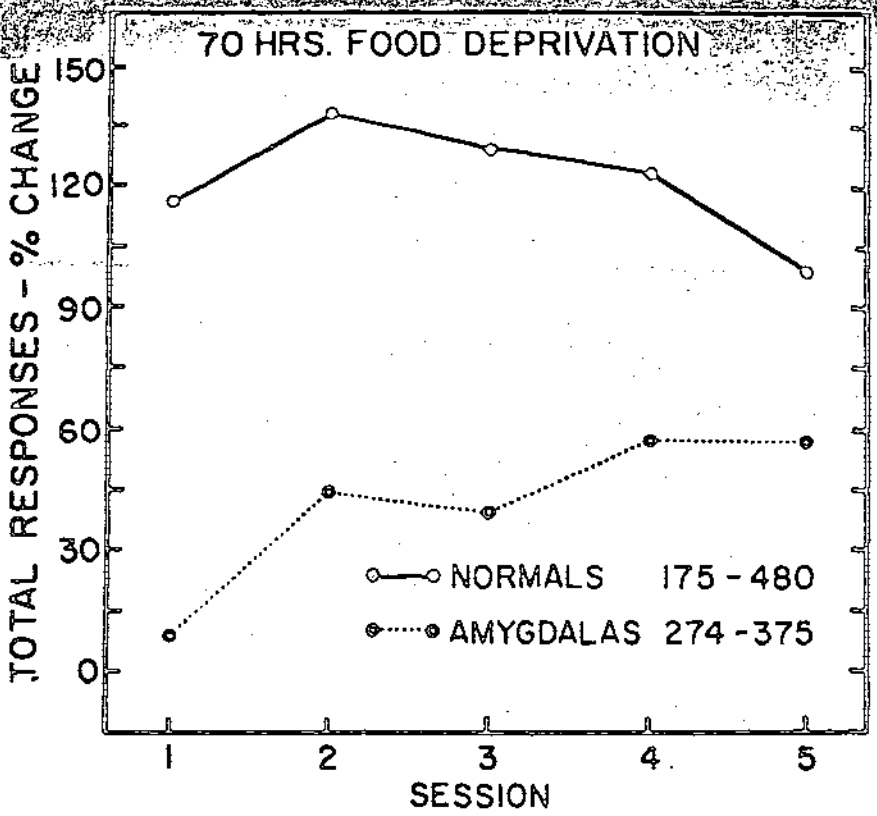

FIGURE 135. The effect of bilateral amygdalectomy on the rate of work (response) accompanying food deprivation.

way. They just go along on an even keel. Increasing the size of reward has little effect on them.

Ashby's homeostat, a machine built of interconnected homeostats, shows a disposition to be ultrastable. So, ultrastability is one attribute of interconnectedness. But this is not the only result of interconnectedness; there is a corollary of ultrastability. An ultrastable system adapts very slowly—so slowly, in fact, that "learning" may be very difficult. On the other hand, learning, i.e., adaptation to perturbation, is much more rapid in a system that is only loosely joined —a system in which each part can adapt to perturbation without affecting the rest of the system. How then do we explain the results of our experiments? After bilateral amygdalectomy, a lesion which supposedly partially disrupts the interconnectedness between home-

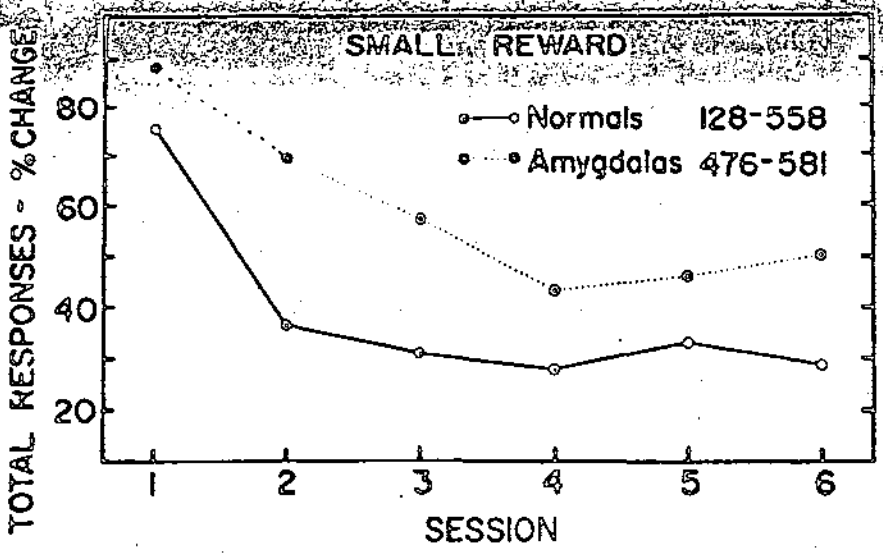

FIGURE 136. The effect of smaller food pellet on rate of work (response) in normal and bilaterally amygdalectomized animals.

ostats, the monkey shows a *more* stable disposition, adapts to changes in deprivation or amount of food reward more slowly, if at all. In fact, given a lighted match, such a monkey may repeatedly burn itself, whereas a normal monkey adapts readily by staying away from the match. What effect has the surgery had?

Whenever a neural system is drastically disrupted, reorganization takes place. Immediately after disruption the effect is maximal: the 'diaschisis' of von Monakow. But, during the entire period of reorganization, malfunctions of the system can be noted. The disturbances of sensation that accompany the phantom of an amputated limb serve as example. Before amputation the limb remains for the most part unnoticed—perceptual constancy has been established with regard to its relation to the rest of the body—any minor change such as the wearing of a new ring is immediately perceived but fairly quickly adapted to.

In a similar fashion, the normal monkey responds quickly to a change in the size of a food pellet and equally quickly adapts to the change since his normally functioning appestatic mechanism has achieved considerable constancy. This mechanism, however, is disrupted by amygdalectomy—probably not directly but by diaschisis and more long-lasting reorganizations that must take place in the

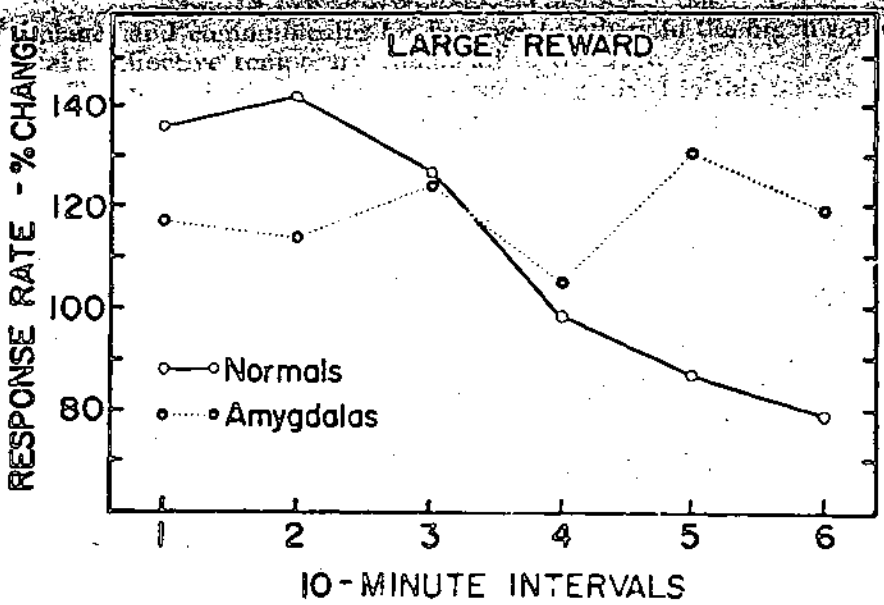

FIGURE 137. Effect of increased food reward on rate of work (response) in normal and bilaterally amygdalectomized animals.

interconnectedness. Disruption leads to a loss of constancy of the functioning part. In a plurally interconnected system such as the homeostat, such loss of constancy enhances the interconnectedness of the entire system: hence the ultrastability and slow adaptation. Once constancies can be re-established, the system is again "cut to pieces"—i.e., becomes loosely joined, less stable, and as a consequence adapts more rapidly.

Fremont-Smith: Do you mean, if the interconnectedness were broken, you would get instability?

Pribram: Yes and no. When connectedness is broken there is instability, but this can be limited if the break occurs by way of the development of temporary constancies. And remember that rapid adaptation demands some temporary instability.

There is, finally, another corollary of ultrastability that must be dealt with here. This final question is how the homeostat model allows for *selective* sensitivity. Look at it this way: If we have a thermostat controlling a system and it works poorly, we can state that the mechanism is not very sensitive. In other words, one of the corollaries of instability is sensitivity. Conversely, a good thermostat,

one that produces stability in the system, is also sensitive to small changes in that system. So, sensitivity is a corollary of stability.

But how does selection enter into this system? Returning to the anatomy of the system, note the multiple interconnections which I, for one, have never been able to keep straight. In fact, I do not know of anyone in this room besides Dr. Magoun and Dr. Ingram who could immediately describe the interconnections of all the structures connecting the limbic, hypothalamic, and mesencephalic systems.

What could be the meaning of such a richly, almost haphazardly connected region; what could be the function of a diffuse reticular type of system that when you do not look very closely has little structure, yet when examined closely is definitely not completely haphazard? How can selectivity occur in a structure of this sort? Chemical and physiochemical detectors provide one mechanism for selectivity, of course. There are two other ways, however, in which selectivity can come about. First, as we have already seen, constancies can develop within parts of the system, thus temporarily disjoining it. The development of such temporary constancies implies specificity—when the food-regulating mechanism is held constant, the remaining apparatus can be selectively applied to the regulation of temperature through varying activity, for example.

Second, selectivity results when temporary dominant foci can develop in such an interconnected system. An analogy developed by Warren McCulloch first clarified for me how selectivities can occur in a seemingly loosely organized structure. He tells the story* that until the Battle of Jutland all navies were hierarchically organized, as were all armies. That is, they had a high command, and this high command received information from its lower echelons, made decisions, and passed the decisions back down along the same lines of communication; in other words, they functioned through a completely vertical system of communication and control. The Battle of Jutland was a fiasco; as a result, several of the navies of the world reorganized.

A set of rules was worked out by the high command; these rules were made known to everyone in the organization; every person had open communication with every other person in the organization; action ensued when input to any person intersected the rules known to that person. As an example, take the following situation. A rule states: "Spot 100 or fewer enemy planes, fight; if more than

*Personal communication.

100 planes appear. So whoever on deck spots the enemy planes and communicates his findings to others in the organization takes effective temporary command of the fleet.

The point is simply that in a system organized in this fashion, in which lateral communication takes place within a set of rules, decision-making nodes can temporarily form anywhere in the system. The man who spots the plane is admiral of the fleet for the moment; he makes the decision, since he matches the information coming in against the established rules, and thus controls action.

Now, this is only an analogy. Yet the work of Rusinov, Morrell and others has shown beyond question that temporary dominant foci can be produced in the central nervous system, and that these function as decision nodes in controlling the behavior of the organism.

Mayer: I point out that this seems to be the picture with regard to carbohydrate metabolism: the body cannot survive long in a state of acute hyperglycemia. At a very low level of blood sugar, whole series of events happen in the body, more or less independently of each other. The concentrations of certain hormones are automatically increased, others are automatically decreased. The possibility is, therefore, that the hunger mechanism may well be linked along this type of information with the regulation of carbohydrate metabolism and thus, indirectly, with that of fat and protein metabolism. So you do not necessarily have to have one command center integrating all such phenomena. We get back to Claude Bernard and the fact that glucose is, after all, a real chemical messenger in that it does influence a whole series of events, only one example of which is what happens in the ventromedial region.

Leake: Dr. Pribram, would you say then, in connection with the analogy, that the one who made all the rules is the whole process of evolution?

Pribram: That, plus the process of learning. Those neuronal aggregates that are essentially random nets at birth can be organized by experience. At any moment the neural organization left behind by previous experience can now act as a rule against which the current input is matched.

Fremont-Smith: You have a reverberatory feedback mechanism in which the decision is the continuing resultant of this interaction.

Miller: It is more like one of the modern houses that has a floor heating system, and that system works so slowly that a single thermostat cannot control it. Therefore, you have one thermostat outside that tells whether it is getting cold or not, another thermostat in

the room that tells whether the room is getting cold, and another in the floor. These would be the mouth, the stomach and the glucostats, and possibly something that senses the amount of fat that you have on you, or something of that kind.

Mayer: Actually, this is not unlike the model that Dr. Davis and I proposed seven or eight years ago for the control of shivering (3), and very similar to that which Dr. Andersson has spoken about here. We visualized that there were really two thermostats for regulation of body temperature, or rather of heat production: one was dependent on central temperature, and regulated chemical heat production, particularly heat in liver through TSH; we suggested that there was another thermostat sensitive to the difference between inside and outside temperature, which regulated shivering, hair-raising, and other "physical" mechanisms of thermoregulation.

Brobeck: Dr. Pribram, when you use the word "selective," do you mean variable, i.e., the sensitivity can be set at various levels, or do you mean selective in the sense of a specific kind of sensitivity?

Pribram: Both. Specific, i.e., selective sensitivity, results from specificity of receptors and from temporary constancies; level sensitivity is a corollary of stability.

Brobeck: By selectivity, do you mean it responds either to glucose or temperature or something else? Or do you mean it has a set point for glucose?

Pribram: Because of the differences in the information coming in at any one moment in time, it can be selective for that particular substance. Once that mechanism is engaged, the set point is controlled by established rules, provided the system is reasonably stable.

Fremont-Smith: Do you not also bring in there the stability of certain components?

Pribram: Yes, the other component of the system must also be stable. If the entire organism is oscillating, there is no opportunity for sensitivity, nor for selectivity. The organism is pronounced overly "emotional," unstable.

Fremont-Smith: It seems to me that one of the functions of a model is to make predictions. Can you, from your model, make certain predictions which will be either validated or invalidated as new information comes in?

Pribram: I think this is where I would draw the line. Remember, a model may have two functions. One stems from the kind of naive model that I presented; the other results when the model is made mathematically or logically precise. Only when it is that precise

can you make testable predictions. We have reached some precision in modeling with regard to frontal lobe function. Have any of you reached this stage in your work on homeostats?

A model such as this should lead to a more precise one, but hopefully it may meanwhile also lead to experiments. It should lead to a different way of asking questions in the laboratory. A prediction must be precise—but an experimental approach may be vague and uncover, by chance, entirely new data tangential to any expectation or prediction.

REFERENCES

1. Ashby, W. R., *Design for a Brain.* Chapman and Hall, London, 1952.
2. Brobeck, J. R., Food intake as a mechanism of temperature regulation. *Yale J. Biol. Med.*, 1948, **20:** 545-552.
3. Davis, T. R. A., and Mayer, J., Demonstration and quantitative determination of the contributions of physical and chemical thermogenesis on acute exposure to cold. *Am. J. Physiol.*, 1955, **181:** 675-678.
4. Delgado, J. M. R., Roberts, W. W., and Miller, N. E., Learning motivated by electrical stimulation of the brain. *Am. J. Physiol.*, 1954, **179:** 587-593.
5. Lilly, J. C., Injury and excitation by electric currents. A. The balanced pulse-pair waveform. In: *Electrical Stimulation of the Brain* (D. E. Sheer, Ed.). Univ. of Texas Press, Austin, 1958: 60-66.
6. Meyer, J. S., Studies of cerebral circulation in brain injury. IV. Ischemia and hypoxemia of the brain stem and respiratory center. *EEG Clin. Neurophysiol.*, 1957, **9:** 83-100.
7. Michael, R. P., An investigation of the sensitivity of circumscribed neurological areas to hormonal stimulation by means of the application of oestrogens directly to the brain of the cat. In: *Regional Neurochemistry* (S. S. Kety and J. Elkes. Eds.). Pergamon, Oxford, 1961: 465-480.
8. Miller, N. E., Bailey, C. J., and Stevenson, J. A. F., Decreased "hunger" but increased food intake resulting from hypothalamic lesions. *Science*, 1950, **112:** 256-259.
9. Weddell, G., Receptors for somatic sensation. In: *Brain and Behavior*, Vol. I (M. A. B. Brazier, Ed.). American Institute of Biological Sciences, Washington, D. C., 1961: 13-48.