



zational or system level. Here we were concerned with the sites or loci of control and the logic of why those loci are utilized. The other was the cellular level. Here we were concerned with the kinds of cellular mechanisms involved in controlling behavior.

We were afflicted by terminological problems throughout the Work Session. Arguments over what is really learning, which have plagued discussions of the present kind in the past, had been largely laid to rest, because (1) workers in the field have come to distinguish carefully the behavioral end product, "learning," from the central causes of behavioral learning, and (2) they have accepted the fact that the range of behavioral phenomena that one chooses to include as instances of learning varies somewhat according to the tastes of the speaker.

However, the problem word "learning" was replaced at this meeting by the problem word "modulation." Modulation is an ambiguous term because it is used in different contexts to describe changes in at least three different levels of organization. On a purely *behavioral level*, modulation has been used in a variety of ways to refer to a change in response strength, such as might be produced by arousal, motivation, or learning. At the *circuitry level*, modulation may refer to the gating of a motor output, the switching from one motor output to another, or control over the intensity of an output. At the *cellular level*, modulation is used to characterize certain types of mechanisms, such as presynaptic regulation of transmitter release or the postsynaptic regulation of the efficacy of one input by another. It is easy to fall into the error of assuming that modulation at the behavioral or circuit level necessarily involves modulation at the cellular sense. It is also easy to forget that, whereas modulation at the behavioral level may be thought of as a relatively minor adjustment in strength or character of response, a similarly minor adjustment at the level of nerve cells can be responsible for a fundamental event at the behavioral level such as response choice or selection.

One of the purposes of the Work Session was to begin to relate behavioral and circuitry modulation to modulation at the cellular and the molecular levels. To determine the mechanisms whereby various forms of the behavioral modulation are achieved, specific instances of behavioral modulation need to be analyzed at the cellular level. Moreover, to examine the generality of these solutions, the organizers of the Work Session felt it essential to examine, within a common theoretical and experimental context, results derived from studies of both vertebrates and invertebrates.

### Analysis of Mechanisms for Regulating Behavior

#### Mediation Versus Modulation

Although there is overlap in many instances, it may be useful as a starting point in the analysis of behavioral control to distinguish between (1) the simple, direct *mediation* of a response on the one hand and, on the other, (2) the *modulation* or regulation of the strength of this response or the probability of its occurrence. Consider, for simplicity, the case of a monosynaptic reflex response (Figure 1). Let us call the neural machinery that initiates the reflex the *mediating system* or *mediating circuitry*. This circuitry analyzes the stimulus, decides whether to produce the behavior, and generates the motor pattern. In many cases the strength of even simple reflex responses produced by the mediating system can be regulated, i.e., either enhanced or depressed by various factors. It is convenient to refer to the machinery that controls the gain of the reflex (or the probability of its occurrence) as having a *modulating effect* on the mediational circuitry. Such modulating effects could be brought about either through the influence of neuroendocrine or neuronal *modulating circuitry or systems*, which play upon the mediational circuits, or through alterations in the mediational circuitry itself as a result of its own past activity, i.e., *intrinsic* regulating or modulating processes.

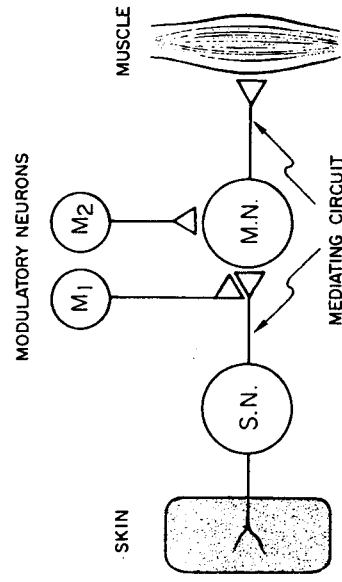


Figure 1. Schematic diagram indicating a simple mediating circuit consisting of mechanoreceptor sensory neuron (S.N.) making a direct connection with a motoneuron (M.N.) to muscle. This circuit can be centrally modulated at two points: on the presynaptic terminals of the sensory neurons ( $M_1$ ) and on the postsynaptic cell ( $M_2$ ). [Kandel]

The same dichotomy can also be established for more complex behavior, such as the recurring behavior involved in feeding or locomoting. Here the mediating circuitry will be more elaborate and will contain the central program for sequencing the behavior. In these more complex instances, there are potentially more parameters of the behavior that might be controlled, and modulation is therefore potentially more elaborate, involving alterations of intensity of various motor components, cycle frequencies, etc., as well as alterations of overall intensities or probabilities of reaction.

Although the distinction between mediation and modulation is often conceptually convenient, it is sometimes not clear how to make it because the distinction breaks down. Consider radio signals. An amplitude-modulated carrier contains carrier and modulating frequencies; but, as frequency of modulation is increased towards that of the carrier, the definition begins not to apply. Similarly, in neural activity, a modulatory synaptic action can be considered that which alters ongoing activity. Yet, with near threshold activation of the modulated activity, the modulatory signal can be the initiator. In rhythmic activity modulation will extend over several cycles; but, if modulation becomes faster again, there is a problem. The definition probably is useful to describe cellular behavior in a variety of systems; but in many of them it is likely that careful manipulation of physiological parameters will lead to situations in which the distinction is obscured.

There was considerable discussion of this problem at the Work Session but not a full resolution. In certain cases one might define as "modulating" that circuitry whose operation does not produce any significant action by itself but that does alter the actions produced by some other "mediating" system. The distinction between mediation and modulation can also, perhaps, sometimes be specified by considering what differentiates the types of stimuli that lead to the mediation of responses from those that produce the modulation of responses. Thus, in the simplest cases the effects of a mediating stimulus are restricted to one response system. By contrast, it might be natural to consider a stimulus that had much more general effects on several related systems (e.g., an appetitive, noxious, or sexual stimulus) as having affected a modulatory system. But, in the final analysis, the distinction is probably useful mainly in those cases where one can easily see how to make it in the first place.

Having tried to distinguish, at least on theoretical grounds, between mediating and modulating circuits, one needs to determine the cellular architecture of each of these circuits in order to address the real question: are the two types of interacting neuronal circuits independent except at their points of convergence? Or is there considerable overlap? Can some neurons be used in different ways (i.e., mediational vs. modulatory) for different behavioral responses? More generally, to what degree is the theoretical distinction an empirically viable one?

Attempts to study the physiology of controlling or "modulating" processes must first (logically speaking) ask about loci of modulating actions and the organization of the systems that impose them; we call these "organizational" questions. As crucial control points are identified, one can then begin to study also the cell-physiological mechanisms of control.

#### Organizational Aspects of Control

*Where and in what way is mediating circuitry altered? Where is the control in a particular mediating system located? Is the locus post-synaptic so that it modulates threshold for impulse initiation in a silent cell or impulse frequency in a spontaneously active (autoactive) cell? Or is the control presynaptic where it can regulate transmitter release? Can a single modulating system act on both sites? Is control exerted primarily on interneurons or can sensory and motor neurons be targets as well? Do systems tend to have special loci, such as, perhaps, "command" neurons, at which modulation due to learning, motivation, occurrence of incompatible activities, etc., all operate? Is control over relatively complex mediating systems usually achieved by producing alterations at a single point in the system or at several points? Such questions probably do not have general answers, because the sites and modes of control over mediational circuitry obviously depend on the organization of the system being controlled.*

Suppose, for example, that decision and motor-pattern-generating networks for different behaviors are parallel and independent, as they may often be in invertebrates (Figure 2A). On-off control of particular behavioral patterns is likely to be easily achieved by adjusting the gain at any *one* of a number of places in this private circuitry for the behavioral pattern in question. By contrast, selective control over

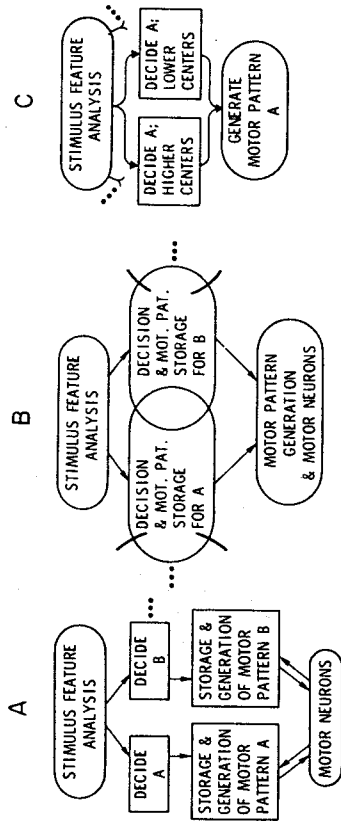


Figure 2. Three modes of organization of a behavior-mediating pathway. A. Lack of overlap of circuitry mediating different behavioral patterns at some level. B. Partial overlap at every level. C. Parallel pathways both competent to mediate the same behavior. [Krasne]

particular behavioral patterns would normally be impossible to achieve via modulation of circuitry for stimulus analysis or final motor paths, because these will normally be used for a number of different behaviors. However, there may be cases where some sensory structures or motor neurons and muscles are used only for single special purposes; in these cases control could be effectively exerted even at the sensory and motor peripheries.

Although parallel and largely independent decision and motor-program storage are the easiest situations for us to envisage, it is possible to construct schemes in which many independent behaviors are mediated by circuitry that partially overlaps at every level of processing (Figure 2B). Decision and motor-pattern generation for a given behavioral pattern would then be a matter of consensual action of a number of elements, many of which are involved in mediating other behaviors as well. Consider, for example, the vertebrate flexion reflex. Many spinal cord physiologists think it is unlikely that there exists a set of interneurons whose members fire only prior to flexion (and not to other reflex behaviors) and therefore signal only the decision to execute that particular sort of response. But, if there are no interneurons unique to the flexion reflex, control of the reflex without altering other behavioral patterns becomes a tricky business, probably having to involve subtle adjustments of synaptic transfer functions at many properly chosen sites throughout the system. Thus, control strategies must be quite different for behaviors whose mediational circuitry overlaps at

every stage of processing with the circuitry mediating other behavioral responses and behaviors whose mediational circuitry is private at some stage of processing. It would also seem that ease of control is fostered by having nonoverlapping decision or motor-pattern-generating networks. This does not mean that there are no advantages to overlapping schemes, but it suggests the possibility that the need for achieving effective control could have placed restrictions on the kinds of mediational circuitry that have evolved.

Another common feature of mediating systems, which has important implications for control, is the frequent existence of several parallel systems that can mediate a given kind of behavior (Figure 2C). For example, behavioral reactions, including learned ones, to simple visual and auditory stimuli can probably be mediated via both cortical and subcortical routes in mammals (Lashley, 1950), and, under certain stimulating conditions, behavioral responses in gastropod molluscs can be mediated by either central pathways or peripheral neurons (see, e.g., Jacklet and Lukowiak, 1974 and Kandel, 1979). Problems of coordination of control between competent levels thus arise and add to the necessary complexity of control systems (see Krasne, 1978).

*Via what routes and means do modulatory signals come?* Modulatory effects could, in principle, be imposed on mediating circuitry by means of classical synaptic excitation and inhibition, by "modulatory" synaptic actions, by direct hormonal action, or by processes intrinsic to the mediating circuitry that change it in reaction to its own past activity. Hormones and effects of past experience can also have primary targets outside mediating circuitry proper and affect mediating circuitry via classical or modulatory synaptic actions, or, perhaps, by secondary (short- or long-range) neurohumoral messenger systems. This wide range of possibilities raised a number of questions concerning whether some routes are more likely than others, either in general or under particular circumstances. For example:

1. What are the purposes for which synaptic modulatory actions are utilized?
2. To what extent is hormone reception (or in the case of learning, primary engrams) located within the mediating circuit itself or in special targets outside of it?
3. When are hormones (rather than nonhormonal regulators) involved in behavior? Hormones are necessary for the physiological or biological function of even the most primitive multicellular organisms. However, hormones become involved in the processes of behavioral

modulation perhaps only in higher invertebrate phyla, such as molluscs and arthropods. This is somewhat expected in the sense that only when animals reach this level do they demonstrate a behavior complex enough to necessitate control of behavioral choice. In higher vertebrates, hormones are important in changing the behavioral state. They induce reproductive behavior; they change the meaning of physiological or sensory inputs by putting the animal in a new (reproductive) context or state. Hormones can also release long stereotyped sequences or programs of behavior (e.g., induction of egg-laying behavior in *Aplysia* and the triggering of emergence of a moth from its cocoon). These hormonal effects on behavior are usually of relatively long duration and have a long latency of onset after the CNS is exposed to the hormone. Hormones have access to the cellular metabolic environment and to the genes, and changes here might be expected to be long-term. In still higher organisms, the nervous system begins to take over many of the functions mediated by hormones in lower animals. For example, in mammals female sexual behavior is strongly influenced by the ovarian hormones; female monkeys, however, are less dependent on these hormones than are lower species, such as the rat, but are more dependent than are human females (Davidson and Levine, 1972). These kinds of systematic changes toward hormone involvement, and then again away from it, would make it worthwhile to study the mechanisms and function of hormones across phyla. This study might lead to an understanding of the particular circumstances under which hormonal rather than neural control is used.

#### Cellular Mechanisms of Modulation

The final question in the analysis of regulation of behavior relates to mechanisms: What are the changes that occur in a cell that holds part of an engram for long-term learning? What sorts of transmitter substances act as modulators? Can any transmitter substance be a modulatory substance or are there special roles in behavior for specific transmitters and specific species of hormones? What similarities and differences exist in the mechanisms of action of modulators that alter synaptic transmission versus altering the endogenous activity of neurons? When and how do modulatory elements exercise their critical action on a target cell? Do they act through intermediary cytoplasmic steps (e.g., cyclic nucleotides) or directly on the cell surface? Is the mode of action of a hormone in nonneural tissue relevant to the action

of hormones in neural tissue; i.e., can the former serve as a model for the latter?

In nonneural cells there are several well-worked out examples of the different ways hormones might affect the nervous system—by acting directly on the genes in one case or by acting through a second messenger in another. These findings might apply to interpretations of a hormone's neural effect. For example, peptide hormones seem to act through second messengers in vertebrates and invertebrates, whereas steroid hormones generally must be transported directly to the genes to have an effect. Does this division of action also hold when we are considering the action of these hormones in causing behavioral changes? In many cases the time course for the appearance of behaviors influenced by peptide or steroid hormones is consistent with what is known of their mode of action in other tissues. Do modulations that have a given time course tend, perhaps, to have common cellular mechanisms whether invoked by hormones, neural modulators, or past activity of the changing cell itself? For example, do monoaminergic synapses and peptide hormones cause similar physiological events in the target cell? Figure 3 compares the amount of time required for a peptide hormone (the eclosion hormone) and a steroid hormone ( $\beta$ -ecdysone) to release

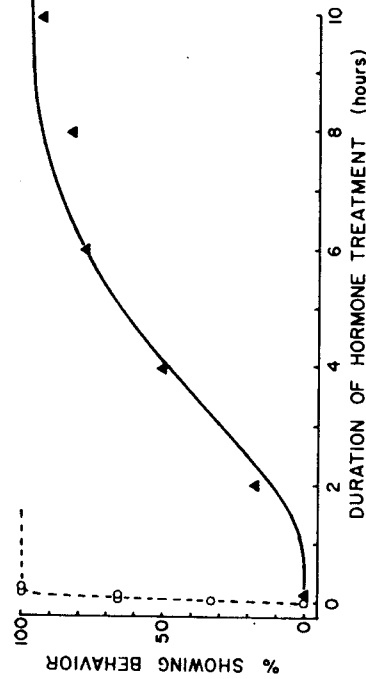


Figure 3. Comparison of the length of exposure needed to induce behaviors by a peptide hormone (eclosion hormone, O) and a steroid hormone (ecdysone, Δ) in moths. The data for the peptide hormone are for the triggering of eclosion behavior in adult moths and were determined in vitro (Truman, 1978b). The steroid data were obtained for the induction of wandering behavior in larvae and were estimated by infusion of hormone into unrestrained animals. [Dominick and Truman]

two different behaviors in moths. In the case of the peptide induction of adult emergence behavior, only a few minutes' exposure is required and the behavior begins within 15 min (Truman, 1978b). This rapid action is consistent with a second messenger system, and the data presented in this *Bulletin* indicate the involvement of cyclic guanosine monophosphate in this response. By contrast, the steroid causes wandering behavior in larvae, but its presence is required for at least 4 hours and the behavior itself does not appear until about 12 hours.\* This long time course is sufficient to allow genomic events to take part in this response.

Using specific examples, the participants next examined the various classes of behavioral modulation. In each case, the instance of modulation had been brought, at least to some degree, to the cellular level; in fortunate instances the molecular level was approached. First, they examined simple behaviors (defensive reflexes) and simple forms of neural modulations (arousal, sensitization, nonassociative learning; see the first section of Chapter II). They then moved on to more complex forms of neural modulations (associative learning) of simple behaviors (second section of Chapter II). Next, they considered the neural modulation of complex and appetitive behavior (Chapter III). Finally, they reviewed the problem of hormonal modulation (Chapter IV). In discussing each of the three topics, the participants endeavored to select current examples of behavioral analysis in both vertebrates and invertebrates in an attempt to extract general principles.

## II. ELEMENTARY BEHAVIORAL RESPONSES

### Simple Forms of Modulation: Attention, Arousal, and Sensitization

Introduction: E.R. Kandel

A characteristic feature of most behavior is that it can change in strength. Changes in response strength that are not attributable to maturation, injury, or fatigue are generally grouped into two classes: (1) learning—a change in behavior attributable to the previous history of exposure to a stimulus, and (2) motivation, drive, or state—a change in behavior attributable to an alteration in the internal homeostatic state of the animal. In this section we will primarily consider the first class, learning. Learning refers to a hierarchy of processes that range from relatively simple nonassociative forms, such as habituation, dishabituation, and sensitization, to more complex associative learning, such as classical and instrumental learning, to even more advanced cases, such as insight learning.

We begin our consideration by examining an instance of non-associative learning, arousal, and a critical component of arousal, sensitization, which is related in different contexts to both learning and motivation. Arousal is a common way in which behavior is modulated. The cellular study of arousal is therefore interesting for two reasons: (1) it can help to clarify an important but vague behavioral construct, and (2) it could lead to the exploration of a large and common class of neural mechanisms for modulating behavior.

Historically, the concept of arousal developed from the well-known observation that most stimuli, particularly weak, familiar ones, have a restricted influence; they affect only a very limited range of behaviors and not others. By contrast, other stimuli—particularly novel, aversive, or appetitive ones—have more general effects. Although they may have a direct mediating action, these broadly effective stimuli also alter an animal's responsiveness to other stimuli. Often, these stimuli can modulate a widespread family of responses (Figure 4). Moreover, the modulating effect sometimes persists for minutes, and even hours, and is therefore reminiscent of a learning process. However, unlike the

\*O.S. Dominick and J.W. Truman, unpublished observations.