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BRAIN MECHANISMS IN CONDITIONING AND LEARNING

A report of an NRP Work Session

chaired by

Robert B. Livingston

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BRAIN MECHANISMS IN CONDITIONING AND LEARNING

A report of an NRP Work Session
held March 15-16, 1965

by

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FOREWORD

Participants at the Work Session were invited to restrict themselves to higher mammals and the corresponding brain mechanisms thought to be involved in conditioning and learning. Thus, this report is complementary to one entitled, "Simple Systems for the Study of Learning Mechanisms," organized by T. H. Bullock (1966). The present Work Session was easily organized. Everyone invited was able to attend. Instead of presenting formal papers we spoke to an outline as if it were an agenda:

WORK SESSION PROGRAM OUTLINE

Growth of Concepts Relating to Brain Mechanisms Involved in Conditioning and Learning

		Panel of Participants as follows:
1.	Growth of concepts of brain mechanisms in the light of emerging techniques	Walle J. H. Nauta
2.	Growth of concepts of brain mechanisms in relation to conditioning	Jerzy Konorski
3.	Growth of concepts of brain mechanisms relating to other forms of learning	Donald B. Lindsley
4.	Growth of concepts of brain mechanisms relating to understanding human behavior	Vernon Rowland

I. REINFORCEMENT, IN TERMS OF BRAIN CIRCUITRY

A look at internal generators of conditioning and learning

A. Operational definitions and typical examples of:

Motivations
Appetites (appetition)
Drives (drive reduction, satiety)
Reinforcements (positive, negative)
Secondary reinforcements

(What do we mean operationally, phenomenologically, by these expressions?)

Discussion leader: Neal E. Miller

B. Neuronal organization and typical examples of:

Appetitive centers
Central reinforcement centers
Circuits presumably involved in unconditional stimulus invasion of brain circuits
Circuits presumably involved in conditional stimulus invasion of brain circuits

Discussion leader: W. Ross Adey

C. Intimate structure and function of circuits involved in conditioning and learning

Central events taking place during orienting response
Intimate processes of reinforcement
Central changes taking place during conditioning and learning, in terms of general circuitry
Central changes affecting sensory input pathways during conditioning and learning

Discussion leader: Frank Morrell

D. Impressions and implications

Changes implied in theory (emergent notions, alternatives)
Implications for experimentation
(Implications for NRP activities)

Discussion leader: Donald B. Lindsley

II. REINFORCEMENT, IN TERMS OF TIME RELATIONS

A look at time dimensions of conditioning and learning (and forgetting)

A. Operational definitions and typical examples of:

"Learning curves"
"Extinction curves"
Requirements for one-trial learning
Limitations on CS-US pairings
(Why not backward conditioning?)
Timing of Pavlovian "internal inhibition"
(What does this imply?)

Discussion leader: Eliot Stellar

B. Neuronal organization and temporal dynamics of:

Changes occurring along sensory, reticular activating, limbic, cortical, and other components during conditioning and learning
Changes in these circuits in relation to:
orienting response
early and later conditioning and learning trials
learned performances
What happens to these dynamic circuits when novelty is introduced?
How are learned performances reorganized into new patterns when experimentally demanded?

Discussion leader: Clifford T. Morgan

C. Intimate structural and temporal dynamics in terms of the natural history of typical conditioning and learning experiences, with typical examples.

(This session was planned for review and overview, and for the contribution of additional pertinent evidence)

Discussion leader: Mark Rosenzweig

D. Impressions and implications:

Changes implied in theory (emergent notions, alternatives)
Implications for experimentation
(Implications for NRP activities)

Discussion leader: Walle J. H. Nauta

Discussion yielded exciting and abundant contents and a fairly complete critical transaction relating to the subject matter. Time was our most precious commodity: each discussion period had to be overcommitted for the allotted time. A typescript was redacted by Dr. J. Carolyn Register from a tape recording made by Mr. Wardwell Holman. The typescript was conspicuously abbreviated, yet it filled more than 300 pages. This document was further condensed and reorganized and distributed to all participants for their correction and further reduction; nearly everyone had something to defend and something to deny. This manuscript was severely abbreviated and further reorganized with the help of Mrs. Anne Rosenfeld.

We did not seek consensus, but instead aimed at providing a working document that would reflect the limits and variants of discussion among experts. The Work Session chairman was perhaps least qualified to cover the subject matter but was selected because of being an amateur (in the true sense of the word, one who loves) regarding the field. He deliberately encouraged simplification during discussion and further simplification during editing. The effect we strived for has been to apply a reducing lens to a most extended and complicated field. The reader is forewarned that this reduction process, as in optics, yields spherical and chromatic aberrations; some will say, with justice, that the lens itself is soiled, thus blocking some perfectly good evidence and introducing some obfuscating fantasies. Such aberrations have been only partially corrected by sending the penultimate draft out for "final retouching" by each participant.

The Introduction to the Work Session was deliberately chosen to be panoramic and historical in context for the purpose of leavening subsequent discussion of the contemporary flux of ideas. The main criterion for retaining discussion in the final draft was not whether everyone could agree but whether such representation might lead to fruitful lines of experimentation or rebuttal. Order of presentation was largely sacrificed in favor of bringing together discussions of closest relationship. At the same time, an effort was made to preserve the style of an open dialogue held by worthy men who were launching strong views among one another. This necessitated tolerance of some disorder and inconsistencies. The reader, we trust, is an expert at broken-field running; this Work Session was a deliberate experiment in group transaction, including the reader.

I. INTRODUCTION

Of all realms of knowledge none is more urgently needed than comprehension of what underlies constructive human adaptation. Education is only one of the bottlenecks. More fundamental is our lack of insight into intimate processes of human perception, judgment, and action, and especially into human conditioning and learning. It is not sufficient that we attempt to understand learning in general; we need to achieve practical insight into how learning takes place in man. Even a modest advance along this line of research would be revolutionary. Furthermore, the search itself is unparalleled fun!

Man seeks intellectual adventure and practical advantage through self-examination and the study of his closest neighbors in the evolutionary procession. Mammalian brains and behaviors show such notable consistencies that we can be confident their study will aid us in recognizing what brain mechanisms are involved in human conditioning and learning.

During learning, certain regions of mammalian brains become differentially engaged in distinguishable activities in distinctive sequences. These gross brain events apparently reflect the grand "circuit strategy" of nervous events involved in learning. Microscopic, sub-microscopic, and molecular events underlying learning constitute the local "tissue tactics" of learning. "Tissue tactics" may be similar in all forms of learners, invertebrate as well as vertebrate. During evolution, vertebrate and especially mammalian brains enormously expanded and specialized many particular regions for neuronal transaction. Particular brain circuits proved advantageous for interrelating and coordinating these areas wherein minute, nimble processes account for learning and memory.

It is assumed that behavior relating to motivation, appetite, reinforcement, conditioning, learning, and memory is exhibited by all vertebrates, and also probably by most invertebrates, even though these latter have nervous systems of radically different structural organization. Even insects possessing brains with only a few thousand nerve cells exhibit what may be analogous behavior (Bullock and Horridge, 1965; Dethier, 1964).

One common denominator in the brains of all animals exhibiting conditionable behavior is the neuropile, an intricate interdigitation of fine processes of neurons and glia. The neuropile is made up of dendritic and axonal arborizations

and synapses. Because the neuropile is made up of an incredibly fine feltwork of interlacing processes, it defies electrophysiological and electron microscopic disentangling. Yet because it is a common denominator among the brains of such a magnificent range of learners, the neuropile is considered by many as the prime locus for the changes responsible for conditioning and learning.

Neuropile - Possible Site of Learning Processes

Years ago, Herrick, Coghill, and others inferred that the neuropile may be the likely site of learning processes. They perceived that learning might consist of minute cellular redistributions within the neuropile. These could modify probabilities of conduction among entrained pathways. There is as yet scant evidence for such postulated morphological changes and the scale and nature of such changes is entirely unknown.

It is widely held that genetically organized (embryologically built-in) connections are so ubiquitous throughout nervous systems that there are no limits to potential transmission of impulses among any given loci in the nervous system. Perhaps these potentially available, built-in circuits can be strengthened and otherwise shaped during learning by means of only slight, subtle, local structural modifications. Such changes might be governed by molecular controls in the perikaryon, or controls acting out among the terminal branches of neurons, or by non-neuronal glia. Perhaps these changes come about as a result of persisting tendencies for cellular growth faced with competition for space. Perhaps cells that are active in signal transmission show differential propensities for growth. The exciting potentiality is that neuroscientists in a number of converging disciplines may be close to identifying and manipulating the mechanisms that account for such important processes.

One goal of this Work Session was to consider afresh the evidence for alterations in the overall patterning of brain activity during conditioning and learning. We aimed to look at the "circuit strategy" involved in conditioning and learning. It was also a central intention to utilize the "zoom lens" of interdisciplinary capabilities of the Neurosciences Research Program, to bring to mind simultaneously what is known about both the macro- and micro-scale processes involved in conditioning and learning. We considered both the global physiological systems and the molecular component processes, and attempted to bring these into meaningful relations with one another.

Some Necessary but Insufficient Conditions for Learning

The background conditions of the nervous system in preparation for learning, although often overlooked, are crucial. These involve processes controlling wakefulness and sleep, attention and distraction, orientation and habituation, appetite and satiety, etc. It is not enough to present certain stimuli or to provide access to a loaded lever. Background states affect the availability of certain internal processes crucial for both classical and operant conditioning. Internal brain processes must be favorable.

This requirement may be fairly subtle: lack of adequate sleep, lack of sufficient hunger in a food-reward situation, or the wrong food, inattentiveness, visceral unrest, various adventitious shifts in bodily state, and other factors can all be disruptive. These indispensable internal conditions constitute background influences which have their effects prior to and overriding any presentation of stimuli or reinforcements. Ordinarily these factors are controlled for by methods such as keeping the animals 15% underweight, not having too many trials at any one session, etc. In short, conditions within the individual subject are of paramount importance in addition to the much-publicized external conditions of the experiment.

Work Session participants sought to establish operational definitions for these necessary internal states as well as for the external events. They gave particular attention to the temporal events, internal and external, associated with the learning process. The machine-like, predictable performance of subjects in a traditional learning paradigm is predicated on certain specifiable physiological conditions: an awake, alert, hungry (or otherwise specially motivated), goal-seeking organism, one that is "at ease" in the given surroundings. An important prerequisite to understanding brain mechanisms involved in conditioning and learning is understanding in detail the biological repercussions of these specific internal preconditions for learning. Perhaps learning involves mainly the setting up of appropriate internal conditions. Learning may be practically unavoidable whenever such preconditions are achieved.

Coordination between Phylogenetically New and Old Systems

Learning obviously involves systems of neurons which

are complexly knitted together, containing pleurisynaptic pathways having elaborate multiple feedback and interconnecting loops. Successful conditioning apparently depends on signals entering the nervous system along both specific and nonspecific sensory pathways. These nonspecific pathways are phylogenetically older and are located inside, that is, medial to the specific pathways. During relatively recent evolution the classical sensory pathways were applicated upon already existing structures which we must recognize were already highly successful in the government of learning and conditioning. Fishes, without any neocortex, learn many cues quite as readily as cats, monkeys, and men.

Medial, nonspecific pathways include limbic, hypothalamic, and granular frontal cortical circuits along with the brainstem reticular formation, the isodendritic central core of the neuraxis (Ramón-Moliner and Nauta, 1966). These medial systems may be understood to fulfill an indispensable role by providing both the strategic and tactical backgrounds essential for learning. The classical sensory pathways may be understood as conveying particularized sensory messages which provide a greater range and accuracy of discrimination.

Background states of the nervous system evidently affect the way incoming sensory signals are processed and distributed among central circuits. Phylogenetically old systems seem designed to provide the "biological significance" which modulates incoming signals and otherwise contributes to shaping the individual's response, his outward expression, and general comportment. Medial systems also appear to provide preparatory messages for cortex; that is, when novel or biologically significant stimuli are presented, an electrical d-c shift takes place across the cortex. Morrell (1961a) in experiments spawned by Rusinov's discovery of what Rusinov (1953) called the "dominant focus effect," has succeeded in experimentally imitating the d-c shift and demonstrating that it markedly affects the activity of cortical units in ways that look like bona fide local conditioning. This effect is characterized by a change in excitability of cortical cells so that they tend to fire more readily and more rapidly; peculiarly enough, the affected circuits tend to repeat the activity patterns that just preceded.

The Rusinov and Morrell evidence has been reinforced by work in other laboratories, as will be apparent in the following pages. A number of such experiments imitate many features of the overall learning process. Since they involve relatively localized brain circuits they contribute greatly to our

confidence that there is abundant plasticity in certain abbreviated nervous system circuits.

Sensory signaling that takes place during conditioning involves at least two differentiable sensory channels: specific and nonspecific. The nonspecific channel apparently establishes background conditions for widespread reception and retention of particular sensory and motor signals which may enter by way of both specific and nonspecific channels. Both specific and nonspecific channels involve both cortical and subcortical stations. The net result of all this is an alteration in distribution and influence of incoming and outgoing signals which increases the likelihood that certain responses will occur in relation to certain previously experienced stimuli.

It does not matter, apparently, whether the learned signals originate outside the body, or internally as evoked by central electrical stimulation. It also does not matter, apparently, whether the biological significance of the experience is generated by externally rewarding or punishing events, or by central stimulation. These radically different situations are all conducive to learning. The most ambiguous topic discussed during this Work Session was the question of the nature of reinforcement: what are the mechanisms underlying biological significance for one individual at one particular time? Participants at this Work Session considered carefully where and how external and internal reinforcement has its indispensable effects.

II. GENERAL CONCEPTS RELATING TO CONDITIONING AND LEARNING

Growth of Concepts Relating to Brain Mechanisms Involved in Higher Nervous Processes

Part vs. Whole

Evolution of scientific insight depends quite as much on conceptual liberations as it does on technical improvements. Searching for the latter usually depends on the former. Growth of concepts and improvement in techniques feed back positively into one another. An important conceptual liberation stems from Descartes' assignment of "soul" and all mentalistic attributes to the pineal gland. This left the rest of the nervous system an "automaton," susceptible to physiological exploration as mechanism. Descartes also instilled widespread confidence that any mechanism, no matter how complex, can be understood through analysis of its components, that is, through disassembling the mechanism, as one would take apart a clock, and studying its interactions, part with part. From such an analysis he postulated that one can eventually obtain an understanding of the operation of the whole.

These assumptions were facilitative, perhaps indispensable antecedents to physiological investigation of the living brain. Their far-reaching effects are comparable to the early Greek assumption that at death the soul flies away, leaving behind a disjecta membra which can be studied as anatomy without violating the individual whose soul once "inhabited" the body.

Three hundred years ago Descartes was contesting the Aristotelian view that living beings functioned as a whole. Aristotle's notion discouraged analysis of living systems in terms of internal mechanisms. In our day it is becoming increasingly apparent that Descartes was perhaps too hasty in throwing Aristotle out altogether. Great complexity, particularly when it involves abundant feedback, is known to provide mechanisms with the goal-seeking attributes that Descartes was trying to eschew (Teleological Mechanisms, N.Y. Acad. Sci., 1948). Both Aristotle's systems analysis and Descartes' component analysis are proving conceptually indispensable to modern explanations of brain functions. One without the other is inadequate, like the odd half of a pair of scissors.

Biological Continuity Throughout Evolution

A further enormous impetus to understanding brain mechanisms was provided by 19th century generalizations relating to evolution. These revealed the likelihood of analogous relations obtaining between man's brain and the brains of other animals. Descartes distinguished man as the only creature not a complete automaton, the only one possessing a "rational soul." Darwin indirectly breached that boundary. Students of developmental and comparative anatomy, following Darwin, laid great emphasis on the developmentally late to appear and phylogenetically recent neocortex. Goltz performed the important experiment of entirely removing neocortex, but he fell into the Cartesian trap of assuming that the absence and derangement of functions observed in the decorticate dog reflected functions of the cortex that had been removed.

It was some time before investigators began to realize that ablation demonstrates not the functions of the missing parts but instead the functions of the remainder of the nervous system in the absence of those parts. In other words, what remains no longer functions as it did before. Notions that assumed an evolutionary hierarchy of parts, with cortex on top, coupled with ideas of specialized cortical attributes made famous by Gall and Spurzheim, became crystallized through phrenological enthusiasm for studying skull bumps (which presumably reflected differential cortical development). These trends contributed to fixing our attention on the idea that cortex is that part of the brain responsible for "higher nervous functions," a notion that continues to have conspicuous momentum. We can be somewhat more guarded about this notion without entirely abandoning it.

Optimism -- Pessimism -- Optimism

In Switzerland, Forel invented a microtome which could make thin slices of brain tissue about the same time that German chemists began producing organic dyes that provided differential stains. These techniques permitted magnificently detailed anatomical differentiation of parts. This, in turn, spawned an optimism that mental and neurological illnesses would soon be identifiable in terms of deranged circuitry. Indeed, mental hospitals soon thereafter came under the jurisdiction of anatomists and pathologists. (In our day this is happening again, but this time with neurochemists and pharmacologists.) This optimism was short-lived; confidence was quickly extinguished by the complexities revealed, and

especially by the fact that vanishingly few characteristic microscopic defects could be predicted in the brains of persons suffering from mental illnesses. Unwarranted optimism was followed by waves of what may be undeserved despair that nothing could be learned through a biological approach to psychological phenomena.

Subsequent conceptual liberations and technical gains have yielded renewed optimism. The possibility, improved in Switzerland by W. R. Hess, of implanting electrodes for stimulation and recording over indefinitely long periods in waking animals in dynamic behavioral circumstances was revolutionary. Opportunities thus provided are almost infinite. Conceptual liberations have encouraged the re-entry of psychological terms into neurophysiological practice and literature, and vice versa. It has become meaningful once again to talk about brain mechanisms, physiological and molecular, involved in sleeping, dreaming, waking, consciousness, perception, motivation, conditioning, and learning. It remains to be seen whether this current optimism is justified!

Growth of Concepts of Brain Mechanisms Involved in Conditioning

Konorski opened discussion on the development of scientific thought regarding the role of brain mechanisms in conditioning. The idea of physiological explanations for behavior and mental processing was well articulated in Sechenov's famous book Reflexes of the Brain published in Russia in 1863. In Germany, Wundt's treatise, Grundzüge der physiologischen Psychologie (1876), claimed to have established a new domain for science, although Wundt's first attempt to bridge the gap between psychology and physiology appeared in 1862, in his Beiträge zur Theorie der Sinneswahrnehmung. In France, the book of J. Luys, Des actions reflexes du cerveau appeared in 1874, while his fundamental and most inspired work, Le cerveau et ses functions, was published in 1878. Reading these works, one is struck by their thoroughly modern character and their insightful conception.

Pavlov not only believed that a physiological approach to the study of mental processes was sound and reasonable, but, with co-workers, completed a stupendous amount of experimental work in this new field. Pavlovian studies on higher nervous activity began about the same time as Sherrington's analysis of reflex mechanisms of the spinal cord and brain stem. Because of a lack of knowledge of cerebral physiology,

Pavlov proceeded by developing entirely independent hypotheses to account for cerebral control of conditioning.

Differences in Interpretive Traditions

Experimental studies of animal behavior similar to those of Pavlov were undertaken in the United States by behaviorists who, like Sechenov and Pavlov, avoided speculation about mental experiences. However, the Americans also felt reluctant to invent hypothetical physiological mechanisms. As a consequence, when the importance of Pavlovian experimental findings was beginning to be appreciated by American students of animal behavior, and the operational terms used by Pavlov, such as "conditioning," "reinforcement" and "extinction" were being assimilated, there was a neglect of Pavlovian ideas dealing with the brain mechanisms postulated to underlie these phenomena. This attitude toward his physiological theories infuriated Pavlov.

For Pavlov, physiological explanations constituted the goal of his research; he considered the experimental undertakings as merely the means to understanding brain mechanisms. Pavlov was strongly disappointed by the fact that most physiologists did not recognize his work as physiological, but thought of it as psychological. A well-known German physiologist declared that "bedingte Reflexe, das ist keine Physiologie." The fact that most textbooks of physiology still neglect conditioned reflexes is evidence of reserve toward physiological interpretation of Pavlov's experiments.

In recent years this situation has changed radically; Pavlovian experimental methods and conceptual achievements relating to physiology of the brain have gained many adherents. Knowledge of brain function obtained by electrophysiological investigations has reached the point of dealing conclusively with some of the problems raised by Pavlov 50 years ago. We can now observe some of the physiological processes underlying the formation of conditioned responses, their generalization, differentiation, and their extinction by non-reinforcement.

A number of physiological, biochemical and biophysical mechanisms to explain conditioning have been proposed recently. These hypotheses must, of course, not contradict knowledge of the structure and function of the nervous system; but they also must conform to the experimental facts obtained by analyzing behavior. They must explain, for example, why only an overlapping sequence of a conditional stimulus (CS) followed

by an unconditional stimulus (US) leads to conditioning, whereas a completely simultaneous pairing or a reversed overlapping sequence does not; why repeated omission of reinforcement leads to suppression but not annihilation of the conditioned response (CR); why a lack of appropriate drive makes conditioning impossible; and why partial reinforcement may improve an instrumental or operant CR but is usually detrimental to a classical CR.

It may be bootless to attempt an all-inclusive definition of conditioning and learning or to propose artificial distinctions between them. From an operational point of view, everything depends on the specific methods employed, whereas linguistic conventions are only gradually affected by new insight. Participants agreed that what are generally subsumed by the terms "conditioning" and "learning" overlap almost completely. Gestalt theory, according to Lindsley, considers learning to be a trial-and-error process whereby insight is gained (Koffka, 1924; Köhler, 1925, 1929; Hilgard, 1948). Grastyán considers insight learning to be perhaps the only form of learning not subsumed by conditioning.

Toward a Definition of Learning

Miller attempted to narrow definition of what he called "Grade-A certified learning." He sought consensus that whatever phenomena met this definition would be considered learning, although not all learning might fit this definition. Miller defines learning as involving functional connections between stimulus and response that are "reasonably specific and reasonably permanent." If "something" done or occurring in conjunction with a stimulus (or a whole stimulus situation), produces a response that is thereafter more likely to take place in relation to that stimulus, but not to other different stimuli, one can say that learning has occurred. If appropriate operations can cause R_1 to appear to S_1, and R_2 to S_2, while the converse operations can cause R_2 to appear to S_1, and R_1 to appear to S_2, we can be highly confident that we are dealing with learning. Another feature of learning is that the reinforcing event (the "something" referred to above) must occur with reasonable contiguity either after S is presented (in classical conditioning) or after R occurs (in instrumental learning) (Miller, 1959).

Learning vs. Lesion Effects and Reflexes

An example that does not meet these criteria for learning involves changes in behavior due to placement of a lesion

in an animal's brain. This behavioral effect is seen in a variety of stimulus situations and tends to be fixed in character. Nauta added that extinction phenomena, involving a procedurally induced alteration or apparent disappearance of a conditioned response, help to distinguish learned from reflex responses. The latter may be modified according to physiological states of the animal but not properly extinguished. Morgan stated that learning may actually be permanent whereas apparent extinction may involve new learning.

Learning vs. Maturation

Galambos sought to challenge Miller's definition by citing as an example the maturation of the suckling reflex in a human fetus. At an early stage, touching the lips with a straw (S) yields no movements of the mouth (R). A few days later the same S_1 yields a specific, local R_1. Over succeeding days, S_1 can be applied farther from the mouth (S_2, S_3), as on the ear, and still elicit the suckling response (R_1). Miller stressed that for "Grade-A" learning one should be able to cause any S to yield any R and to elicit any R from any S. The fault in equating maturation with learning lies in the fact that in maturation the S-R pattern always follows the same sequence, i.e., lip-touching always produces suckling. Although it can be arranged that touching some other part (the ear) can induce suckling, lip-touching consistently yields suckling and not some other response.

Morgan considered it unlikely that nature would employ two different mechanisms, one for differentiation and maturation, and another for learning. Even though the definition of "Grade-A certified learning" may be used to rule out maturation, when we look at the process of maturation, it is fairly obvious that nature provides during early development for all of the initial capacities of the organism, including the capacity for those plastic adaptations we call "learning." In the main, this involves internally determined organization; but even in embryonic life, especially in higher organisms, the environment participates increasingly in completing the development of these initial capacities. During neonatal life, we can observe that imprinting is important for the development of skills and social attachments. Maturation brings organization to the point of potentiality, but its final full realization requires individual experience and practice closely resembling, if not identical with, learning.

Even the smallest circuits of nervous tissue in which we can test and find learning undoubtedly include processes

for both what we call "embryogenesis" and "learning." Morgan proposes that these would be identical except for the mechanisms of initiation or triggering. Embryogenesis would be initiated by DNA-RNA processes from the perikaryon; triggering of plastic reorganization or continuing organization of terminals might be affected according to individually idiosyncratic (local molecular) experiences. These latter might even affect the same nucleic acid processes somewhere "downstream" from DNA.

Grastyán suggested that there may be two types of learning both of which would fall within Miller's definition: in one, the response already belongs to the repertory of the animal and the learning process involves connections affecting largely the sensory side; the other involves a new motor response pattern elicited by a stimulus that previously produced a different motor response.

Schmitt expressed the concern of biochemists and biophysicists with respect to such terms in a definition of learning as "reasonably" specific and "reasonably" permanent. After finding a chemical change relating to some behavioral procedure, how can we be confident that this change is related to learning when the latter can apparently be so ephemeral and plastic?

Stellar responded that for chemical studies, one could easily arrange conditions so that the behavioral changes would be quite permanent. Following such procedures, the animal could be kept for its full life span without further training; its learned response could be obtained with great constancy whenever desired. Even after an animal is subjected to extinction procedures, and on testing does not show the learned response, there is evidence that the mechanism has merely been covered up and that the learning is still retained (with chemical correlates presumably still retrievable?) despite the disappearance of the outward response.

Learning vs. Immune Reaction

Suggestive similarities exist between learning and immunological phenomena: There are specific immunological challenges (S_1, S_2, S_3, ...) and specific responses (R_1, R_2, R_3, ...) with cross-reactions also possible. The immune response, although generally thought of as being permanent, may require reactivation (reinforcement?) and is subject to desensitization (extinction?). Specificity may be quite impressive.

Experiments reveal that an animal may respond not only in relation to a specific chemical challenge, but in some situations may so respond only at one time of day and not at another. Miller conceded that if the immunological response can be made specific to a tone by one kind of treatment and to a light by another kind of treatment he would consider this evidence for learning.

Shashoua asked whether coupling a hapten group with a carbohydrate and then coupling the same hapten with a protein would be analogous to S_1 and S_2. Miller would take some recognizable response and then canvas to find what might constitute effective stimuli for that animal. For example, whether or not polarized light is a stimulus for a bee can be tested by observing whether a specific response, such as flying in a certain direction, can be made dependent on the polarization of light. Taking the hapten combination, if one could make a rat turn to the left when it is given a hapten combined with carbohydrate, and to the right when it is given a hapten combined with protein, then these would constitute stimuli for the rat and learning experiments could be done.

Plasticity

According to Konorski, the term "learning" is not very useful because it means so many vague things in French and English and, at the same time, is quite restrictive and limited in meaning in Polish, Russian, and German. He would prefer to substitute the term "plasticity" of the nervous system, "plasticity" of behavior, etc. Konorski believes that we can provide a general definition for plasticity which is exhaustive and inclusive: plasticity is "a change in response of an organism or its parts (perhaps just nerve impulses and not necessarily any overt response) to a stimulus, the change being due only to repeated presentation of that stimulus (the n may be as few as one), in combination with other stimuli (combination may include a stimulus combined with nothing)." Trauma, fatigue, sensitization and other impairments are to be excluded. There may be learning of classical conditioning, instrumental conditioning, habituation, extinction of conditioned reflexes, or increase of a learned response.

Two processes are to be recognized: plasticity and excitability. Plasticity concerns the permanent change in the nervous system. Sensitization concerns excitability states not considered to involve learning. For Stellar, the problems of definition are most troublesome in reference to any organism not previously studied, for example, paramecia or planaria.

Where the properties of a species are not known, one can readily be fooled by such phenomena as sensitization.

Question: Backward Conditioning?

Konorski considered the question of backward conditioning to be resolved by the work of Varga and Pressman (1963) and by Lelord (personal communication). There are experiments in which CS's delivered after US's eventually produce CR's but in a low and unstable percentage. Varga and Pressman presented the US and CS in random order, widely separated in time, and obtained the same result. Their work implied that backward conditioning is not truly backward but that a slight degree of unstable conditioning emerges from the fact that two stimuli, CS and US, are both presented in the same general situation. Lelord confirmed this. Konorski calls this type of phenomenon a "coexistence conditional reflex," because CS and US coexist in the same situation and thereby become weakly associated with one another.

The main fact about so-called backward conditioning is that if there is a conspicuous overlap between CS and US with CS leading, conditioning is very easy. If there is complete overlap or no overlap, and particularly if the CS is presented after the US, conditioning is very difficult. Between highly successful and highly refractory learning experiences, the jog in time relations may be small, involving a change of only a second or considerably less; yet it can produce a learning curve stable at 100 percent conditionability which abruptly falls practically to zero.

A study by Nagaty (1951) using operant conditioning techniques was described by Miller as providing further evidence for unidirectional effects in learning. Nagaty found that a reward coming immediately after a bar-pressing response reinforces the response whereas a reward coming immediately before the response has no effect. Thus, both operant and classical conditioning techniques provide evidence that the nervous system is organized in such a way that the time-sequencing of experience makes a colossal difference. Olds also emphasized the unidirectionality of reinforcement effects. There is not only failure of backward conditioning but also failure of simultaneous presentations of CS and US to produce conditioning.

Question: One-trial Learning?

During discussion of the significance of time in regard

to learning, Stellar asked whether "one-trial learning" exists. He believes that it does, but that there are probably very different mechanisms for different instances of one-trial learning. One way of obtaining one-trial learning, which he cited as being similar to what is seen in man, is Harlow's (1949) technique of showing a novel problem to a sophisticated monkey (which has made hundreds of different discriminations), but a novel problem of a kind similar to those he has previously learned. The monkey in this situation can often make the correct discrimination on the basis of one trial.

Morgan emphasized that although in Harlow's experiments the actual measure is one trial, it depends on very sophisticated prior learning. The animal has learned "the rules of the game." The experimenter does not change the rules every trial. What appears to be one-trial learning is, in this case, an artifact. Stellar agreed that from a neurological point of view it certainly is artifactual and that one-trial learning cannot be usefully analyzed unless more is understood about the brain changes induced by the processes of sophistication. Konorski suggested, and Stellar agreed, that if all conditions for learning a given discrimination are fulfilled, then all preliminary problems are solved and one-trial learning becomes the rule rather than the exception. Konorski added that if an animal has been conditioned by a series of many trials to respond to one stimulus with a specific response, it will learn in many fewer trials to make the same response when a different stimulus is introduced.

Stellar referred to the importance of punishment in other types of one-trial learning. If an animal is traumatized when it is in a meaningful situation that fits its natural repertory, it will not forget the trauma. This is what Jarvik and Essman (1960) have tried to demonstrate by putting a mouse on a small perch, high enough so it does not jump off, then lowering it down toward a shock grid. When the mouse steps off the perch it receives a strong shock. Normally a mouse will step down within a few seconds after the perch arrives within an inch of the floor; but on the second trial after a shock experience, even after some days of delay, the mouse will stay on the perch for a criterion period of about 30 seconds.

Other methods of producing one-trial learning were used by Skinner (1938) whereby an animal is traumatized during a learned response such as pressing a lever to obtain food or water. This technique takes advantage of prior training and imposes on the learned performance an inhibition induced by

punishment. Other examples of one-trial learning came from Miller and his students (1944) who trained rats to run down an alley to obtain food and then gave them an electric shock at the goal. In this case, the learning involves inhibiting performance of a well-learned response. While such inhibition can be produced by a single strong electric shock, the results are much more stable and reliable if a weak priming shock that is not strong enough to cause the rat to stop is given on one trial and a strong shock on the next. Chorover and Schiller (1965) and Quartermain, Paolino, and Miller (1965) have confirmed one-trial learning in rats in situations analogous to that employed by Jarvik and Essman (1960) with mice.

It was generally accepted that a satisfactory theory of learning and memory must be able to account for such kinds of one-trial learning. Morgan emphasized that if the nervous system were already organized so that most learning were one-trial learning, organisms would be extremely unadaptive. There needs to be some confirmation of environmental consistency among events if conditioning is to yield coherent behavior. Although one-trial learning is interesting and needs to be accounted for, it is biologically advantageous that most learning <u>not</u> be one-trial learning. Indeed, if prior sophistication is taken into account, there probably is little or no one-trial learning.

III. REINFORCEMENT

Toward a Definition of Reinforcement

Reinforcement involves that "something" which occurs or which is done in order to obtain learning. All events that are reinforcing have biological significance for that individual at that particular time. The same reinforcements, e.g., food for a hungry animal, may be used for both classical and operant conditioning.

Learning is selective. Simply repeating a stimulus or response does not necessarily induce learning. Tolman and his students contributed a classical experiment showing that mere frequency does not strengthen learning (Tolman, 1932). They placed hungry animals in a D-shaped maze which led to food. Although some animals began by taking the roundabout course more frequently than the short path, eventually all the animals took the short path. Selectivity in learning can thus override frequency of repetition. This is biologically advantageous since if frequency were prepotent, whatever was tried initially would become increasingly ingrained. There would be positive feedback; behavior would tend to become increasingly extreme in whatever direction once begun and would be difficult to modify.

The selective factor in learning concerns reinforcement. As is well known, two types of reinforcement have been identified. Reinforcement presented in relation to a given stimulus produces Pavlovian, classical, or type 1 conditioning. This shapes behavior in relation to similar stimulus situations. A second type of reinforcement yields the Konorski, Thorndike, or Skinner type of operant, instrumental, or type 2 conditioning. This involves trial-and-error learning in which reinforcement is presented after a desired response has been spontaneously emitted. Food presented to a hungry animal makes the emitted response more likely to occur in similar situations. It does not matter whether the food is presented by the environment or whether the animal searches and finds the food. In operational terms, for both types of learning, reinforcement is that which increases the probability of a specific response's occurring in a specific situation. Reinforcement thus contributes selectivity to learning.

Where does reinforcement have its influence? It evidently can have effects along the pathway between stimulus receptors and the cortical display of sensory signals. Or reinforcement might predominately affect response mechanisms. With this latter view Guthrie would certainly agree. It might also modulate connections that are centrally disposed, midway between input and output. Of course, reinforcement could have effects on any or on all of these three artificial and arbitrary divisions of the whole.

Motivation and Reinforcement

What are the relations between motivation and reinforcement? And what is meant operationally by "motivation"? Escape from pain seems to be reinforcing for trial-and-error learning whereas onset of pain seems to be especially reinforcing for avoidance learning. There is some disagreement as to whether reinforcement may occur at both onset and escape. Food serves as reinforcement, but food eventually produces satiety and may even become a negative reinforcer. The general question is: Are reinforcements possibly both drive-inducing, that is, yielding increased excitation in appetitive centers, and drive-reducing, yielding drive-quenching or slackening?

Grastyán proposed that from an internal point of view, reinforcement results from the simultaneous occurrence of a definite pattern of increasing excitation in two different systems. According to Grastyán, any two systems that sustain rising excitations of similar pattern will become connected. Stellar suggested that Grastyán's proposed mechanism would be consistent with classical Pavlovian conditioning but that other conceptions would be needed to account for operant conditioning. Miller (1963) has a new alternative to drive-reduction theory which he thinks may be similar to Grastyán's. Reinforcing events may activate a "go" mechanism or mechanisms, which function to intensify ongoing responses to cues and also the traces of immediately preceding activities. Such a hypothetical "booster" effect could play the same role in instrumental learning as does the US in classical conditioning, namely, causing extra firing of the neurons that have just been involved in the response. It should be possible to find out whether or not this actually happens by suitable electrophysiological recording on trials when rewards are given or are omitted.

Response-Release Reinforcement

Miller (1959) called attention to yet another possibility, namely, that whenever a response is activated but blocked, any event allowing that response to occur will have a reinforcing effect. Roberts and his students, (1964, 1965) recently secured evidence supporting this hypothesis of his. They have shown that if rats in a metal T-maze are electrically stimulated in an area of the brain that elicits strong gnawing responses (which they cannot execute in the smooth-walled metal maze), they will learn to choose the side of this T-maze where they find wooden cleats that they can gnaw. Similarly, cats electrically stimulated in the area of the hypothalamus that elicits an attack response will learn to choose the arm of a T-maze leading to a rat which they can attack.

Miller concluded that if a potential response is aroused by electrical stimulation of the brain so that the response is ready for actual release, some other prior activity that permits the release of this response will act as reinforcement. Even eating may be considered within this scheme: a hungry animal primed to eat food but prevented by lack of food will find the act of eating the food reinforcing. Wikler (1957) has hypothesized that the hustling necessary to satisfy a drug habit may have a reinforcing effect on narcotic drug addicts. Perhaps escape from punishment fits into the same paradigm.

Morgan advocated the Premack (1965) position that any time two responses are made to occur, or if a response is made to occur in the presence of two stimuli, learning will probably result. Various means exist by which a biological propensity is manipulated and responses are elicited, for example, electrical stimulation, and food deprivation. This minimal statement is essentially an operational statement involving association. The necessity for reinforcement was questioned by Nauta. In Corson's (1962) experiments, for instance, dogs were led into a room where they ordinarily received an overload of water so that their kidneys had to effect a diuresis. When in later sessions the dogs were brought into the same room in a dehydrated state, they responded paradoxically by diuresis. What is the reinforcement which led to this apparent learning?

Olds restated the Premack position: Any stimulus that induces a behavior is reinforcing. To learn whether a stimulus is a good reinforcing stimulus or not, one applies it to the animal and sees whether predictable responses occur.

Olds expressed some reservations concerning the Premack position, however. It is possible in some cases of brain stimulation that one does not see any direct or predictable consequences of the stimulus. For example, if one stimulates an animal while it is, say, scratching, the animal may continue to scratch. Or if one stimulates while the animal is doing nothing, the animal may continue to do nothing. One cannot tell from stimulation alone whether this might be a reinforcing stimulus. Yet, if the experiment is set up in an orderly way so that there is a response contingency, that response will become increasingly likely. If this is true, the Premack position can be further simplified. It is possible that a reinforcing stimulus does not need to induce any overt response. The distinction between elicitation of response and reinforcement should be borne in mind.

Implications for Research

Miller summarized by saying that there are many procedures one can follow after presentation of a stimulus or after the appearance of a response that will produce learning. The presence of a common element, if any, among various procedures that yield learning, has not yet been agreed upon; that is an excellent area for investigation.

It is particularly crucial that we record what goes on in the brain at the moment of reinforcement. What has generally been attempted in earlier electrophysiological work has been to determine the effect of one or more reinforcements on brain processes during subsequent trials. For example, during a series of trials with a given stimulus, evoked potentials become weaker in a phenomenon that is described as "habituation." If the same stimulus is then followed by reinforcement, it is found to elicit larger evoked potentials on subsequent trials. Miller would like to know what happens in the system aroused by that stimulus during the very trial when the first reinforcement is given. Will we find a common process occurring at the moment of reinforcement produced by different techniques -- by following the CS with a US, by following the CS with the termination of pain, or by giving food to a hungry animal? Or will we find that there are several different kinds of central processes that occur during several different kinds of reinforcement?

There is some argument about whether reinforcement is essential to all learning, but there is no question about the fact that reinforcement is important for both performance and learning (Miller, 1963; DeBold, Miller, and Jensen, 1965). We

can define reinforcement operationally by its effect on learning and performance, but we do not know what it means neurologically. Reinforcement lies close to the center of the problem of learning and performance. Physiological research involving known techniques can go a long way toward demonstrating the underlying mechanism.

Olds suggests that reinforcement does not, as Livingston (Nauta, 1964) has suggested, say "Now print!" but rather "Repeat that behavior!" Olds does not think of central stimulation as having anything directly to do with learning; it simply causes a learned behavior to be repeated. It is possible that a trace is laid down for every behavioral sequence of an animal, and that a given trace may be "redintegrated" at a later time. But the release of behavior will not occur unless there is an accompanying discharge, perhaps hypothalamic as Grastyán suggests.

Olds' interpretation is that the hypothalamic discharge does not cause the trace to be laid down but rather causes or permits the release of the behavior. This was likened by Morgan to the classical position of Tolman (1932) that learning may occur without reinforcement: reinforcement merely makes behavior overt.

Attention and Reinforcement

Miller repeated that selectivity of learning is controlled by reinforcement. He asked whether this control primarily (or exclusively) affects input pathways, central "Now print!" mechanisms, or outgoing behavior. (These processes may be affected either independently or interdependently.) Olds responded that while direction of attention may be one process and reinforcement of behavior another, they may often be elicited in tandem. Attention may be essential for learning and reinforcement for release of behavior. Forcible shaping of behavior exercises aspects of the animal's attention: it forces exposure to certain stimuli. Moreover, since these stimuli are instrumentally important to the animal's needs, that is, they yield reinforcement, they reinforce his attention. The notion that reinforcement processes and attention processes are one and the same does not seem necessary.

Morgan opposed the treatment of attention as a separate mechanism. The organism asleep has a protective filter, one through which only certain kinds of stimuli are allowed to penetrate. When awake, the individual may be responsive to a

wider variety of stimuli, the attention filter may be wider open. An aroused individual may have an even wider open filter, coupled with more available responsiveness.

Orientation

An orienting response provides the first filtering stage by which the organism becomes especially receptive to certain parts of the environment or certain classes of stimuli. This is a preliminary or low-level stage of what is called "attention." Attention also includes the further focusing, filtering, and processing of sensory signals. There may be electrical correlates of attention which appear only at a certain stage in learning and then disappear. Experienced animals will slap the lever in a Skinner box while half asleep, obviously not attending as conspicuously as before. An intermediary stage in the process of discrimination learning, when an animal really strains at the discrimination task, is just the point at which the learning curve starts to rise steeply. Morrell considers this to be the "Now print!" stage, the stage at which the animal has found the situation to contain biologically significant information.

According to Grastyán's experience, orientation occurs when there is conflict, such as that produced by two conflicting stimuli. If the conflict exists on the motor side, it is obviously impossible to carry out two incompatible actions. In this sense, orientation may be nonspecific; the animal may be seeking more information in order to resolve the conflict and carry out some action. Reinforcement seems to be involved in orientation. Olds noted that he and Grastyán were using the term "reinforcement" in different ways. Olds intends that reward or punishment be taken as a terminus of a behavioral sequence. This would have the effect of changing the frequency of occurrence of the behavior, that is, of making its recurrence more or less likely.

Reinforcement: Drive Reduction or Drive Increase?

Grastyán described his view that reinforcement occurs when drive is substantially reduced over a short period, the occasion for emergence of a new drive. This is the moment of steep slope toward increased excitement in the involved center, probably involving simultaneously drive reduction and drive induction. In normal conditions, this occurs during the brief period of drive reduction. Usually drive builds up slowly but may be diminished rapidly. Learning is seen chiefly during drive reduction. It may not be the decrease in the drive but

the degree of energy shift relating to the drive that is important to learning, according to Grastyán.

Olds pictured learning as involving usually an increase in drive. It involves conflict situations in which the animal is behaving, presumably under the influence of several drives, experiencing some signals that suggest he go one way and other signals that he go another way. Olds thinks that learning occurs in this kind of situation, which he considers a situation of conflict and drive increase, not drive reduction. Grastyán made the appeal that this may involve increased drive but at the same time may not involve learning. One obtains learning following the conflict situation; the animal looks around, approaches various objects, and stops at an object where his drive is most significantly reduced. Olds believes that the animal will tend to repeat those actions associated with "reward" or even reduction of drive but that it is mainly during exposure to a conflict situation that the animal learns associations between salient things which guide his future behavior. The animal encounters the conflict and looks; it is the looking at that moment that yields the learning.

According to Ames (1955), learning occurs only when there is a "hitch" between past experience, expectations, and purposes and what actually eventuates in the environment. To Ames it is during exposure to events that do not correspond to past experiences that learning occurs. What Ames called a "hitch" may involve the experience of orientation. If one does not experience this hitch because he is unaware of the non-correspondence, or otherwise does not respond (presumably by orienting), the occasion for learning is lost.

Konorski felt that what has been said applies to instrumental conditioning but not to classical conditioning. We are employing the term "reinforcement" in two quite different ways. For Pavlov, who dealt only with classical conditioning, "reinforcement" meant the effect of the action of a US upon the response to the CS. This is the essence of classical conditioning. In instrumental conditioning, however, something is needed to make the instrumental response more likely to occur. This is thought to be drive reduction. But this notion is already a theoretical construct. Drive reduction has not yet been clearly identified in an operational, neurophysiological sense, as a phenomenological explanation.

In instrumental conditioning, cessation of a CS may constitute a good reinforcer for avoidance. In Pavlovian conditioning this is not necessarily true. Therefore, when one

speaks of drive reduction as "reinforcement," it is likely to be correct only in reference to instrumental learning. Reinforcement in Pavlovian conditioning is primarily focused around the stimulus, whereas in instrumental conditioning reinforcement is focused primarily around the response. We are left to design experiments to test whether there may be two categorically different internal processes involving reinforcement which parallel the striking experimental and behavioral differences between Pavlovian and operant conditioning.

IV. TIME PARAMETERS

Learning and Extinction over Time

Stellar led a discussion of the time parameters involved in learning. These range from milliseconds, seconds, minutes, and hours to days and lifetimes. Typically, several learning processes go on at once. Learning curves have various shapes, generally showing some incrementally progressive function but also having great variability. Extinction is a decremental process, also exhibiting great variability. Curves derived from learning and extinction experiments undoubtedly represent more than one learning process. For example, in a simple avoidance situation in which an animal is eventually going to learn to listen for a signal to move across a barrier into another compartment, the animal first has to get used to the experimenter and the situation, and then has to learn some appropriate reactions to shock being applied to its feet. Only then can it begin to learn a specific response to the signal.

As pointed out earlier, temporal contiguity is one "law" of learning. There is no question that it makes a great deal of difference what time relations exist between the CS and the US. There are empirically determinable optimal temporal relations but we cannot be as sure of the universality of these optima as we would like, because they are estimated from widely different experimental situations. The generally accepted optimum for classical conditioning, at least, is about 0.5 to 1 second between the onset of CS and the onset of US. In shock avoidance, however, approximately a 4-sec interval between CS and US is optimal in a flexion situation. Possibly a 10-sec interval is needed in a situation requiring locomotion. If these time relationships are violated, so that there is either complete CS-US overlap or no overlap, with CS following termination of the US (as recounted previously in connection with backward conditioning), there is no conditioning.

A second, related problem is that of delay of reinforcement. For example, in the operant situation when, as in Grice's (1948) experiment, food does not appear for a certain length of time after the animal makes the desired response, there is little or no learning. The delay interval Grice found for loss of reinforcement effects in rats was 5 seconds. No comparable data for the delay of negative reinforcement are available.

Lindsley cited the generally accepted optimal CS-US interval of about 0.5 seconds, but added that there are recent experiments which show that this may be reduced to the order

of 0.3 seconds in certain situations. These time relations suggest that certain extremely important physiological events take place centrally during these brief intervals and that both the timing and sequencing of different events are highly critical. There are secondary and other effects which become committed during these brief time intervals. If the time interval is of the order of 0.2 or 0.1 seconds, and the US is more intense than the CS, Lindsley has found that it can interfere with the immediately enduring electrophysiological effects of the CS (see below).

Timing of Trials

As a third temporal parameter, Stellar next discussed the significance of repetition rate of training, i.e., the optimal spacing of repeated trials. In ordinary food-reward situations with an animal like the rat, one usually sees maze learning in the fewest number of trials if one trial a day is applied. Investigators, trying to save time, generally run blocks of ten trials a day or try to accomplish conditioning in one day if it involves a sufficiently simple problem. The advantage of longer intertrial intervals is thought to relate to "interference with learning" and "consolidation of learning." Stellar has found that in simple avoidance discrimination, in comparing repeated trials every 30 seconds with one trial a day, one-trial-a-day training takes more trials, contrary to what is found in food-reward training. He thinks that in avoidance learning, massing of trials may serve to keep the level of emotional motivation high, whereas in the food reward situation, massed rewards may lower motivation through partial satiation.

Interference with Consolidation

In closely massed trials, it is possible that subsequent trials may interfere with the consolidation of earlier trials. We need to know more about the processes and temporal course of consolidation. A related set of problems attends the phenomenon of extinction. One concept of extinction that has been challenged very little is the concept of interference in which new learning competes with and weakens the original learning. Unfortunately, the interfering learning is not usually observed very well except for the fact that it inhibits the original learning. It would be well to measure interference learning and to identify it more specifically, particularly as to its internal neurophysiological mechanisms. Interference results in failure of the CR to appear; implicit in the notion of interference is the thought that learning, other-

wise permanent, is simply being masked by the adventitious interference.

Gellhorn (1945) performed experiments reported as "the recovery of lost conditioned or inhibited conditioned responses." Basically, his concept was that by anoxia, insulin shock, and other interferences, he could destroy the interfering new learning, and unlock an extinquished response in an avoidance or escape situation to the point where it could reappear in full strength. His interesting observations have not been repeated.

Short Time Interval Interferences

Many have tried to ascertain when interference with memory storage takes place, usually by applying some kind of traumatic insult. Out of this type of experiment have come some general notions about memory formation, namely, that memory goes through a number of separate stages which have different time parameters.

Duncan's (1949) classical experiments provide a model for others in this field. He gave animals one trial a day in a one-way avoidance situation of the following type: Animals in a start box were shocked 10 seconds after being put in, and could then escape to a safe box, from which they were removed. Following removal they were given an electro-convulsive shock (ECS), either immediately or at 1 minute, 4 minutes, 15 minutes, 1 hour, 4 hours, or 14 hours. Duncan found a significant decrement in learning up to an hour; beyond an hour there was no significant effect. The number of avoidances was used as a measure of strength of learning when plotted against time of convulsion. Consolidation, as judged by this procedure, would appear to take about an hour.

Duncan recognized the need for special controls. He repeated his experiments, shocking the animals to test for the influence on learning of discomfort rather than convulsions. He apprehended that negative reinforcement rather than the postulated anti-consolidation effect might be interfering. He did get negative reinforcement effects in his immediately shocked group but not in those shocked later, which behaved like other controls. Thus, there seemed to be some immediate punishment effect as well as some enduring anti-consolidation effect. Rosenzweig suggested that internal repetition may be needed to ensure consolidation. It is difficult to preclude internal repetitions and to be confident that only one-trial learning has occurred.

Miller described experiments done in his laboratory (Fig. 1) (Quartermain et al., 1965) which were similar to work published simultaneously by Chorover and Schiller (1965). Rats were confined to a narrow ledge, then lowered to the level of a large arena; a door was opened and, as the rats stepped out, they received a strong shock to their feet. On the next day when the ledge was lowered again, about 80% to 85% of the rats remained huddled on the ledge and did not step off. If, however, after the electric shock to their feet, the rats receive ECS, they are likely to step off on the next trial. Miller and Chorover consider this behavior indicative of retrograde amnesia. Tests varying the interval between foot shock and ECS show the greatest interference lies somewhere between 0.1 and 2.0 seconds; this interference virtually disappears between 15 and 30 seconds. Miller's conclusion, like Chorover's, is that there is genuine retrograde amnesia in this simple one-trial learning situation and that the consolidation period is very short, being practically completed by 15 seconds.* This may not generalize to other learning situations, however.

In view of the longer consolidation time reported by Duncan, Stellar pointed out two differences in these ECS experiments. First, Miller and Chorover's experiments involve passive avoidance; it is known from McCleary's (1961) work that passive avoidance is different neurologically from the active avoidance Duncan used. Second, Miller and Chorover used one-trial learning, which has already been discussed as a particular kind of conditioning, perhaps different from that requiring many trials such as Duncan used.** Thus it remains possible that there are different consolidation times for different kinds of learning.

Schmitt mentioned the NRP Work Session on "Information Storage and Processing in Biomolecular Systems" (Eigen and

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* Work by Paolino, Quartermain, and Miller (1966) shows that in the same experimental situation, considerable amnesia produced by CO_2 anesthesia may be observed after 3 minutes. Unpublished work by Miller and his associates, completed after the Work Session, indicates that in a one-trial appetitive learning situation in which thirsty rats are rewarded by water, some amnesia from ECS may occur after one hour. [NM]

** See Coons and Miller (1960) for an experiment demonstrating an artifact in Duncan's (1949) study. Other studies, however, have demonstrated apparently genuine long gradients of retrograde effects [Flexner et al., 1963].

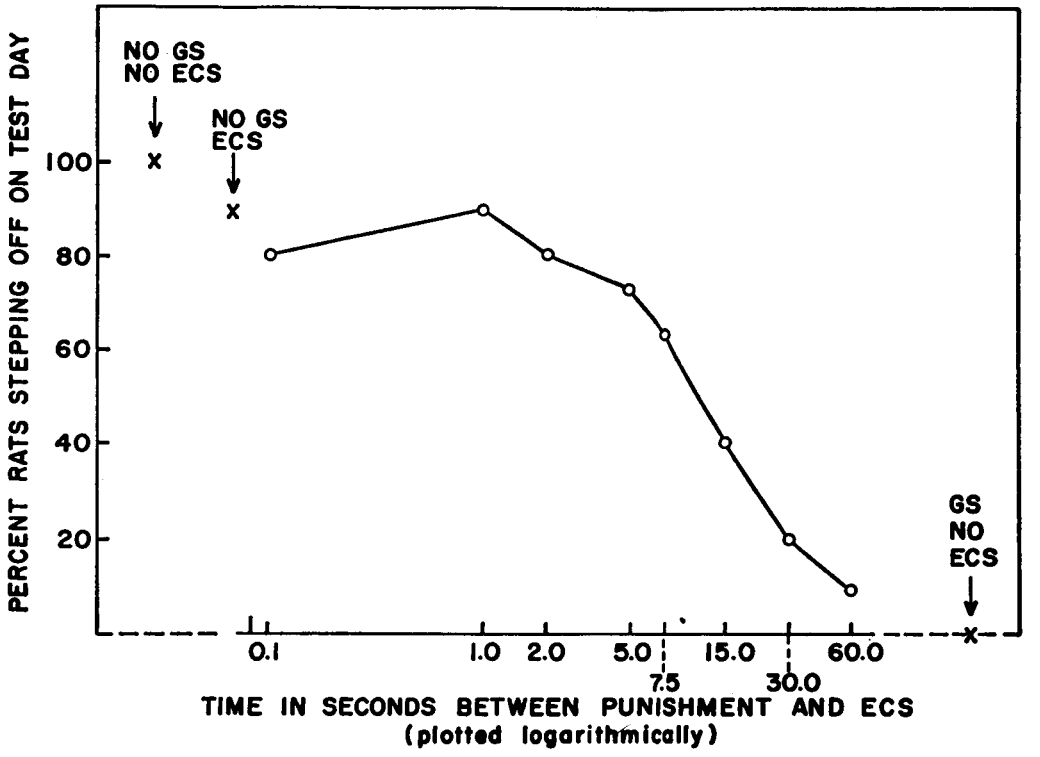

Figure 1. Effect on avoidance behavior in rats of GS-ECS (grid shock-electroconvulsive shock) interval. Ss were placed in a small compartment and lowered onto the floor of a larger compartment. On stepping out, they received a 1 ma foot shock for 2.0 seconds. Electroconvulsive shock (100 ma for 0.3 sec) through ear clips was administered to different groups at the following intervals after the termination of the foot shock: 0.1 sec, 1.0 sec, 2.0 sec, 5.0 sec, 7.5 sec, 15.0 sec, 30.0 sec, 60.0 sec. Three additional groups received, respectively: grid shock-no ECS; no grid shock-no ECS; and no grid shock-ECS. Twenty-four hours later all Ss were placed in the small compartment and time taken to step out was recorded. Ss not responding within 180 sec were removed from the compartment and returned to their home cage. Percentage of Ss in each group that stepped off within 180 sec on the test day is shown [Quartermain et al., 1965].

De Maeyer, 1965) at which the question of consolidation time was considered to be of crucial significance in providing clues about the nature of consolidation. If it takes 30 to 40 minutes for consolidation, there is plenty of time for a neuron to make a new protein and maybe even to transport large macromolecules from one place to another. In contrast, if consolidation takes place in much less time, that kind of biosynthesis is probably ruled out. Rather, some kind of tag or prosthetic group must be produced. Participants at the present Work Session registered caution about assuming, as does Chorover, that whatever consolidation requires is necessarily completed sufficiently for one-trial learning in a matter of 2 seconds or less. In terms of simple diffusion rates this interval is meaningful to individuals concerned about the possible mnemonic requirement for readout from macromolecules. Of course, demonstration that consolidation can no longer be interfered with after a few seconds does not necessarily mean that consolidation has already been completed. It may mean only that enough mechanisms are underway toward consolidation so that, despite ECS interference, consolidation can still be completed.

Stellar expressed misgivings which arise from having to rely on such gross techniques as ECS, strychnine, and anoxia for experimental interference with consolidation. Electrical, chemical, and structural changes may be involved, together or seriatim. Miller noted that the maximum time interval for ECS interference with consolidation in his experiments is of the same order of magnitude as the maximum tolerable time interval for delay of reinforcement. It may also be in the same time range as some of the slower perceptual effects with which Lindsley is working (see below).

In support of Duncan's finding that consolidation requires from 15 minutes to about an hour, are the results of Milner and Penfield (1955) in their analysis of temporal lobe lesions. They encountered memory processes in which intake can be remembered for 15 minutes to an hour but cannot be retained longer than that unless entered into permanent storage, a second-stage process that cannot be completed in subjects with temporal lobe lesions. Boycott and Young (1955) found an analogous defect in permanent memory storage in the octopus after removal of the vertical lobes. The octopus can learn and remember well if recall is demanded within 15 minutes of stimulus exposure, but after 2 hours it does not remember its prior experience.

Longer Time Interval Interferences

With regard to still longer time intervals, there are older experiments on recent and remote memory. For example, Zubin and Barrera (1941) did experiments with patients receiving ECS. The patients learned a list of nonsense syllables a week before receiving ECS, and another list 15 minutes before shock. Following ECS, they had a very high level of performance on the first list but did poorly with the more recent list. This, of course, gave impetus to the concept of distinctions between recent and remote memory processes.

The Flexner et al. (1963) experiments with puromycin suggest that some memory storage processes take a matter of days. Puromycin was injected into the temporal region in mice, grossly affecting the hippocampal area and entorhinal cortex, as judged by fluorescein dye accompanying the injection. Control injections were made into the cerebral ventricles and frontal regions. As judged by fluorescein, ventricular injection affects the hippocampus markedly but not the entorhinal cortex. The experimental (temporal) group shows an interference with memory when injection occurs up to about 2 days, possibly 3 days after learning; but there are no effects after 4, 5, or 6 days.

Mice were tested in a Y-maze with the choice of going either right or left. They were given 5 seconds in which to reach the safe side, and were punished by shock for not moving or for going to the wrong side. It takes only an average of 10 trials before the mice reach criterion of 9 out of 10 correct choices. The animals were put away for 3 weeks and then brought back and tested in reversal training. One day later, they received puromycin and were allowed to recover for 3 or 4 days from any acute effects the injection might have had. They were then retested but without shock so they could make free choices. Control animals not given any injection or given a control injection invariably go to the last side learned.

Every animal that received puromycin one day after reversal training went to the original side learned. Thereafter they went predominantly to that side although no reinforcement was given. Thus, puromycin injected into the temporal region of the brain can apparently destroy memory if given within a few days. Injections of puromycin in the ventricular-frontal regions alone are ineffective. However, putting puromycin into more extensive regions of the brain, using three bilateral injections (temporal, ventricular, frontal), yields effects lasting up to 5 weeks. This latter may imply interference with readout rather than with consolidation.

Possible Consolidation Processes

Schmitt pointed out that when protein synthesis is stopped with puromycin, many critical reactions are interfered with. He noted that Stanley Appel, at the NRP Stated Meeting in February, 1965, reported a different chemical effect of puromycin in different parts of the brain, as measured in vitro, both with respect to protein synthesis and the incorporation of tyrosine. These processes apparently vary greatly from one part of the brain to another. If puromycin interferes with learning differentially in different parts of the brain, this might be due to more or less effective blockade of protein synthesis or tyrosine incorporation.

What is being synthesized normally that is inhibited by puromycin? A current idea is that neurons are continually synthesizing neuroproteins which move down the neural axon. They are also undoubtedly synthesizing morphologically distinguishable proteins in the form of neurofilaments, microtubules, etc. There is an experimental disease called "neurolathyrism" which enormously increases the production of protein. The question arises whether this may influence mnemonic consolidation.

Flexner and Stellar believe they have controlled for brain tissue damage by puromycin, thereby eliminating gross tissue destruction as a cause of the observed behavior. However, what is being done to the tissue in terms of subtler dynamics cannot yet be vouchsafed. Stellar's objective is to inquire whether or not we need to accept memory as perhaps involving a series of processes. The suggestion that nervous activity may lead to some form of anatomical change, perhaps by neuronal sprouting, has been made by Hebb (1949) among others. Eccles (1953) has thought of it as perhaps involving synaptic terminal swelling.

Morrell thought it would be of fundamental importance to molecular biologists to distinguish carefully electrically sensitive from electrically insensitive consolidation processes. Probably the ECS interferes with a trace that has a very short lifetime; puromycin may interfere with another process, perhaps a non-electrical process which may have a longer duration of susceptibility. Schmitt felt that if the engram were a molecule it would presumably be something big enough to be an encoding molecule, like a protein. It would likely be charged (acidic) and small enough to move fairly rapidly in an electrotonic field. The engram, so to speak, might be driven electrically during the electrosensitive interval which lasts a matter of seconds or minutes.

Conditioning as Observed in Unit Responses

Adey introduced experimental data (Kamikawa, McIlwain, and Adey, 1964) apropos of time intervals needed for permanent memory. Using single thalamic unit recording during conditioning he found that the minimal effective CS-US interval to produce changes in firing patterns is 250 msec, optimally 500 to 750 msec. The trial-repetition interval should be not less than 10 seconds; the minimum number of trials to produce a change is between 50 and 100. The minimum time for appearance of changes in patterns of firing during the CS-US interval in repeated trials is about 15 minutes. If any one of the parameters is crowded, such thalamic unit changes are not seen. The changes last about an hour, though some have been recorded up to 4 or 5 hours. Adey said that in relation to behavior, during classical conditioning these changes occur somewhere between the orienting response and the appearance of a conditioned motor response.

Olds also conditions single units, but he waits for a particular single-unit pattern to occur and then applies a reinforcing stimulus. He uses a half-second CS-US interval. Brain responses are conditioned in a situation where the animal is restricted in movement, and reinforcement is canceled if the animal makes a movement. Olds finds he cannot condition single spikes when these appear against a silent background and he cannot "condition" burst patterns. Unitary responses that could be operantly conditioned included "random" patterns found by Evarts to be characteristic of the waking activity of cortical motor units.

Olds' conditioning procedure involves first getting a background on the unit's activity for a day, then picking a high frequency that is sustained for half a minute, a discharge pattern so high that it tends to occur on the average only about once every 15 minutes or less. He triggers reinforcement with a "burst discriminator." The "reinforcement" is a food pellet. Training usually takes 2 days. After 3 days, Olds shifts procedures so that every 10-minute interval is divided into 8 minutes of "S-delta time" and 2 minutes of "S-D time," i.e., 8 minutes with the stimulus signal one way and 2 minutes with the stimulus signal the other way. The unit is only reinforced during the 2-minute periods. Olds looks for a discriminatory response to build up over time. At first, the animal does not show any particular recognition of the stimulus pattern by modification of the unit's response; but over a period of 4 days, discrimination begins to be quite evident.

Using this method almost any unit has a pattern that can be brought under operant control. The animal may have to assume a particular posture to control the unit; it may have to orient to a particular stimulus or produce a certain somesthetic feedback. Olds has not found many differences based on the location within the brain of different conditionable units.

Possible D-C Influences on Local Electrophoresis

Schmitt quoted Morrell as saying that 10μ amp/mm^2 is sufficient transcortical polarization to alter markedly local cortical conditioning. If the effector of this process is an electrolyte and if one is using electrical stimulation, why couldn't the effector be moved electrophoretically if other electrokinetic parameters, such as ionic strength, are favorable? Changes in neuronal circuitry effecting consolidation might be very much slower, especially if the effector is something proteinaceous whose production might be blocked by puromycin.

Morrell pointed out that in using electrical signs as indicators, one deals with very partial reactions. He can alter the firing pattern of the single cell he is recording from, but it probably takes the effect of changed behavior in thousands of cells to effect any permanent change such as might be retrievable in molecular form. That might require a long time and many cellular transactions. If the appropriate activities are interrupted before a sufficient number of cells has become involved, no permanent trace is likely to result. Morrell assumes that something electrical is important because consolidation can be disrupted by electrical interference, but such disruption may occur long before the achievement of permanent storage.

Local Sine-Wave Interference

Schmitt asked what would happen if, instead of testing consolidation times by stopping the firing of nets (for example, by ECS or other interferences which have many other effects), one approached the problem from the viewpoint of electrophoretically driving a protein with a molecular weight of ca. 30 thousand within particular microregions using 10μ amp/mm^2 and testing for behavioral changes.

Olds has not done electrophoretic work but has used 60-cycle sine-wave stimuli in various parts of the rat brain during discriminative reversal learning. In these experiments

the rat goes to one end of a box, selects a particular pedal to press, and must return to the other end of the box to receive the food reward. Brain stimulation 1 second out of every 3 occurs before and after pedal choice. Interference with learning is produced by stimulating brain regions shown by other central stimulation experiments to be positively rewarding. Olds infers that since this interference might be caused by potential emotional effects induced by the stimulation, he cannot insist that any particular change within these regions is disturbing to learning.

Olds has also stimulated monkeys with sine-wave currents during the delay interval in delayed response tests; i.e., during the time the screen occluding vision of the cups is down, and after the cups have been baited in full view of the monkey. The monkey is stimulated for 5 seconds and the screen then raised. Again it turns out that the so-called motivational areas are the effective interference zones. Olds found that in the monkey, negative reinforcement centers are as disruptive as positive reinforcement areas. In rats, however, there is a marked difference: stimulation of positive reinforcement areas does interfere.

Miller asked whether some superstitiously reinforced learning was produced which interferes with the memory of which cup is baited. Olds agrees that this is an argument used by those who consider this stimulus to be an emotion-arousing one, but that there are also various other arguments, all potentially valid.

Other Interferences

Morrell finds that applying surface-cathodal current on the cortex disrupts acquisition of new learning specific to the area being polarized but does not interfere with overtrained behavior. Schmitt suggested polarization of different parts of the brain to see what happens in an amnestic test situation. Miller asked whether there might be a chemical having an amnestic effect that would act more quickly than puromycin and would not produce electrical effects like those involving cortical polarization and ECS. Morrell suggested that heparin might act in this way if injected rapidly. Schmitt, assuming that the mnemonic system might depend on a protein, would look for a small protease capable of chewing up any proteinaceous molecules lying in or upon neuronal, synaptic, or glial membranes, thereby destroying information coded in the proteinaceous material. Such a protease presumably might attack synaptic regions but not enter the cell

proper; it might, however, liberate toxic amino acids and other products. Conversely, if a protein is the effective agent necessary for consolidation, then identifying that protein and driving it electrophoretically would be important.

If an antibody is made against a specific protein and tested for its effect on the metabolic activity of neurons in vitro it has a very rapidly inhibitory effect, greatly reducing metabolism over a period of about 20 or 25 minutes. Rubin and Stenzel (1965) have succeeded in biosynthesizing protein in subcellular ribosomal systems. This protein reacts with antibody against a glial protein (Hydén, 1966), thus providing an in vitro system for direct testing.

What May Be Involved in Memory Storage?

Schmitt said that the nerve-growth-factor type of protein studied by Levi-Montalcini (1961), which stimulates the development of sympathetic neurons, might be involved in Livingston's (Nauta, 1964) "Now print!" order. Livingston suggested that a "Now print!" substance might be released on command at the terminals of the diffusely projecting system of neurons. Perhaps a growth-producing factor would be delivered quite generally throughout the brain each time there is a biologically significant event. Neurons active just before the "Now print!" signal would be stimulated to grow; repetition of similarly reinforcing events would be accompanied by repeated "Now print!" growth stimulations. Random components adventitiously associated with the biologically significant events would cancel out and not build up significant growth. Thus repetition of those coincidences regularly followed by the internally rewarding experience that yields the "Now print!" order would eventuate in remembered events.

Miller postulated that this would have to be something that would act quickly and could scarcely be a chemical circulating in the blood. Livingston agreed, saying that the diffusely projecting nerve impulses would be able to release such a substance locally within the neuropile, but simultaneously to widespread areas of neuropile. Diffusely projecting neurons ascend from brain stem to cortex and affect all important ganglionic areas throughout the brain. These ascending impulses are known to have some local preparatory action that affects other signals invading these regions; they could perhaps release locally a growth factor or some other substance that conveys the message "Now print!" or "Now grow!". The intricate neuronal patterns responsible for precisely

what is learned would develop according to what exactly were the ongoing sensorimotor and central neural events just preceding the reinforcing discharge that releases the "Now print!" command.

Everything unessential, i.e., not involved in bringing about reinforcement in the ongoing situation, would gradually drop out as the "Now print!" discharge recurs only in response to the biologically meaningful components of experience. Thus only particular neuronal coincidences testifying significant drive increase or reduction would become consolidated. Learning thus would be initiated by generalized and diffuse alterations which represent the whole environmental situation. Then patterns gradually would become more reinforcement-specified and particularized. Such a system could account for the obviously intricate circuitry called for by the phenomena of learning. It would also account for the precise ordering of spatio-temporal events in the brain. It would, for example, account for forward but not backward conditioning.

V. INFORMATION PROCESSING OF SENSORY SIGNALS

Interference among Sequential Stimuli

Lindsley reported work concerning perceptual processes fundamental to the intake of information upon which learning and memory depend. Simple patterns can be recognized by attentive subjects with 20-μsec up to 1-msec flash durations. Humans and monkeys can discriminate simple patterns effectively in this range of durations. A subject can perceive and report immediately on the information contained in a stimulus flash if the event is not interfered with by a second flash that is without information content. If the second flash occurs close enough in time to the first (0 to 50 msec) it tends to interfere by masking the information content of the first stimulus. However, Lindsley thinks that at the right interval (80 to 120 msec), the second flash may facilitate perception of the first stimulus (Donchin, Wicke, and Lindsley, 1963; Wicke, Donchin, and Lindsley, 1964; Donchin and Lindsley, 1965a, 1965b).

Information can be utilized even when the duration of the first flash presentation is exceedingly brief (20 msec to 10 msec). Interaction between stimuli depends on the interstimulus interval and the luminance of the flashes. In an experiment consisting of presentation of a test flash alone, generally 5 to 10 msec in duration, the subject will perceive the position of a test sector 100% of the time. When this is followed by a second briefer flash, the luminance of which is usually 2 or 3 log units greater, if the second flash follows within a period of 0 to 50 msec, one witnesses a blanket retroactive masking of what would be perceived in the first flash.

If the order is reversed so that the brighter flash comes first and the test flash later, there is proactive masking from 0 to 150 msec. Lindsley thinks proactive interference may be due to a retinal light-adaptation effect from which the subject has to recover before he can begin to perceive the dimmer test flash. Retroactive interference, however, he thinks of as a neural (retinal and central) effect interrupting the processes of perception. In regard to control for dilution of contrasts, as questioned by Morgan, Lindsley described controls with different stimuli -- black on white, white on black, and various forms and patterns. In fact, according to Schiller and Wiener (1963), if the second flash displays a pattern, it is more effective as a masking agent than is a blank flash. There is also brightness enhancement,

that is, some kind of retroactive facilitation by the second stimulus upon reception of the first stimulus. This occurs generally beyond the retroactive masking range with inter-flash intervals of 80 to 150 msec. Brightness enhancement is maximal at about 100 msec and disappears beyond about 150 msec.

Discrimination of Flash Separation

In the perception of oneness or twoness, two flashes have to be separated by 75 msec to be seen as two, for a given luminance level. When the flashes, however, are put in a repetitive series so as to produce either flicker or fusion, one finds a critical flicker-fusion frequency (CFF) when the flashes are about 40/sec, which means they are separated by only 25 msec. Thus, for an individual to see a pair of flashes as two rather than as one, they have to be separated by 75 msec, but to see flashes flickering in a repetitive series, they need be only 25 msec apart.

Reaction Time and Decision Time in Relation to Central Processes

It has been known for years that any alerting or priming of the individual will reduce reaction time. In studies in which the subject is told to press a key as fast as he can when he sees a flash of light, simple visual reaction times are found to be about 280 msec. When the subject is alerted by a forewarning signal, say an auditory stimulus that is presented anywhere from 0.3 sec to 1.0 sec prior to the visual stimulus, the reaction time is reduced to about 206 msec. Moreover, the variability of reaction times is cut in half by such alerting. Forewarnings of 1.0 sec to 0.3 sec in duration are either not effective or reduce reaction time by a lesser amount (Lansing, Schwartz, and Lindsley, 1959).

Since desynchronization of the EEG to the alerting stimulus occurs by 0.3 sec, it appears that the reticular activating system is involved in the alerting and the resulting decrease in reaction time. In support of this, Lindsley cited Fuster's (1958) experiment with monkeys in which discrimination reaction time, which Lindsley calls "decision time," was measured with and without reticular formation stimulation. Monkeys were trained to discriminate two objects that were momentarily illuminated by a tachistoscopic flash; the animal had to make its decision and reach through a trap door to the correct object to fetch a food reward beneath the object. Opening the door stopped the timer and provided an overall reaction time from the flash's exposing the objects to the time of reaching the correct door. Electrical stimulation of the reticular

formation prior to and during the exposure of the objects shortened the reaction time by 80 to 100 msec, on the average. It also significantly improved the number of correct responses.

With respect to temporal intervals involved in conditioning, most people select 0.5 sec as the optimal CS-US interval; but some studies suggest that for some species and some types of conditioning the optimum may be as short as 250 to 300 msec. It is of interest to note that alpha-wave blocking time (desynchronization or reticular activation) in an adult subject or older child with a 10/sec alpha rhythm occurs in about 0.2 sec or after two cycles of the alpha waves. A one-year-old child with a 5/sec alpha rhythm shows alpha blocking in an analogous two cycles, but the latency for blocking is now 0.4 sec instead of 0.2 sec (Bernhard and Skoglund, 1939; Lindsley, 1938). Correspondingly, the latency to an evoked potential in newborn and young infants is at least three or four times that of an adult. The same is true for some components of the response in kittens (Ellingson, 1960; Ellingson and Wilcott, 1960; Rose and Lindsley, 1965).

The first time an auditory stimulus is given, when a subject is not expecting it, the stimulus generally blocks the alpha rhythm for a number of seconds (an initial arousal or orienting response). However, if the same auditory stimulus is repeated 10 to 20 times there is a gradual reduction in the degree and duration of blocking; finally, after 20 or so trials, there may be no blocking at all. This has been called "habituation," a possible type of learning or inhibition of arousal. In contrast, a visual stimulus, when repeated, will continue to show blocking effects to individual presentations, though the blocking duration is reduced and remains residually at about 1.0 to 1.5 sec. If the habituated response stimulus, the sound, is paired with the non-habituated light stimulus in a CS-US paradigm, the blocking response to the sound will return; thus a dis-habituated or dis-inhibited condition is achieved, which may also be considered as conditioning or learning.

Some 36 years since Berger first described the human EEG we still do not know the precise source, mechanism, or central controlling factors of the alpha rhythms. Present thought tends to identify them with dendritic potentials, but synaptic or cell-body potential variations may also be involved. An idea proposed by Adrian many years ago suggested that they might arise from synchronized axonal discharges which might combine to make wave-like forms. Alpha blocking or desynchronization supposedly reflects activation via the reticular formation, but electrical stimulation of thalamic nonspecific

nuclei located medially will also produce desynchronization or activation. There appear to be at least three kinds of electrical activity which can be demonstrated in the cortex: classical spikes signaling axonal discharge; synchronized waves, perhaps reflecting spontaneous dendritic or cell-body activity; and d-c shifts of potential. Lindsley believes that all three kinds of activity are intimately interrelated.

Analysis of Sensory Evoked Responses

Lindsley conceives of interferences between stimuli in terms of specific mechanisms, meaning the so-called classical sensory pathways, in comparison with nonspecific mechanisms, meaning the reticular activating system and the diffusely projecting thalamic nuclei. Evoked sensory potentials recorded from the respective sensory cortices involve a surface-positive wave, a negative wave, and subsequent secondary waves. Heretofore there has been no adequate basis for separating the components of a cortical evoked response. Rose and Lindsley have found, however, that in the 10- to 20-day-old kitten, there are two clearly separated response components: one of short latency, a positive-negative complex; and one of long duration, a negative wave, when the response to a flash of light is recorded at the visual cortex. By 30 days of age the two responses have usually coalesced into what would be recognized as a traditional evoked potential; but at 10 to 15 days of age they are still separated. At this age lesions affect them differentially. The short-latency surface-positive and -negative complex is eliminated by lesions of the lateral geniculate body. The long-latency response is markedly reduced or eliminated on the side of the lesion only by lesions of the superior colliculus and pretectal region or of the brachium of the superior colliculus. Even in adult cats, by changing the parameters of the stimulus, especially stimulus intensity, the two main components of flash-evoked responses can be separated.

Any sensory input seems to give rise to activity which reaches specific sensory areas of the cortex by way of the classical sensory path. Triggered by the same sensory event, the medial nonspecific system delivers an electrophysiological conditioning signal which yields a more pervasive, longer-lasting change in the background cortical activity. Some investigators feel that each of these systems may be carrying messages of importance to perception, perhaps carrying different kinds of messages or different aspects of the sensory situation. Lindsley thinks that only the classical sensory pathways carry specific coded messages relating to the sensory

modality and that the nonspecific system provides a sensitizing or conditioning effect upon associational and other more remote areas of the cortex. The background message would enable the specific coded messages to spread out and elaborate themselves during the processes of perception and learning.

When one records simultaneously in the reticular formation (RF) and along classical sensory pathways or from sensory cortex, a quick-acting anesthetic will eliminate responses in the RF and yet leave normal or perhaps augmented responses in the sensory pathways and sensory cortex. Under such an anesthetic, of course, the animal is unable to perform learned habits and the human subject is unable to recognize people or respond to commands. When the effects of the anesthetic wear off and the response in the RF returns, the animal is again able to carry out previously learned responses, and the human again becomes aware of his surroundings. It appears necessary to have both systems operating for normal perception; the specific system is essential, presumably, for specific message-carrying and the reticular activating system and diffuse thalamic projections essential, presumably, for the subsequent processing of information conveyed. Rosenzweig added, however, that Chow and Randell (1964) by applying two-stage operations to animals in long-survival experiments, can eliminate large sectors of the RF; the animal can nonetheless act normally, learn, and preserve experiences in memory.

Contingent Negative Variation

Both Rowland and Galambos mentioned Grey Walter's contingent negative variation experiments (Cohen and Walter, 1966; Walter et al., 1964). If human subjects are exposed to clicks, and six to eight responses from the vertex referred to the mastoid are averaged, nothing happens during the 1-sec interval between the click and delivery of a series of light flashes. If then the subject is told, "As soon as you hear the click, prepare for the flashes and turn them off as quickly as you can," he shows a rising baseline shift of 20 v to 25 v, which decays when he turns off the flashes. It is impressive that this d-c shift occurs immediately following a simple verbal instruction; the "acquired" EEG response appears to single-trial learning.

Another situation described by Galambos is the experiment of Anderssen and Wyrwicka (1957) in which shocks are applied to the hypothalamus in the goat to evoke both learned and unlearned responses. Miller believes that the drive of thirst that normally elicits these responses is being aroused

by electrical stimulation of the central neurons involved with this drive; Galambos, however, thinks this may come about through the mediation of alterations in standing d-c potentials. He considers that the standing potential and variations in it may be directly related to drive as well as to the deposition and retrieval of learned responses.

VI. ELECTROPHYSIOLOGICAL PROCESSES

Adey pointed out that if one stimulates brain tissue electrically, a volume of tissue lying closest to the electrode is held in a clamped, unresponsive condition. Surrounding this is a volume of excited tissue of varying dimensions. This volume is larger than one would expect from currents within so-called physiological limits, say 50 to 100 μamp. Beyond this secondary zone is a third region that is not directly activated but may be subliminally excited. Each of these three zones has a great many local and remote connections. A series of patterns is established far and wide throughout the brain on the basis of stimulus interference with many probably functionally different components having clamped, excited, and subliminal fringes.

The delivery of electric current to the brain as a means of discovering brain organization is difficult to pursue as a dynamic. One can look at the overall response, which may be very interesting, and may show consistent effects from each application of current; yet what is occurring within the brain, in detail, remains difficult to discern.

Invasion of Cortex by Conditional Signals

Adey summarized events in the cortex during the invasion of conditional and unconditional stimuli, i.e., how specific and nonspecific systems activations are responsible for much of the background activity in the cortex. Adey related how Morrell began being concerned some years ago with the nature of cortical processes that might be conditioned. One of two stimuli is given conditional significance. Traditionally, it is considered that when the RF is activated, the principal change in cortical activity is from synchronized activity, like the alpha rhythm, to fast, desynchronized activity. However, by computer analysis of this transition, Walter and Adey (1965) found that the alpha frequencies remain the predominant rhythms in an apparently desynchronized record.

In a study (1965) designed to test the vigilance ability of NASA's Apollo trainees (Fig. 2), Adey recorded from bipolar scalp-EEG leads during presentation of three successive tones 5 seconds apart. The subject was told to press a button each time he heard the third tone during a 6-minute period. Spectral densities were analyzed against cycles per second from 0 to 15. During the first 4 minutes there is a broadening of the alpha band from a somewhat narrow pattern, as well as a

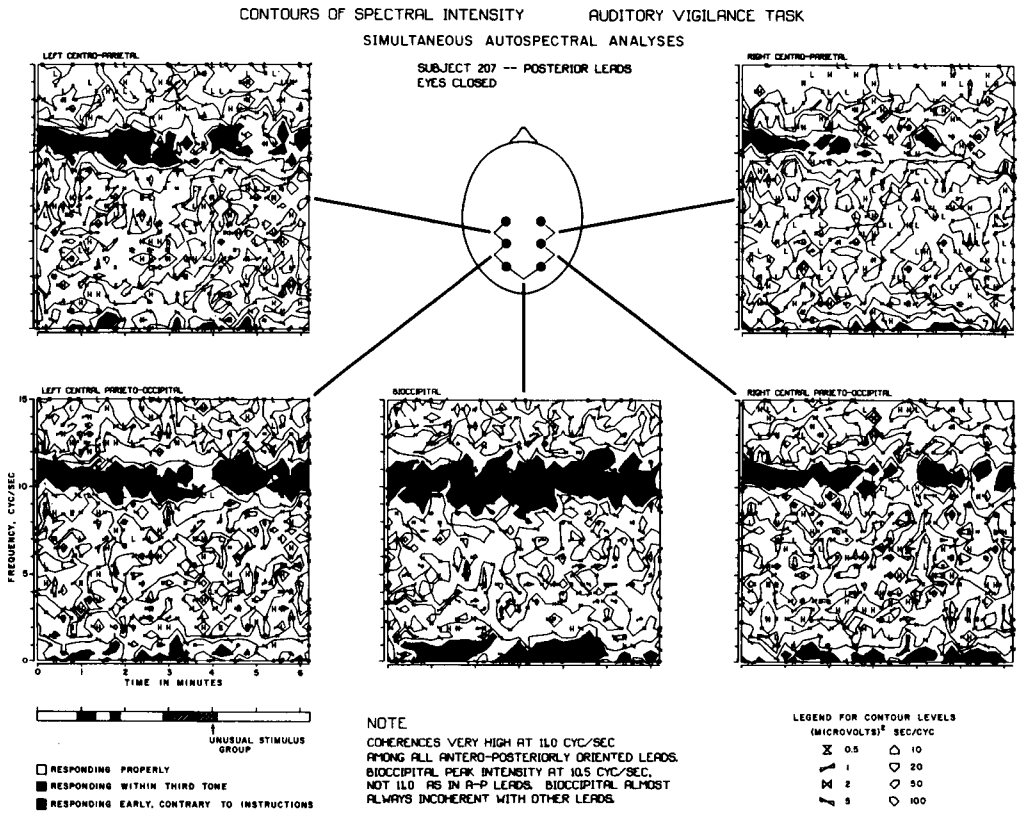

Figure 2. Continuous spectral density technique developed by Walter and Brown. This analysis of scalp leads during performance of a vigilance task shows broadening and downward drift in frequency of alpha band (shaded) in longitudinal leads in monotonous phase of repetitive performance during first 4 minutes. Many errors occured after 4 minutes on presentation of unusual stimuli. Alpha activity disappeared abruptly at this stage, but returned thereafter, initially in a quite narrow band at 10.5 cycles/sec, with resumption of monotonous task. Transverse bioccipital leads did not show this responsiveness [Adey, 1965].

lowering of the mean frequency. Afterwards the subject begins to make frequent errors by anticipating the third tone; he seems to become bored and his state of attention deteriorates. At this point he receives unusual stimulus groups; immediately, the alpha band disappears completely and there is a marked increase of lower frequencies. When the stimuli are returned to the original sequence, alpha reappears again as a narrow-frequency band and then widens out gradually during continuing repetition of the stimulus pattern.

There is general similarity among subjects, and anteroposteriorly from one point on the scalp to another. However, the transverse leads display none of this lability of alpha responses. This indicates an apparent antero-posterior orientation of the alpha-rhythm generators as they relate to situations requiring attention. How one region of cortex relates to other parts of cortex is analyzed by obtaining what is called a "coherent or linear predictability measure" (Walter, 1963). When this measure is high during a task, there are dark areas which are most fully developed between bilaterally symmetrical, homotopic regions. Between transverse leads there is virtually no coherence. Recently, transient nonlinear interrelations have been found to provide an additional index of changing states of attention.

Corticifugal Outflow

The nature of corticifugal downflow as it may determine activity in thalamus, hypothalamus, and midbrain has been investigated by studies of conditional responses in the dorsal thalamus (Kamikawa, McIlwain, and Adey, 1964). After a series of repetitions of conditional and unconditional stimuli, single thalamic cells change their activity during the CS-US interval. The extent to which this occurs appears to depend on the integrity of cortical systems and their controlling influence on the cells' activity. During extinction trials a plot of the mean firing rate reveals tremendous plasticity. A common finding is that an increased firing rate is often preceded by a profound inhibition; later, after a couple of hours of repeated blocks of training and extinction trials, the cell may become completely inhibited during extinction trials (Fig. 3).

Hippocampal-Diencephalic Relations

Adey discussed ways in which the hippocampal system may relate electrophysiologically to the rest of the forebrain. Many parts of the hippocampal system show continuous theta

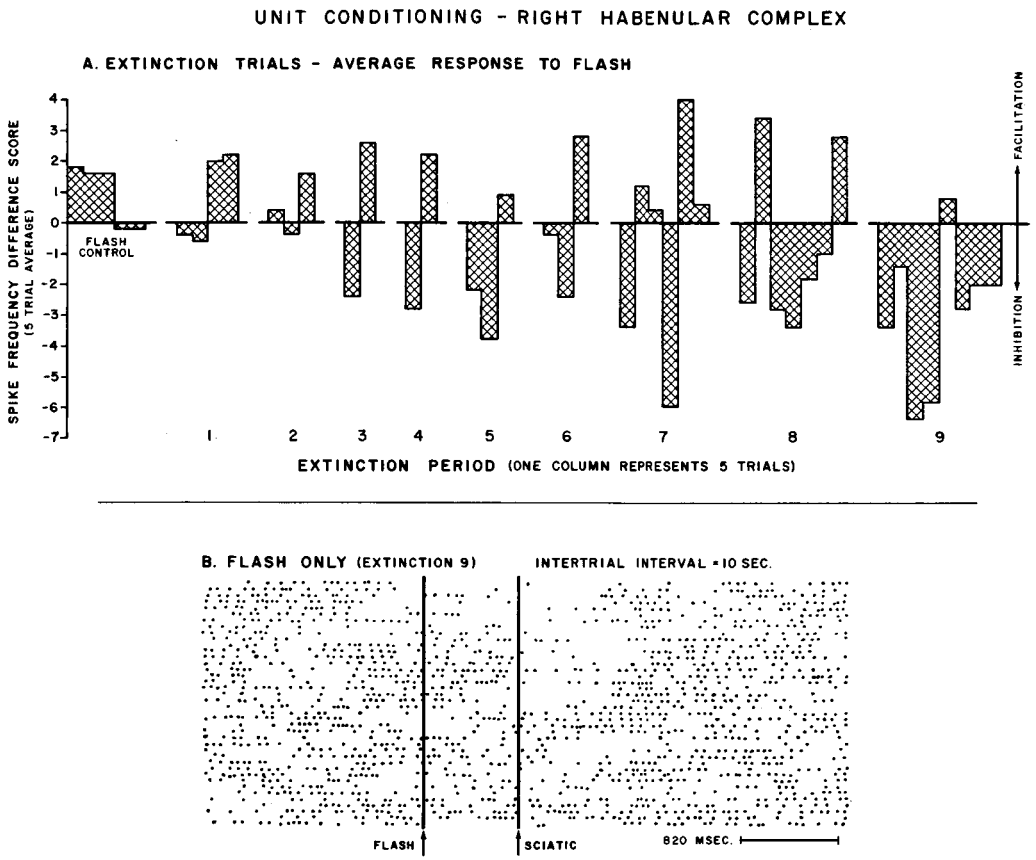

Figure 3. Repeated extinctions of inhibitory conditional response in a habenular neuron. A: Histograms depict difference scores (numerical difference between firing rate in pre-CS control period and epoch of 820 msec beginning 820 msec post-CS) for flash control and all extinction sequences. Each column represents average score for five trials. Columns are below the abscissa when the CS caused inhibition. B: Spike discharge record of final extinction sequence [Kamikawa, McIlwain, and Adey, 1964].

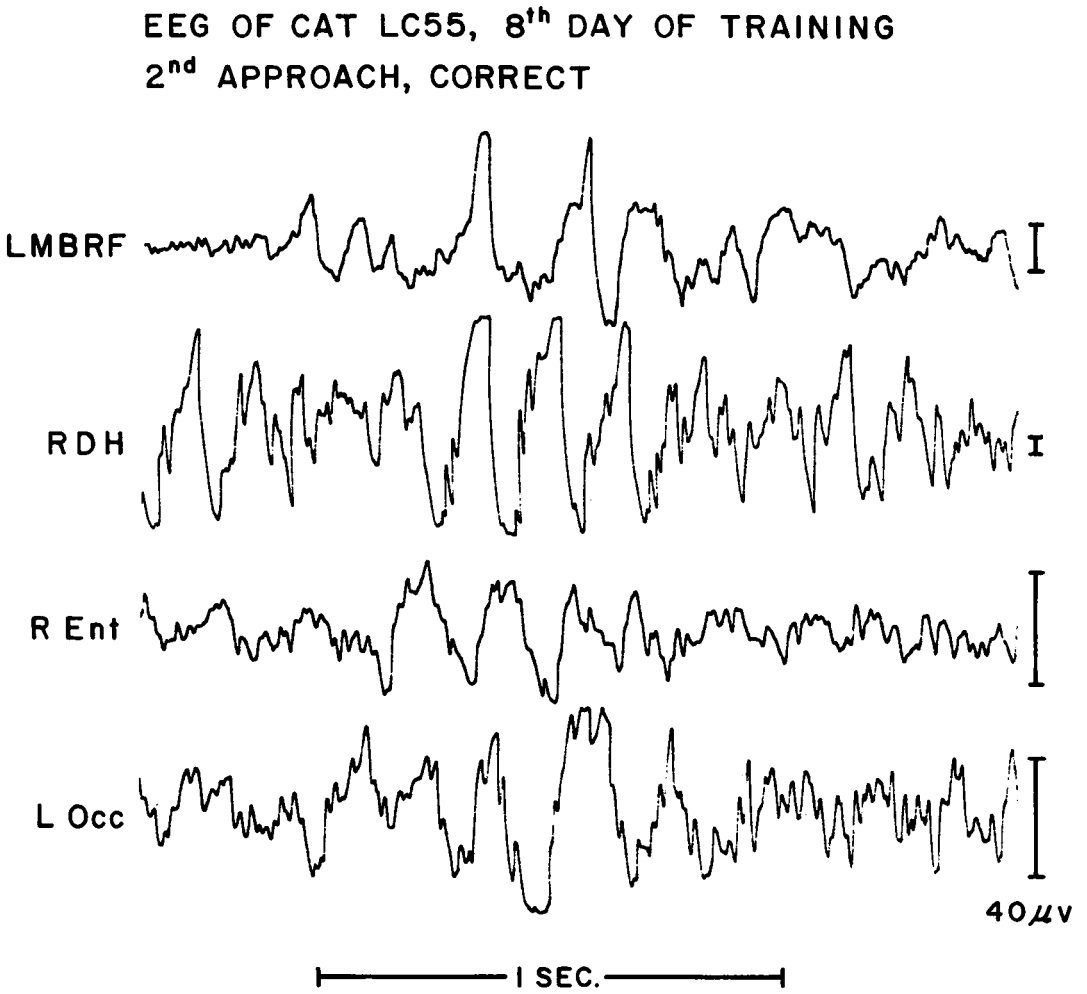

Figure 4. Typical theta-rhythm bursts in dorsal hippocampus (RDH) and entorhinal cortex (REnt) of cat during discriminative visual performance, beginning at left edge of time-marker bar. Similar, less regular rhythms appear in midbrain reticular formation (LMBRF) and visual cortex (LOcc) [Radulovački and Adey, 1965].

rhythms, whereas other parts may be desynchronized and only occasionally become synchronized during the occurrence of powerful rhythms in adjacent tissue. During approach to food on the basis of a light cue, animals show a powerful theta train having characteristics of a single frequency that is not present before or afterwards (Radulovački and Adey, 1965). Simultaneously there are signs of this same rhythm in subthalamus, midbrain, and visual cortex, although without the pacemaking characteristics appearing in the hippocampus (Fig. 4).

The way-station by which the hippocampus appears to influence diencephalic structures seems to involve a subthalamic region which is itself involved in feeding mechanisms. A small unilateral lesion in this subthalamic region results in a deterioration of the discriminative performance for a food reward to the light cue in a modified T-maze (Fig. 5) (Adey, Walter, and Lindsley, 1962). The performance decrement is temporary, lasting about a week. If, after recovery, one makes a similar lesion on the opposite side, there is a longer, although still temporary, decrement. With each of these unilateral lesions, the animal fails to discriminate and does not retain information coming in from the opposite half of its environment. The subthalamic lesion disrupts the regular hippocampal theta rhythm, replacing it with irregular waves. Following recovery, theta-rhythm activity returns to the hippocampus.

Does this subthalamic lesion interfere with sensory input invading the nervous system and refluxing either caudally through the subthalamus into the RF (Hugelin and Bonvallet, 1957) or upward through subthalamus into septum and thence into limbic structures (Lindsley and Adey, 1961)? There is a profound reduction of unit activity in the midbrain RF (Adey and Lindsley, 1959). The upstream effects include powerful subthalamic pathways to cortex that bypass the thalamus. This finding relates to the studies of Morison and Dempsey who showed that an animal practically moribund from very deep barbiturate anesthesia can be roused by subthalamic stimulation (Morison, 1954). The subthalamus is definitely a traffic intersection for hypothalamic, limbic, cortical, and midbrain transactions going both upwards and downwards through the neuraxis.

Drug Effects

Psychotomimetic drugs like the cyclohexamines and hallucinogenic drugs like LSD injected systemically have marked

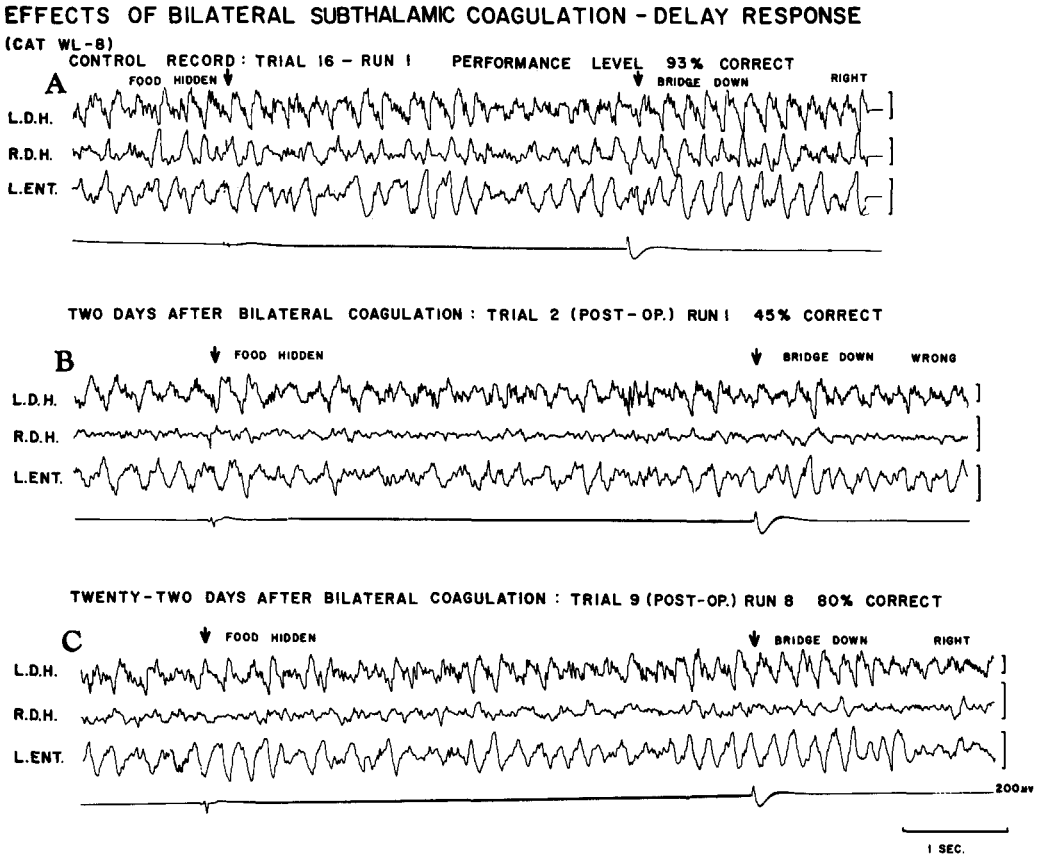

Figure 5. Effects of bilateral subthalamic coagulation (B) on theta-wave activity in hippocampus (LDH and RDH) and entorhinal cortex (LENT) and on delayed performance. Recovery of theta activity and performance ability occurred gradually over 14-20 days (C) [Adey, Walter, and Lindsley, 1962].

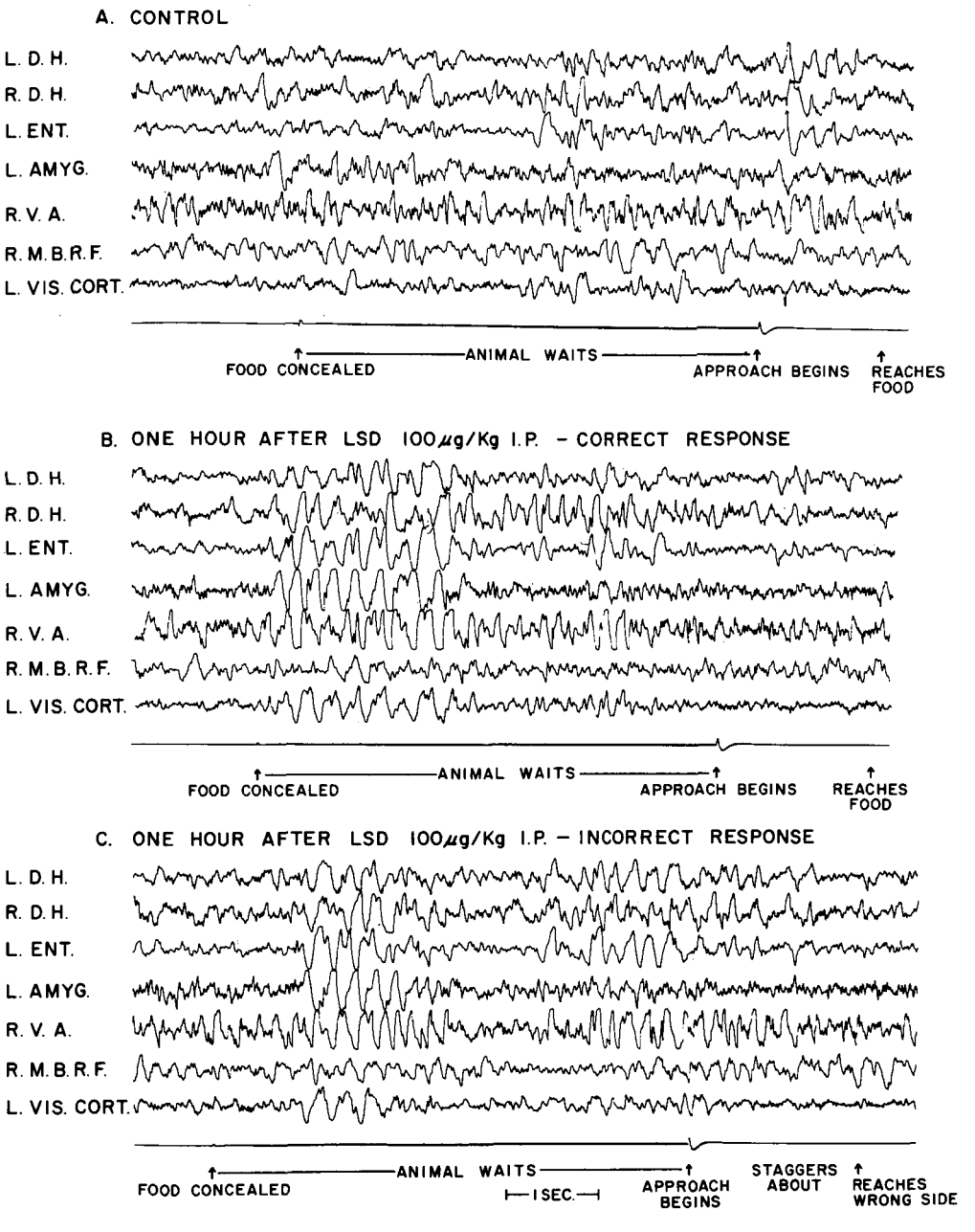

Figure 6. Effects of LSD on cat's ability to perform a discriminative motor task in delayed-response testing. Paroxysmal discharge immediately after animal has seen food concealed (B) does not interfere with subsequent correct performance. When, however, the paroxysm overlapped into the period of attempted discriminative performance (C), the animal staggered about aimlessly and ultimately made an incorrect decision [Adey, Bell, and Dennis, 1962].

effects on behavior. The first electrical abnormality following these drugs appears in the hippocampus and thereafter propagates into seizures that disrupt performance in delayed response tests (Adey, Bell, and Dennis, 1962). A seizure before or during food concealment disrupts performance, but a seizure beginning shortly after concealment is not associated with any loss of choice-making capability (Fig. 6).

Is the hippocampal theta activity seen during performance of learned responses a measure of orientation or something nonspecifically related to the learned act? When overtraining is used, behavioral orientation and the concomitant hippocampal theta during orientation both tend to disappear (Radulovački and Adey, 1965). LSD produces a very profound disinhibition of orienting behavior which continues for about 3 weeks. During approach performances following introduction of LSD, there is a great exaggeration of theta rhythms in the hippocampus; there is also an exaltation and increased regularity in theta rhythms accompanying orientation. For 1 to 3 weeks after the drug is given, theta activity during orienting responses is clearly slower and less regular than during discrimination (Fig. 7).

Adey stated that conditional responses can be induced in the absence of the greater part of any forebrain mechanisms. Sherrington (1897) showed, for example, that beautiful conditional responses can be elicited in decerebrated animals. About 6 years ago, Doty, et al. showed autonomic cardiovascular conditional responses in animals with huge diencephalic lesions that undoubtedly cut off the bulk of if not all forebrain connections (Doty, Beck, and Kooi, 1959). Rhinencephalic mechanisms appear to be involved in the focusing of attention by which we differentiate environmental stimuli. Adey suggested that the hippocampus is involved in controlling the degree of attention necessary for discriminative responses where visual or auditory cues require generalization and differentiation.

Central Events During Conditioning

Morrell deplored the tendency of physiologists to overemphasize negative feedback systems and homeostasis to the neglect of equally important positive feedback systems. The crucial feature of learning is that an organism changes its state and its organization and retains this altered configuration. At some time during the course of acquisition of learned responses, positive feedback systems must be involved.

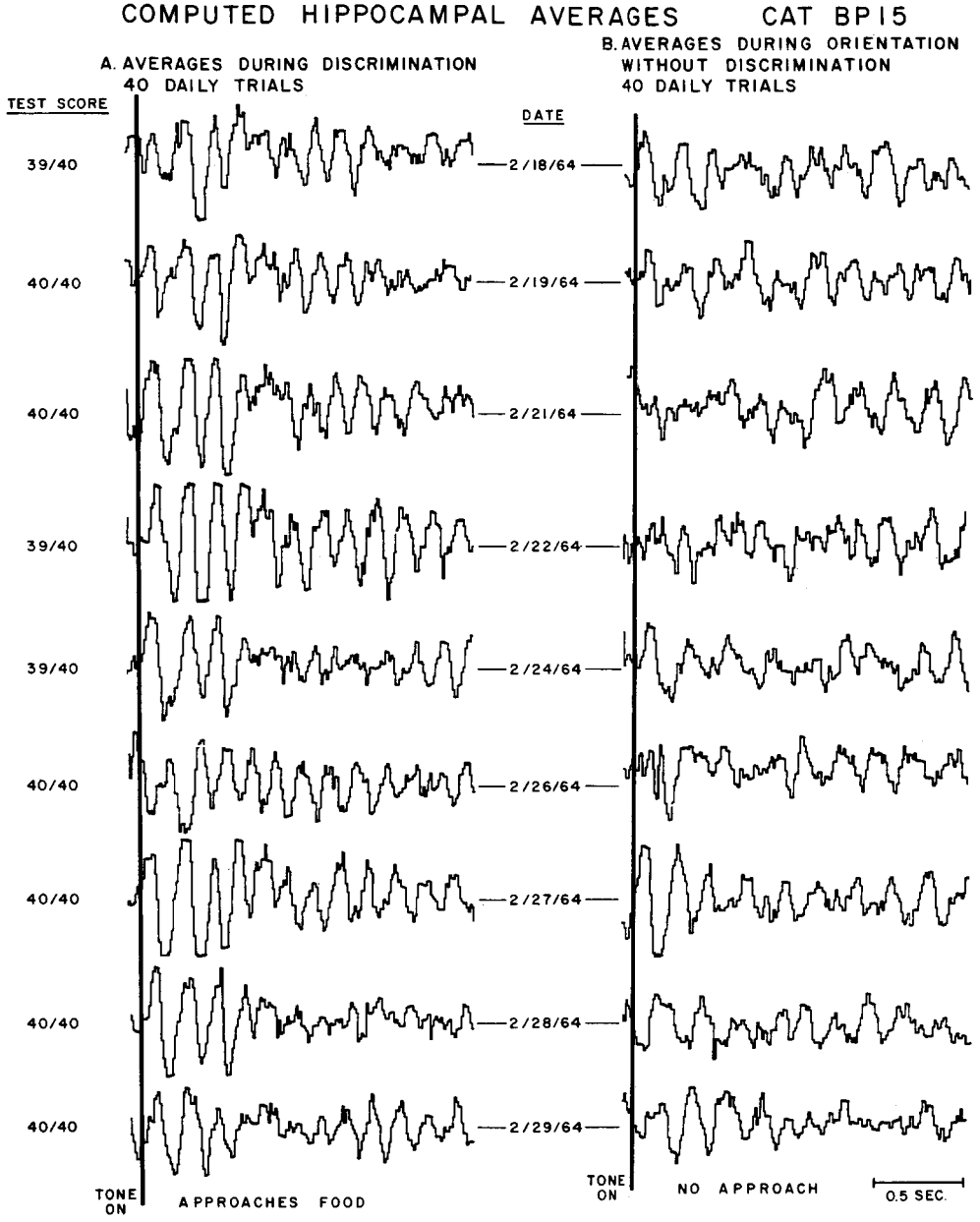

Figure 7. Effects on hippocampal wave trains of introduction of orienting trials (B) randomly interspersed between an equal number of discrimination trials (A). Characteristic 6 cycles/sec rhythmicity occurred in the early portions of the approach averages. In orienting trials, slower rhythmicity at 4 to 5 cycles/sec occurred in later portions of average [Radulovački and Adey, 1965].

Instances of this include the self-regenerating action potential and the self-propagating seizure discharge. Some such mechanism must take place at the cellular level in order to execute what Livingston calls the "Now print!" signal.

Central events that are generally thought to take place during an orienting response include: 1) desynchronization of the EEG recorded from widespread regions of the brain; 2) evoked responses to reiterated abrupt stimuli which initially are widely distributed but after many repetitions become restricted to limited sectors of the nervous system; 3) prominent d-c shifts, generally in a surface-negative direction with reference to a depth electrode; 4) increased activity of many nerve cells, with only a few showing inhibitory effects; and 5) increased local blood flow. Following repeated trials involving orientating responses to the same stimulus, the pattern of electrical activity of single-unit evoked activity becomes more localized, more specific, and more distinctly patterned. Later in the course of learning, a brief phase occurs in which there is a marked shift of cortical steady potential in the direction of surface positivity.

Cortical Conditioning

Some years ago Morrell began working with what is called "sensory-sensory cortical conditioning." He used as a model a flashing light US with a tone CS preceding the light and overlapping with it, and a CR involving repetitive driving of rhythmic waves in visual cortex at the frequency of the light flash (Morrell, 1957). Several distinct stages in this electrocortical conditioning can be identified: When the tone is first paired with light flashes and then tried alone, it has no effect. A generalized desynchronization is then observed as low-voltage fast activity throughout all brain areas. Still later, the tone alone elicits a rhythmic response in visual cortex at a frequency that closely approximates that of the light used as the US. The train of activations ordinarily induced by the light can now be triggered by an acoustic stimulus that has been paired with the light. This transitory phase lasts only a few trials and is replaced by localized desynchronization, that is, the tone alone now elicits desynchronization limited to visual cortex. (Fig. 8). This last stage is permanent as far as can be determined; no further changes have been observed.

Subsequent to this work, Morrell and Naitoh (1962) studied the effect on acquisition of learning of altering

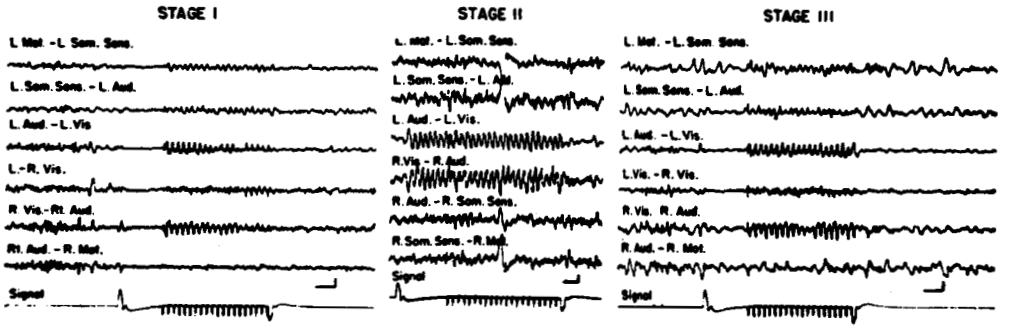

Figure 8. EEG records during sensory-sensory conditioning using a frequency tracer. The lowest trace is the marker for the sensory signals. The upward deflection signals the tone which precedes the 6/sec light flashes. The CS-US interval is therefore the period from the tone signal to the light signals.

Stage I: Generalized desynchronization of low-voltage fast activity in all main areas during the CS-US interval.
Stage II: 6/sec activity appears during the CS-US interval.
Stage III: 6/sec activity disappears from the CS-US interval and the desynchronization is localized to visual cortex [Morrell].

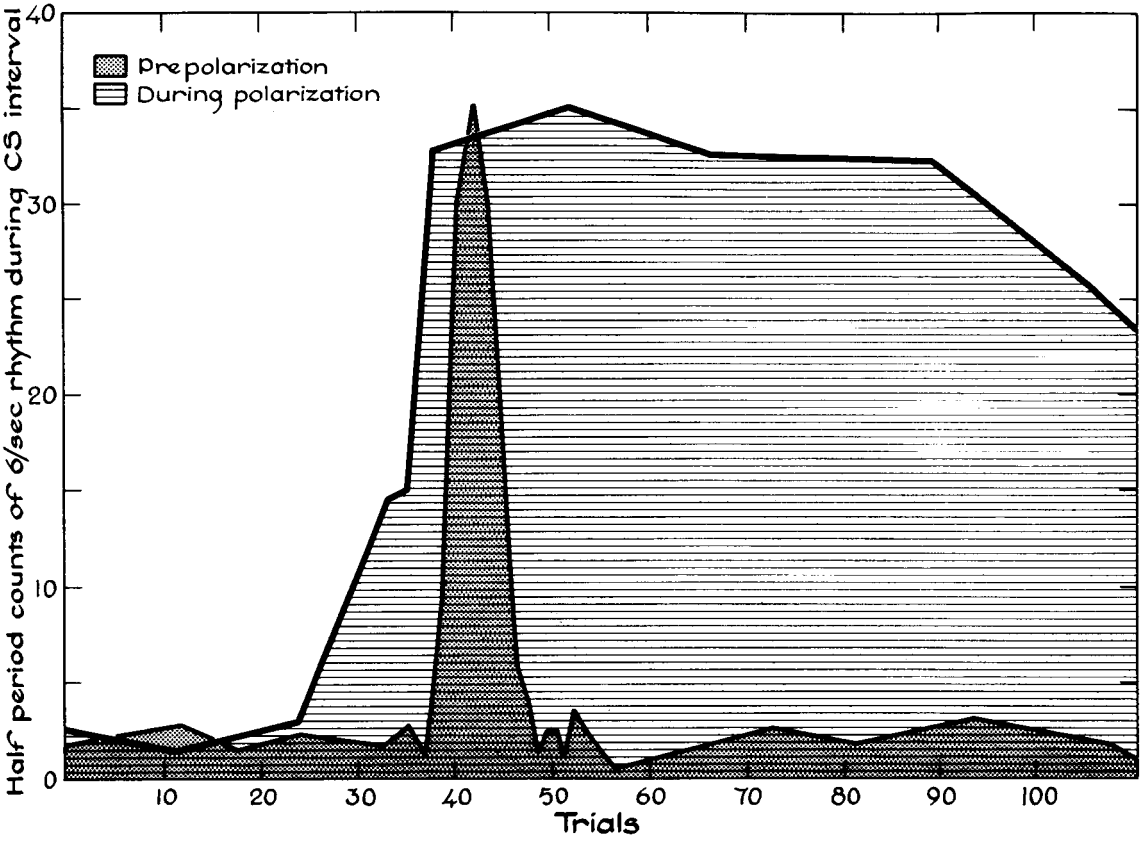

Figure 9. Effect of anodal polarization on conditioned repetive responses. This figure plots the quantity of 6/sec rhythms during the CS-US interval as a function of the number of trials. In the presence of the US the 6/sec rhythm would be expected as a consequence of 6/sec stimulation by the light (US). Pairing the CS with US leads to the appearance of the 6/sec activity to CS alone but only after a number of trials; it disappears again after a few trials. This event defines the three stages described in Fig. 8. Stage I is the period up to the sharp rise in 6/sec activity during CS-US interval. Stage II is the period of rise, and Stage III is the period after the decline. With anodal polarization Stage II appears a little earlier, and is prolonged over many trials [Morrell].

cortical d-c potentials. He found that units are influenced by polarization in a surface-positive direction in such a way that they retain stimulus patterns externally imposed upon them. He also found that in a behavioral situation it is possible to disrupt early phases of training by applying surface-negative, or cathodal, polarization. At this stage of Morrell's experimental work, Konorski suggested to Morrell that he utilize the results of his d-c experiments to explore further the sensory-sensory conditioning paradigm, particularly with respect to the second stage of cortical conditioning, during which repetitive phenomena are observed. Konorski's suggestion was that sensory-sensory conditioning is transient because it has no biological significance, and that even when two stimuli are paired, the connections are likely to be evanescent. The question was whether it would be possible to make the connections more lasting by applying anodal currents across the visual cortex.

The effect of anodal polarization was quite dramatic. Anodal, surface-positive d-c polarization, at the level of 10μ amp/mm^2 extending about 5 mm in diameter, resulted in a prolonged second stage of sensory-sensory cortical conditioning. (See Fig. 9.) Morrell considers that these effects are not correlates of conditioning, but veritable conditioned response induction itself. Because these changes were recorded in the Flaxedilized animal, they were not correlated with behavior. However, they follow all the laws of Pavlovian conditioning and can be differentially elicited.*

*Chairman's note: At the NRP Stated Meeting in August, 1965, Morrell showed evidence that certain nerve cells under experimental conditions suggested by Rusinov's work can be triggered so that they discharge in a way reminiscent of their past experience. It requires stimulation (e.g., light flash) to see this: the response obtained is a doubling or halving of the stimulus frequency or some similar change. When the stimulus is discontinued, the cell discharge stops; thereafter even a single flash may elicit a discharge having a periodicity previously entrained. When tested, the cell "remembers"; but how is the remembrance retained during the interval when there is no stimulation? Of course, no one can say that that particular cell remembers; it may well be driven from somewhere else, and many cells are likely to be in the entrained circuit. All one can say is that he is tapping in on a cell that shows the results of learned behavior. This does not prove that the information is actually stored in that cell.

Morrell elaborated further on experiments with anodal current application. He [footnote continued on next page]

The Nature of Anodal Current Effects

Konorski presented an interpretation of how anodal current might have these effects. In classical conditioning, presentation of a neutral stimulus (S_1) is followed by a so-called unconditional stimulus or reinforcer (S_2). That stable connections can be obtained between the two stimuli, S_1 and S_2, is shown by the fact that the animal begins to respond to S_1 alone as it had to S_2. Why must S_2 be an unconditioned stimulus, a biologically significant stimulus? Why is there little or no effect if S_1 is also a neutral stimulus? (There may be latent learning, but no real conditioning.)

The answer, in Konorski's opinion, is that both classical conditioning and instrumental conditioning occur only when there is not only appropriate pairing of the stimuli but also nonspecific excitation of the synaptic areas involved. Although he is less certain that there is nonspecific excitation

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[footnote continued from previous page] illustrated an increase in spontaneous firing induced by a pulse of 10μ amp/mm^2 surface-anodal current and a suppression of ongoing spontaneous activity with a surface-cathodal pulse, as has been observed by others. Using a bright light flash delivered to the atropinized eyes of a Flaxedilized cat, cells were easily fired during anodal polarization. Cells were chosen which responded with only a single action potential to each flash. After about 3 minutes of driving the cells, the flash frequency could be reduced from 8/sec to 4/sec and the cell would continue to fire at 8/sec for several seconds. In order to test more complex patterns, stimulation with doublet light flashes was given and the cell responded with doubled action potentials. This was carried on for 3 minutes, then flash stimulation was stopped and resumed at about half the frequency with single-flash stimulation. The cell responded for some time with doublets; another cell then made its appearance at its own firing rate but soon began to assume the same doublet pattern.

This kind of experiment may be important because it can be exploited in examination of synaptic changes related to anodal polarization. Morrell also showed a cell responding in triplets to a single flash, following conditioning with triplets. After a change of stimulation from doublets to single flash, another cell continued to respond with doublets for some time. When stimulation was stopped the cell became quiescent, then resumed its spontaneous firing rate. When flash stimulation was resumed at 4/sec and then followed by single flashes, the cell gave a couple of doublet responses, then adapted to the new frequency.

in the S_1 area (the CS), he believes such excitation definitely exists in the area of S_2 (the US). In classical conditioning the S_2 area is unspecifically excited by the intrinsic biological characteristics of the stimulus, i.e., by the fact that an animal sustains a noxious stimulus or a hungry animal obtains food. Thus, the animal is provided with not only the gnostic side of the learning phenomenon but also the unspecific stimulation which ensures connections between the two stimuli, S_1 and S_2.

What is the influence of the positive d-c potential? Anodal current provides the same local background that is normally brought about by the reinforcer. Thus, Konorski predicts that whenever S_2 is accompanied by a positive d-c shift, whether because of natural or imposed conditions, classical conditioning will occur. If it is accompanied by a negative d-c shift or by no d-c change, no conditioning will result. Galambos asked whether this differed operationally from Rusinov's (1953) notion of the dominant focus, whereby with anodal current Rusinov sensitizes a particular area of cortex to respond to signals to which it ordinarily would not respond. Konorski said that probably it does not differ significantly; perhaps only the verbal description of the process differs.

Miller asked whether the facts support Konorski's explanation. For example, is the orienting response to visual stimulus maintained longer if a positive d-c potential is applied? Morrell answered that the generalized electrical desynchronization disappears or abates a little more quickly in the presence of positive polarization. If such desynchronization is accompanying orientation, the orienting reflex does not persist longer. However, since the animal is Flaxedilized, overt orienting behavior cannot be observed.

Gumnit (1961) has shown that a novel acoustic stimulus produces a local <u>negative</u> d-c shift. This would appear to be in contradistinction to positive d-c effects. Gumnit found that if he introduces a novel tone lasting a few seconds, a cat shows localized surface-negative d-c shifts which are habituated within a few trials. Maintaining the same electrode placement, Gumnit learned that slight changes in the tone-stimulus characteristics yield d-c shifts which last for a few trials each time a change is introduced. Konorski suspects that this negative shift may be followed by an electrical rebound, that is, that the important positive shift may follow the observed negative shift.

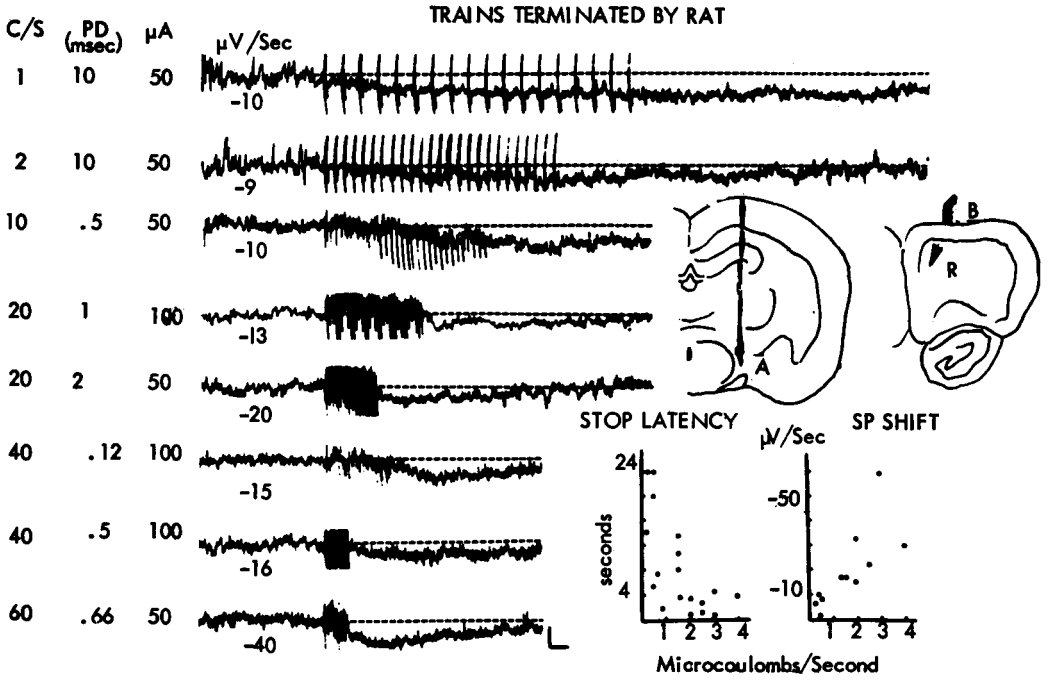

Figure 10. Inverse relation between stop latency and slope of steady-potential shift to lateral hypothalamic electrical stimulation started by the experimenter and terminated by the rat. Representative samples of the electrographic responses and the accompanying stimulus patterns are shown with the onset slope indicated in μV/sec (determined by the time required to reach the maximum amplitude of steady-potential shift). Table to the left indicates frequency (C/S), pulse duration (PD),and current (μA) used for the associated tracing. Point A shows terminus of stimulating electrode, 1 mm above optic tract in region of extreme lateral hypothalamus. No overt behavioral response from internal-capsule stimulation was observed to any stimulus condition. Recording electrode was on pial surface at B, referred to a penetrating white-matter electrode (R). Left plot shows declining tolerance (stop latency) of stimulus as a function of increasing energy (μcoul/sec) calculated from parameters shown at left. Right plot shows increasing onset negativity in steady-potential shift (μV/sec) as a function of the energy in the stimulus input. Points on the plot represent averages of three trials. Calibrations show 100 μV and 1 sec [Rowland].

Evoked D-C Responses

Whereas Gumnit's observation on evoked d-c responses were incidental to other phenomena, Rowland has been deliberately analyzing evoked d-c responses. A d-c shift, usually negative but not always, of anywhere from 100 to 200 μv, is frequently observed during a 10-sec conditional signal which is reinforced by food (Rowland and Goldstone, 1963). It is maximal when the cat is hungry; when the cat approaches satiation, the d-c change gradually diminishes; when satiety is reached, the d-c shift is no longer exhibited. This implies that the endogenous d-c potential is motivationally controlled. Rowland found that the d-c shift may begin within about 50 msec of a novel stimulus.

Rowland introduced preliminary data on conditioning with negative reinforcement. With lateral hypothalamic stimulation, which the animal will work to turn off, there is a prominent negative cortical potential shift. (See Fig. 10.) The slope of this d-c potential diminishes as the animal's behavioral tolerance of the hypothalamic stimulation increases. If the hypothalamic stimulation is increased in strength, the animal tolerates the stimulus a shorter time and there is a great increase in the negative potential generated. Rowland has also seen negative potential shifts with respect to reinforcement by exciting self-stimulation loci in the brain. These have been shown to be independent of any blood-pressure changes. The strength of the d-c potential appears to be proportional to the animal's endogenous motivation.

Rowland has seen many positive and negative shifts recorded from various areas of cortex but is not certain whether the direction of shift depends on which cortical areas are most particularly involved. Lickey and Fox (1966) have interpreted their own findings according to the "primary negative rule," i.e., when an auditory stimulus is given, the auditory cortex responds negatively and at the same trial the visual and somatosensory cortices respond positively, or more commonly, less negatively (i.e. relatively positively). If a visual stimulus is given, visual cortex goes negative, while somatosensory and auditory cortices go positive. Much of this, according to Rowland, depends on the characteristics and location of the reference electrode. Rowland has seen definite examples of cortical surface going negative with the immediate subjacent fourth cortical layer going positive, the d-c potential being a local dipole effect.

Morrell assumes that the application of a surface-

positive anodal current to the cortical surface results in relative depolarization of cell somata in deep layers of the cortex that tends to increase their rate of discharge. This is confirmed by microelectrode penetrations of cells in the depths, where marked increases in spontaneous cell-firing rates are observed following surface-anodal stimulation.

Miller asked whether this type of conditioning has been combined with behavioral experiments, for example, by presenting the animal with a tone associated with a flashing light during the anodal polarization and then quickly establishing an avoidance response to flashing light. Would avoidance to the light be transferred to the tone more quickly and better than if the d-c potential had not been used during the S-S conditioning? According to Morrell, no one has done the proper experiment, although transfer experiments were attempted by Chow, Dement, and John (1957) without accompanying d-c measurements. Schuckman and Battersby (1965) obtained transfer to a sound of behavior which had previously been conditioned to light. They all used electrocortical conditioning.

Morrell said that the d-c current is not immediately effective when pulsed; pulses take time to sum up and provide a net surface positivity. Olds suggested using a sine wave. Morrell has found that Metrazol definitely has an influence similar to surface-positive d-c current (Morrell, Barlow, and Brazier, 1960). He is inclined to think that any method of activating cortical cells would have a similar effect; subliminal excitations should contribute additively.

Implications

Stellar commented that this work seems to be the first real neurological advance toward understanding reinforcement. Physiological understanding of these processes should contribute significantly to an explanation of how discontinuing shock or putting food in an animal's mouth can modify central connections. Olds feels it would be a mistake to suggest that cellular activation constitutes reinforcement. Morrell, however, thinks he may be adding the sine qua non of reinforcement with d-c stimulation. One of the potent controls of cortical d-c potentials is subcortical activation. Putting this d-c potential shift directly into the cortex may be akin to stimulating the subthalamus, midbrain RF, or hypothalamus in ways that will indirectly shift the cortical d-c potential.

Morrell speculated on how such baseline changes may be

produced: Steady potentials of the magnitude recorded from cortex might be produced by synaptic potentials impinging on the large vertically oriented cortical cells. What is recorded as a d-c shift may be an epiphenomenon, a consequence of synaptic activation. Livingston asked whether this might instead arise from activation of ascending fibers, i.e., inputs to cortex from reticular or diffusely projecting thalamic systems causing activation of cells intrinsic to the cortex. Stimulus novelty, which is known to invade the reticular formation, could be affecting the cortical d-c shift as a consequence of the RF activation. Morrell agreed, recalling that when Arduini (1958) stimulated the RF he observed generalized surface-negative d-c shifts such as are obtained with arousal.

Rowland reported an experiment pertaining to this question. A cat was conditioned to yield a d-c shift during 10 seconds of 2/sec clicks. Rowland then inverted the stimulus conditions so that the animal received continuous clicks and the food reinforcement was now associated with 10 seconds of silence. After 2 weeks of training on this regimen the cat produced the same kind of d-c shift to silence that it had to the clicks, indicating that activation of specific sensory systems is not needed for the occurrence of the d-c shift (Fig. 11).

In conducting intracellular microelectrode studies, Morrell is impressed with a relative lack of transmembrane potential change associated with cortical polarization. Schmitt stated that Lorente de Nó (1946-1947) found strong effects of anodal polarization on activity in axons whose membrane potential had not been greatly altered. Even where there was complete lack of external sodium, anodal polarization restored excitability without introducing a change in membrane potential. Adey would not expect changes in membrane potential. The work of Granit, Kellerth, and Williams (1964) on spinal motoneurons shows that either intracellular or extracellular currents can induce inhibition in the absence of a shift of membrane potential, even in the absence of anything that can be construed as presynaptic inhibition, as judged by the size of EPSP's. This is evidence for what they call "motor inhibition," for which there seems to be no conventional Eccles type of electrophysiological concomitant.

Schmitt asked whether cathodal polarization decreases the stability of conditioning. Morrell replied that cathodal polarization does affect cell firing and that it produces more dramatic behavioral effects than does anodal polarization. This may simply reflect the fact that an experimenter can more readily disrupt behavior than improve it.

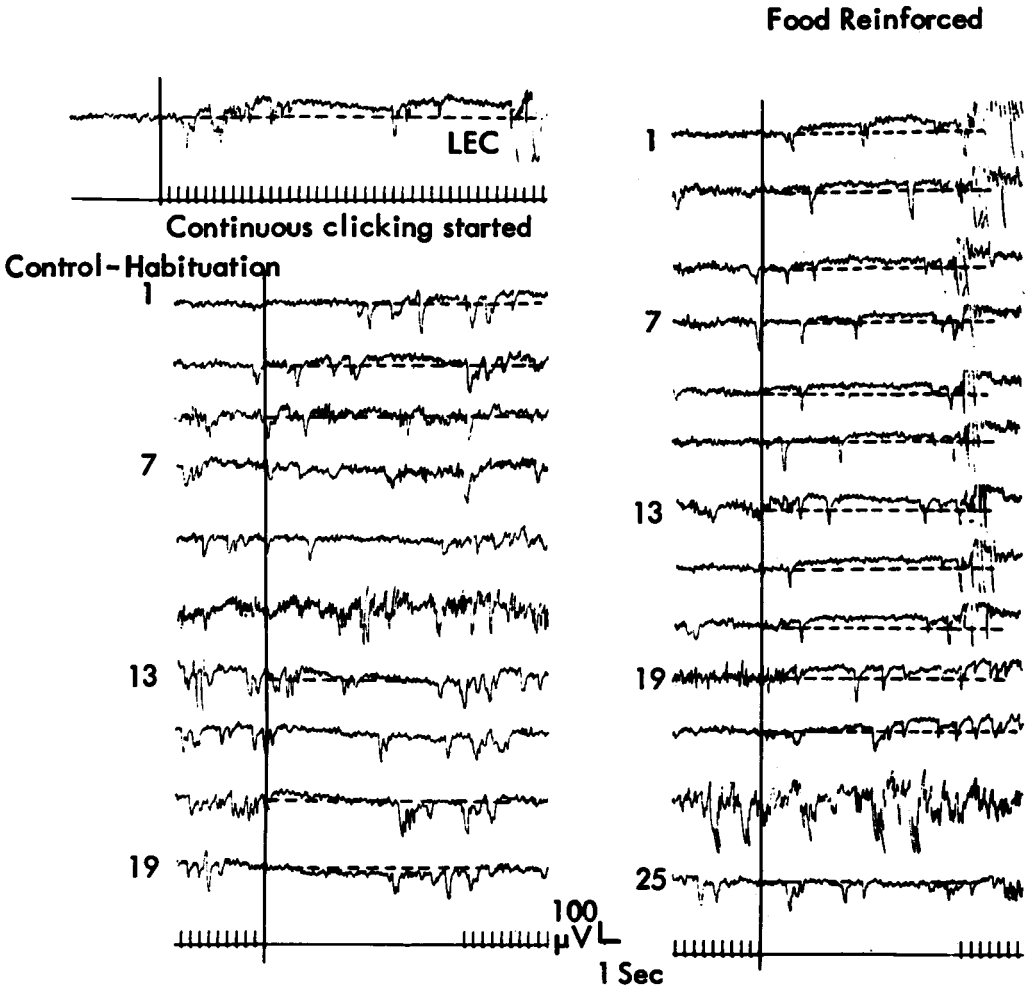

Figure 11. Independence of steady-potential (SP) shift from a sustained environmental stimulus. Top left tracing shows transition for a CS of 2/sec clicks to extinction. The SP shift was that characteristically acquired by this animal in visual cortex. The left column shows every other trial during introduction of 10 seconds of silence into otherwise continous clicking without reinforcement. Only a few brief shifts are observed and there was no indication of accompanying behavioral generalization to the inverted stimulus conditions. Right column shows a similar sampling of responses after 2 weeks of training with good acquisition and restoration of shift to silence with hunger, subsidence with satiety. Downward deflections, negative spikes appearing with each movement of the eyes indicate independence of the steady potential from eye movement [Rowland].

Neuronal Organization of Appetitive Centers

Adey delineated appetitive "centers" as comprising integrated cortical and subcortical systems. An anterior hypothalamic inhibitory region projects onto a more posteriorly situated excitatory region. Both inhibitory and excitatory zones can be affected by peripheral stimuli and also by changes in the milieu intérieur. In relation to learning, we must be concerned with connections between internal mechanisms and final behavior paths as well as with sensory inputs. Feedback loops among these various components always focus on final behavioral performances. Consummatory behavior, in turn, modifies sensory information returning from somatic and autonomic receptors in the body wall and viscera as well as central receptors.

Cortical and subcortical thalamic and mesencephalic mechanisms mediate such general states as arousal and the control of stimulus inputs. Temporal selections are probably determined by thalamocortical interrelations, for example. Selectivity is obviously critical for experiencing the reinforcing stimuli; this is one of the characteristics of consciously learned responses that distinguish them from simpler classical conditional responses which may involve no more than an increase in heart rate or salivation. These latter kinds of responses persist even after substantial damage to brain regions interrelating hypothalamus and cortex.

Hierarchy of Appetites

Biological priorities may be assigned to peripheral stimuli in terms of reinforcements that determine learned responses. Adolph (1947) introduced the notion that the regulation of variables contributing to internal homeostasis is based upon selection among possibilities according to priorities, competitions, and compromises. For example, the highest priority is assigned to pulmonary regulation. As Adolph pointed out years ago, the appetitive regulation of respiration has priority over regulation of almost any other homeostatic need. Second priority goes to the regulation of body temperature, which apparently outweighs priorities for regulation of body water and food intake. Body-water regulation ordinarily has a higher priority than food intake; but this can be reversed, as was done by Adolph, by simply watering the food.

Two subcortical regions in mammals appear to serve some role in thermoregulation: in the anterior hypothalamus, one

region extends into the preoptic area; in the posterior hypothalamus, a somewhat larger region is located above and behind the pituitary. The anterior hypothalamic region is concerned with heat production; when this area is stimulated with an electrode or its temperature raised by local heating, peripheral vasodilation, panting, and other manifestations of heat loss are induced (Ström, 1950). The nervous outflow for these effects appears to be through the posterior hypothalamic region. This has led to the notion that there may be a posterior region in which heat conservation is controlled. But this has not been definitively demonstrated. Cooling of the anterior hypothalamus induces heat conservation, including shivering, whereas lesions in the posterior hypothalamus impair shivering (Hemingway, Forgrave, and Birzis, 1954).

Medial and lateral zones of the hypothalamus are differentiated embryologically and morphologically. Medial hypothalamus is characterized by large groups of cells and very few fibers. Lateral hypothalamus contains mostly the fibrous pathways making up the medial forebrain bundle, which interconnects the entire basal forebrain. Olds has shown this lateral region to be one of the main reinforcing regions, as measured by bar-pressing for central stimulation. Medial and lateral hypothalamic zones are separately related to feeding and satiety: medial lesions result in failure of satiety mechanisms whereas lateral lesions lead to failure of eating. Yet it is in the lateral areas that stimulation is rewarding. There may also be some zones dorsal to the hypothalamus, transitional subthalamic, and ventral thalamic regions involved in hunger, but not in rewarding effects.

Effects of Lesions

Because the hypothalamus is elaborately organized, with nuclear constellations and fibers of passage going to and from remote regions, the effects of lesions do not represent the result of cell destruction alone. Following lesions there is always a surround of tissue which is abnormal to some degree. Often such an area shows epileptiform activity alternating with long periods of depressed activity. If lesions in this region are combined with spreading depression (a phenomenon in which widespread cortical activity is made abnormal for periods of minutes to hours by local application of potassium chloride solution, a technique that Bureš (1963) in Prague has found to interfere with conditioning), the resultant modification of feeding behavior suggests that the area surrounding the original hypothalamic lesion has become hyperactive (Teitelbaum and Cytawa, 1965). It also suggests a

hypothalamic "release" following cortical spreading depression. Spreading depression is associated with a profound surface-negative shift and depolarization of cortical cells. Its effects are reversible. When the normal cortical standing potential returns in due course, so do appropriate behavioral responses.

Stellar noted that, as with many other lesions, there is recovery over time following lateral hypothalamic lesions (Teitelbaum and Stellar, 1954). If, after considerable recovery, lesions are made in the periphery of the original lesion, the syndrome is reinstituted and recovery begins once again. This can be observed repeatedly. It is possible that there may be initially depressed tissue surrounding the successive lesions which then becomes active and functional, only to be destroyed by later lesions. Perhaps the remaining system-as-a-whole, that is, the remainder of the brain surrounding the lesions, in some way imposes on the immediate surround to take on functions previously served by the destroyed tissue. As indicated earlier, Chow has demonstrated that if a single large lesion is made in the midbrain, destroying an extensive region of the tegmentum, the animal lapses into coma and may die. If, however, the same-sized lesion is inflicted progressively over a period of months, it is quite difficult to discern from outward behavior that the animal has sustained a major insult to its central tegmentum (Chow, Dement, and John, 1957).

Although lesions in the medial and lateral hypothalamus produce what appear to be opposite behavioral results, the situation is actually more complex. Lesions in the lateral hypothalamus may cause the animal to refrain from spontaneous eating, to the point of death; yet Adey and Lindsley (1959) have found that food placed in the mouth of lesioned cats and monkeys is chewed vigorously and swallowed. Animals may be maintained in this way until they begin to eat spontaneously again. Adey thinks that there may be defects, if not in perception, at least in visual interpretations and judgments relating to food recognition and signification.

Effects of Stimulation

Miller pointed out that electrical stimulation of the medial hypothalamic region causes hungry rats to stop eating, but that it also elicits aversive reactions which complicate any simple interpretation of this effect as the result of activating a center that inhibits hunger. Rats will learn to press a bar to turn off such stimulation (Krasne, 1962)

although Olds finds that there is also some tendency for them to press a bar to turn it back on again. Stimulation will cause rats to stop drinking as well as to stop eating. The interference with eating and drinking may involve more than general aversiveness, however, as is shown by Wyrwicka and Dobrzecka's report (1960) that termination of such stimulation in satiated goats may be followed by eating, apparently as a rebound effect. Similar unpublished observations on satiated rats have been made in Miller's laboratory. Stellar added that if a cannula is put into the ventromedial hypothalamic area and a tissue stimulant such as mildly hypertonic saline is introduced, feeding can be depressed for a long period without there being signs of generalized distress (Epstein, 1960).

Relative to the question of the significance of central stimulation, Adey mentioned that the Valensteins recently (1964) allowed animals to turn central stimuli on or off. Does central stimulation have both a specifically rewarding and specifically aversive quality? The Valensteins' article suggests to Olds that parts of the brain have general properties such that animals will turn central stimulation on and off; changes in intensity will affect the time relations involved. Olds finds regions where animals will turn the stimulus off and never turn it on. There are other regions, such as the cingulate cortex, where animals will turn the stimulus on and never turn it off. There are also places where animals will turn stimulation on and then turn it off, or turn it off after it has been turned on by the experimenter.

Olds considers the hypothalamus to constitute a large junction box between two major pathways: the medial forebrain bundle entering, and the great paraventricular system leaving. Stimulation of incoming fibers will induce animals to work to turn the system on; stimulation of the outgoing fibers will induce animals to work to turn it off. Stimulation of the hypothalamus itself gives mixed results.

Hypothalamus and Hippocampus in Conditioning

Hypothalamic Release of Behavior

Grastyán detailed his experimental work on the role of the hypothalamus in conditioning. By stimulating some points in the hypothalamus of cats, chiefly the lateral hypothalamus, Grastyán, et al. (1965) found it possible to induce pre-established approach and aversive reactions. He refers to

this phenomenon as "hypothalamic activation of conditioned reactions." Operant approach to food and operant avoidance of water inundation of the bottom of the cage are used. In the cage there is a small bench onto which the cat can jump to avoid the water; a food box is also available. The animal's EEG and body movements are monitored. Two different auditory stimuli are used: 10/sec clicks for the alimentary approach reaction and 1000 cycle/sec tone for the avoidance reaction.

During sound stimulation, stimulation of the lateral hypothalamic region tends to activate an avoidance response; in the absence of sound stimulation, hypothalamic stimulation tends to elicit an approach reaction. In such a double conditioning situation the animal's orientation toward the food box or the escape perch and the intensity of hypothalamic stimulation will affect which reaction will be obtained. Avoidance is ordinarily more likely to result. But when the animal is facing the food box, hypothalamic stimulation releases approach to the food box. If the cat is looking toward the avoidance platform, hypothalamic stimulation releases avoidance behavior. This hypothalamic release of behavior takes place in the absence of the conditional reflex signal for approach or avoidance. There is apparently something common to hypothalamic excitation and release of conditional behavior. Alternation between the two conditioned responses, i.e., repeated approach and avoidance behavior alternating five or six times, can be elicited by strong continuing hypothalamic stimulation. Recordings from the hippocampus suggest that two different hippocampal regions are showing reciprocal activity patterns during this behavioral oscillation.

By not reinforcing responses to the conditional sound stimulus, extinction is obtained after about 20 non-reinforced trials; yet hypothalamic stimulation will still activate the responses. After about 35 non-reinforced trials, activation is no longer elicited by hypothalamic stimulation. Loss of CR's and of the behavior-releasing effects of hypothalamic stimulation may be reversed, as in classical conditioning, by disinhibition following an unusual external stimulus.

Hippocampal Choice of Reactions

Activation of conditioned responses seems to Grastyán to be closely related to the drive-reduction hypothesis. Termination of stimulation apparently plays an essential role. If, during several trials, stimulation is continued beyond the moment when the animal reaches the conditional goal, then the activation process is abolished and sometimes also the

conditional stimulus itself becomes temporarily ineffective. A new experimental arrangement, the so-called pedal-switch off method, has proven useful in revealing what happens following discontinuation of stimulation. Electrical hypothalamic stimulation is started by the experimenter and stopped by the animal's own action in stepping on a large pedal in the course of locomotion elicited by the stimulation. Such interruption of stimulation induces remarkable aftereffects, antagonistic to those elicited by the stimulation itself.

Weak hypothalamic stimulation elicits approaching, orienting behavior; strong stimulation in the same place induces flight or withdrawal. The importance of the rebound-like aftereffects manifests itself in the formation of conditional locomotor stimulation reactions relating to the place of interruption of the stimulation, the pedal. That is, after several interruptions of a weak stimulation, pedal avoidance develops; after several interruptions of a strong stimulation, pedal-approach reactions develop. Moreover, a strict correlation has been found between behavioral and hippocampal electrical effects both during and after stimulation. Approach reactions elicited by weak hypothalamic stimulation, or appearing as an aftereffect of strong hypothalamic stimulation are characterized by a slow 3/sec-5/sec theta rhythm. Avoidance reactions induced by strong stimulations or appearing as an aftereffect of weak stimulations are accompanied by a definite desynchronization in the hippocampus. These findings have emphasized the role of hypothalamic stimulus aftereffects in the formation of conditional reactions and have supported the assumption that the importance of drive reduction lies in its capacity to induce a strong drive, indispensable for conditional coupling. The hippocampal electrical correlates of the two basic motivational forces (approach and withdrawal) have helped to extend the drive-reduction concept to the formation of conditional reflexes during natural experiences.

When hippocampal theta rhythms are elicited by mild hypothalamic stimulation, or by sudden interruption of hypothalamic stimulation, both goals are avoided despite the animal's having very stable conditional reflexes. If stimulus intensity is increased to produce desynchronization in the hippocampus, immediate activation or release of either response or of alternating responses occurs (Grastyán et al., 1966).

Grastyán stated that the arrest reaction which frequently follows the interruption of strong stimulation may play an important role in the fixation of new motor skills. During

the arrest reaction there are two extremes of hippocampal rhythms: very slow potentials, sometimes slower than theta, interspersed with high-frequency discharges. It appears that the patterns of approach and avoidance that relate distinctively to these two different hippocampal rhythms are mixed whenever the rhythms are mixed. The arrest reaction appears to represent an outward expression of the simultaneous occurrence of two incompatible motor tendencies of approach and avoidance.

Grastyán thinks that in the lateral region of the hypothalamus there is a system responsible for approach reactions, i.e., a motor system that generates searching, exploring, and approaching behavior. He conceives the role of the hippocampus as being to direct information coming in from the outside world toward approach or avoidance responses. Destruction of the hippocampus is conceived of as yielding predominantly approach reactions like those following bilateral temporal-lobe ablations in the classical Bailey-Klüver syndrome. It is still possible to elicit avoidance reactions to painful stimuli but it is no longer possible to condition avoidance. Approach reactions are assumed to predominate because of lack of a hippocampal brake on the lateral hypothalamic approach system.

According to Grastyán, conditional reflexes are exhibited at moments of rapid fluctuation in excitation level between relevant drive systems. Natural motivational processes generally build up by slow increments; at the moment of drive reduction, the situation changes rapidly and at such times conditional reflexes are consolidated. The moment of drive reduction is thus optimal for forming conditional behavior. The amplitude of changes in level of excitation depends on the sensitivity of the hippocampus, which in turn depends on its various inputs.

The finding of a cyclic variation of the two characteristic electrical patterns in the hippocampus in the course of self-stimulation helped to formulate a more dynamic interpretation of self-stimulation.

Konorski raised a problem concerning hypothalamic activation of CR's. If an animal is trained in two instrumental CR's, one for food and the other for avoidance, there is evidence that the two responses are established by connections among different structures, a hunger-drive system, and a fear-drive system, or intermediaries of these systems. Grastyán indicated that stimulation of the hypothalamus, a region where many different kinds of drives converge, is highly unspecific;

either one or another pattern of movements can be produced by the same stimulation. Konorski questioned how hypothalamic stimulation could lead to such different kinds of responses. The region activated may be widely diffused or these functions may overlap closely; what Grastyán is observing may represent a physiological artifact.

Konorski cites experimental findings opposite to Grastyán's, published by Wyrwicka et al., using goats with electrodes implanted in the lateral hypothalamus (Wyrwicka et al., 1960, Balinska et al., 1964). The animals were trained to perform lever-pressing to get food only in response to a whistle. When the animal was satiated it did not perform the response to the whistle or to hypothalamic stimulation alone. But when the whistle was added to electrical stimulation of the hypothalamus, the correct response was performed.* Olds added that Balinska et al. (1964) lost avoidance CR's after lesions in the lateral hypothalamus. In Grastyán's view, during theta rhythm in the hippocampus the hypothalamus activates avoidance behavior; during desynchronization in the hippocampus the hypothalamus induces approach behavior. Adey pointed out that there are regions of hippocampus which are continuously desynchronized except when a theta burst appears during a discriminative response.

Reciprocal Cortical and Hippocampal Patterns

Lindsley described experiments by Weinberger, Velasco, and himself (1965) in which they sought with classical

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* Our observation, according to which hypothalamic stimulation can activate seemingly antagonistic conditional responses, is not necessarily contradicted by Wyrwicka et al.'s findings. In their experiments, the effect of stimulation was tested only in relation to approach conditional responses. The dilemma of how specificity can be ensured by a system releasing responses of such an ambiguous mixture can be resolved by specifying the role of drive reduction. The appetitive actions of a special drive may cover a wide range of nonspecific behavioral actions. On the other hand, a special drive, like hunger, in natural circumstances is reduced only by means appropriate to decreasing hunger. If a drive is induced artificially, i.e., by electrical stimulation, it can be "specifically reduced" at will by termination of the stimulation. This point is discussed in more detail in Grastyán et al., 1965. [E.G.]

differential conditioning in the cat to differentiate electrocortically between the reinforced (CS) and non-reinforced (DS) stimuli. The CS was a row of lights above the food cup flashing at two per second and indicating food reward. The DS, or differential stimulus, was the same row of lights, lighted continuously. They expected synchronized cortical slow waves during the inhibitory behavioral period following the DS, but this did not occur. They then used thalamically induced recruiting responses as a measure of the difference between the electrocortical state associated with CS and DS. It was found that the CS promptly blocked recruiting responses, whereas the DS produced only a momentary blocking, associated with a brief transitory orientation toward the food cup, followed by prompt return of recruiting responses. Thus blocking of recruiting by the CS and not by the differential stimulus, during which behavioral orientation and attention to the food cup were minimal, demonstrates the sensitivity of thalamically induced cortical recruiting responses to reinforced versus non-reinforced stimuli. It also suggests that the recruiting blockade is due to CS-induced reticular activation associated with behavioral orientation and attention. No hippocampal responses were recorded, but since cortical activation and recruiting blockade accompany the CS and not the DS, one might expect hippocampal theta activity during the former but not the latter.

In this connection Lindsley restated the fact that Adey and associates (Adey, 1961; Holmes and Adey, 1960) and Grastyán and collaborators (Grastyán et al., 1965) find synchronization or theta activity in the hippocampus at a stage when the animal is about to make a decision and act. As was reported by Green and Arduini (1954), there tends to be some reciprocation of rhythmic activities between cortex and hippocampus when desynchronization is occurring in the cortex. Blocking of recruiting as well as desynchronization of synchronized activity in the cortex would seem compatible with the effects Adey, Grastyán, and their collaborators are observing in the hippocampus during the time that an orientation or discrimination is taking place. Lindsley reported that blocking of recruitment generated by stimulation of either ventralis medialis or ventralis lateralis results from stimulation of the forebrain, caudate nucleus, reticular formation, sciatic nerve, or the thalamic nucleus contralateral to the one from which the recruiting is being generated. This has been known for a long time, but only recently was it found that if a lesion is made in the rostral mesencephalic tegmentum, recruiting can no longer be blocked by stimulation of any of these forebrain areas. Thus it appears that forebrain stimulation

requires an intact midbrain reticular formation as a relay or source of upstream blockade of the thalamocortical recruiting (Schlag and Chaillet, 1963; Weinberger, Velasco, and Lindsley, 1965).

Hypothalamus and Operant Conditioning

Olds presented studies relevant to those of Grastyán, relating to the role of the hypothalamus in conditioning. Olds found that a rat will turn on and leave on current stimulating the medial forebrain bundle. This bundle contains, among many others, fibers descending from olfactory cortical systems. Some medial forebrain bundle fibers enter the hypothalamus, others originate in the hypothalamus and pass up and down via the bundle. Stimulation of the periventricular system of fibers has an opposite effect; an animal will turn off applied stimulation and not turn it on again. If hypothalamic nuclei are stimulated, there may be positive as well as negative reinforcement from probes in the same location.

Olds described experiments in which rats press a pedal to escape from stimulation applied in the boundary region lying between the tectum and tegmentum just beneath the superior colliculi, where Olds believes the periventricular system of fibers courses. However, when stimulation of the septal area is added, this escape behavior disappears. It is probable that the escape behavior is suppressed by activation of some parts of the corticifugal olfactory system. In similar experiments, rats will press a pedal to receive stimulation in the posterior lateral hypothalamus. If the experimenter then adds stimulation in the tecto-tegmental region, an aversive reaction is produced and the self-stimulation behavior stops.

Olds postulates two inhibitory relationships: 1) between olfactory cortical areas and periventricular fibers originating in the hypothalamus; 2) between these (via a recursive-collateral) and the lateral hypothalamic "reward" systems. Stimulation of the lateral "rewarding" paths does not give inhibition of avoidance behavior as might be expected if there were just a simple reciprocal inhibition; rather, avoidance behavior is augmented. Lesion studies show that when the animal is self-stimulating via electrodes implanted along lateral hypothalamic paths, cutting their outflow upstream to the telencephalon does not cause any reduction of self-stimulation. But when such an animal is self-stimulating via electrodes implanted in anterior parts of the same paths, cutting off

posterior outflow effectively terminates the self-stimulation. The posterior region therefore would seem to be a critical focus for positive central reinforcement.

An astonishing effect found by Olds and by a group including Wyrwicka occurs following a small electrolytic lesion just lateral to the mammillary bodies in an area where fibers of the medial forebrain bundle terminate or pass from diencephalon into midbrain. This is a region from which Olds has elicited the strongest positive reinforcement -- one in which he might have said earlier that the main "pleasure center" of the brain might be located. But he finds that a large lesion in this region almost completely eliminates aversive behavior. Nauta suggested that the lesion probably causes only a partial interruption in outflow from the hypothalamus. Olds said that the probes are pretested for positive reinforcement before the lesion is made; the lesion is not large. In some cases, if a small lesion is made in the region yielding aversive behavior at the base of the colliculus, self-stimulation is augmented, again suggesting an inhibitory connection between periventricular fibers and lateral hypothalamic areas. Olds has a hunch similar to Grastyán's that there is a spontaneously active mechanism in the hypothalamus which is probably under the control, among others, of inhibitory inputs from other spontaneously active systems.

Olds has never produced a lesion that would stop self-stimulation when the stimulating electrodes were located in posterior parts of lateral hypothalamus. He feels that this is a really powerful focus for positive and negative reinforcement. If there is a common denominator for positive and negative reinforcement, it is at the behavioral level of release of instrumental activity, i.e., such activity is required both to escape from pain and to approach food. Olds supposes that the extrapyramidal system yields such directed action and that the reinforcement mechanism itself is located nearby (i.e., in areas such as lateral hypothalamus).

Central Control of Sensory Transmission

Extraclassical Conduction Systems

The brainstem reticular formation is often looked upon as an extraclassical sensory pathway. Incoming sensory signals pass along the main classical sensory pathways to reach the cortex. Collaterals from these incoming pathways also

reach cortex by activating ascending reticular pathways. Activity along both of these two avenues is probably indispensable for conscious perception. The question often asked is whether and to what degree this extraclassical ascending pathway contributes sensory "information." Traditionally, physiologists have analyzed both the classical and extraclassical auditory pathways by introducing short-lasting stimuli such as clicks or tone pips. Six years ago, Starr and Livingston began studying these paths using long-lasting sound stimuli. Stimulus duration lasted from 5 minutes to as long as 24 hours, but generally was kept at 2 hours. Their unexpected results were as follows:

The only pathway that continued to be activated during continuing sound stimulation was the classical auditory pathway (Starr and Livingston, 1963). This pathway changes in averaged electrical activity most spectacularly when the stimulus goes "on" or "off" but it sustains a conspicuous degree of increased electrical activity for as long as the sound stimulus is continued. The extraclassical reticular pathway also changes abruptly with the stimulus "on" or "off"; but during continuing sound stimulation, activity in this pathway returns after only 20 or 30 seconds to what appeared to be a normal level of activity.

They view the nonspecific pathway as contributing to perception mainly by responding to change occasioned by the beginning and ending of events. The traditional method of sensory signal analysis, using short-duration stimuli, induces a change signal for both "on" and "off" with each test stimulus and thus overlooks the return to normal activity during steady-state stimulation, either continuing sound "on" or continuing sound "off." Perhaps what is mainly signaled by extraclassical sensory and motor pathways is that some bodily or environmental change has occurred.

Nauta pointed out that this would provide a means for signaling novelty throughout the brain, as would occur with either a stimulus onset or offset. Livingston agrees and thinks of this effect as a first-order abstraction of the neural events needed to define novelty. The reticular message would provide information useful to both the neocortex and the limbic system by announcing widely that a change has occurred, and perhaps also by arousing discriminative systems necessary for making comparisons between incoming and stored (remembered) sensory signals. Events need to be identified

for their potential significance at moments of change. The signal "change" would perhaps initiate identification of what is biologically significant and the release of emotional discharge and modification of appetitive systems necessary to learning or release arousal essential for orientation and discrimination.

Control of Sensory Input

Livingston introduced a study by Galin (1965) of events along the classical auditory pathway when a 5-minute steady-sound stimulus is associated with punishment or reward. If neither reward nor punishment is associated with the steady sound, there is a sustained response at the inferior colliculular level for the duration of sound. If punishment is introduced at random times but only during sound stimulation, there is a marked reduction in amplitude of the acoustic response at the inferior colliculus. The evoked response diminishes to the point that there is only an "on" and an "off" change in averaged electrical activity. It is as though "input gain" at the collicular level had been reduced to almost zero. If the association of punishment with sound is then discontinued, the acoustic response returns to approximately control levels after a few days of such "extinction" trials.

Galin's work suggests that during conditioning a considerable amount of control may be exercised over sensory input. If changes in other sensory systems prove to be as dramatic as Galin's evidence indicates, and if they occur at levels as low as the inferior colliculus, then those sensory stations above the midbrain, upon which we presumably depend for perceptual experiences and for the establishment of new connections for discrimination and learning, must receive an already vastly altered pattern of sensory input.

Miller wondered whether the sound used by Galin had become aversive because the electric shock had conditioned fear to it, so that the reduction in amplitude of evoked response at the inferior colliculus might be an attempt by the animal to give itself hysterical anesthesia to avoid the sound. Miller asked whether a different effect would be seen if the sound were associated with reward. Rowland ventured that there ought to be a change in the opposite direction. Livingston reported that although giving reward apparently does not change the collicular response from control levels, in a few cats Galin observed an increase in amplitude of

sound-evoked response in the medial geniculate to reward only. This nucleus normally yields extremely little response to continuing sound, as compared, for instance, with the inferior colliculus and lower auditory stations (Starr and Livingston, 1963).

Morrell questioned how an animal could afford to have information excluded at the input level. The central representation would then be distorted and it would be impossible to reassess continually whether or not it was important. Livingston said it would be possible for the animal to "turn down the gain" at the inferior collicular level but while doing so, to retain the information that the gain had been turned down. Thus, the animal would be able to apply an appropriate correction relating to any information reaching higher levels. The fact is, however, that the animal behaves as though the perceived signal were being attenuated. Even though it may be controlling the signal from some higher level, and even though it may theoretically have access to corrective information, the animal behaves as though the sound were being shut out. If the animal perceives the sound correctly, it is both shutting down input amplitude at the collicular level and disregarding the correction. Livingston and Galin believe it more likely that the animal does not apply any such postulated correction, and may not have access at higher levels to anything other than the attenuated input.

Olds reported a similar and confirming experiment by Bogacz, Olds, and Olds (1964). They used a light flash as CS and brain shock as US and averaged evoked potentials responding to the light flash during the CS-US interval. They applied the brain shock via the recording electrodes. A sensitization control was first conducted where the same flash and central stimuli were delivered but without being correlated with each other. An area at the base of the colliculus very near where Galin was recording sound-evoked potentials proved to be the only place in the brain where they were able to detect changes effected by stimulus correlation. Following correlated stimulation between flash and electrical activation of the recording site, there is a lasting attenuation of the evoked response recorded at that same point; following discontinuation of correlated stimulation there is augmentation.

Extraclassical Conduction of Evoked Responses

Galambos described a study in which the classical auditory pathways were cut bilaterally (Galambos et al., 1961).

He is convinced that the lesions in the brachium of the inferior colliculus completely destroyed the classical auditory path from inferior colliculus to medial geniculate, leaving only more medial routes for auditory impulses to reach cortex. When the animal is under anesthesia, clicks produce no cortical response; but when it has recovered from anesthesia a day or so later, the cortex still shows very short-latency responses, only about 1 msec longer in latency than the original responses from ear to cortex. The only route available for this signal is medial, perhaps reticular.

To Livingston this latency paradox appears to have a parallel in the pyramidal system. If motor cortex is stimulated, impulses travel down the pyramidal pathway. Pyramidal fibers give off collaterals into the reticular formation of the bulb where cells fire relayed discharges of impulses into the spinal cord. Parts of the reticular relayed responses may reach the spinal cord before the direct pyramidal responses reach the same cord levels. In other words, the bulbospinal relay is fast enough in conduction to make up for the synaptic delay. On this analogy, one is not surprised that Galambos finds an ascending collateral pathway via the RF that may also get there promptly.

VIII. LIMBIC-HYPOTHALAMIC-BRAINSTEM CIRCUITRY

Nauta spoke on the possible significance of the limbic-hypothalamic-brainstem systems in relation to motivation and learning. He has come to the conclusion that granular frontal cortex is the major neocortical representative of the limbic system. The concept of "limbic system" should be expanded to include prefrontal cortex, in the same way that motor cortex is included in our concept of "motor system." In primates, descending connections from granular frontal cortex have been traced to the hypothalamus; this is the only area of neocortex known to have direct hypothalamic connections.

The prefrontal cortex also has the most immediate relationships to hippocampal mechanisms, although this connection is a bit less direct, since it involves parahippocampal cortex, specifically, the presubiculum. One would not a priori have supposed prefrontal cortex to stand in such close neural proximity to the hippocampus, yet this is what the anatomical evidence indicates. Parts of the temporal lobe likewise are closely linked to the limbic system, but this part of the neocortex appears to be oriented more strongly to the amygdala than to the hippocampus. The functional connections of the fronto-temporal cortex were shown by Fulton and others to be related to visceral controls providing limbic and hypothalamic mechanisms their highest central representation.

Limbic Forebrain System

Nauta presented an anatomical diagram (Fig. 12) showing the existence of reciprocal connections between the limbic forebrain structures (hippocampus, amygdala, cingulate gyrus), and an extensive zone of the midbrain tegmentum, including the central grey substance. This "limbic forebrain - midbrain circuit" is composed largely of plurisynaptic connections in which the septo-preoptico-hypothalamic continuum is a major intermediary. (A less massive and more roundabout route involves the habenula.) It appears likely from this diagram that the functional state of the hypothalamus is continuously affected by the prevailing impulse traffic in the circuit as a whole. The prefrontal cortex, judging from its known anatomical connections, appears to be the only part of the neocortical hemisphere that is in a position to influence the circuit directly at points along its entire extent, i.e., at levels of limbic forebrain, paramedian midbrain zone, and hypothalamus.

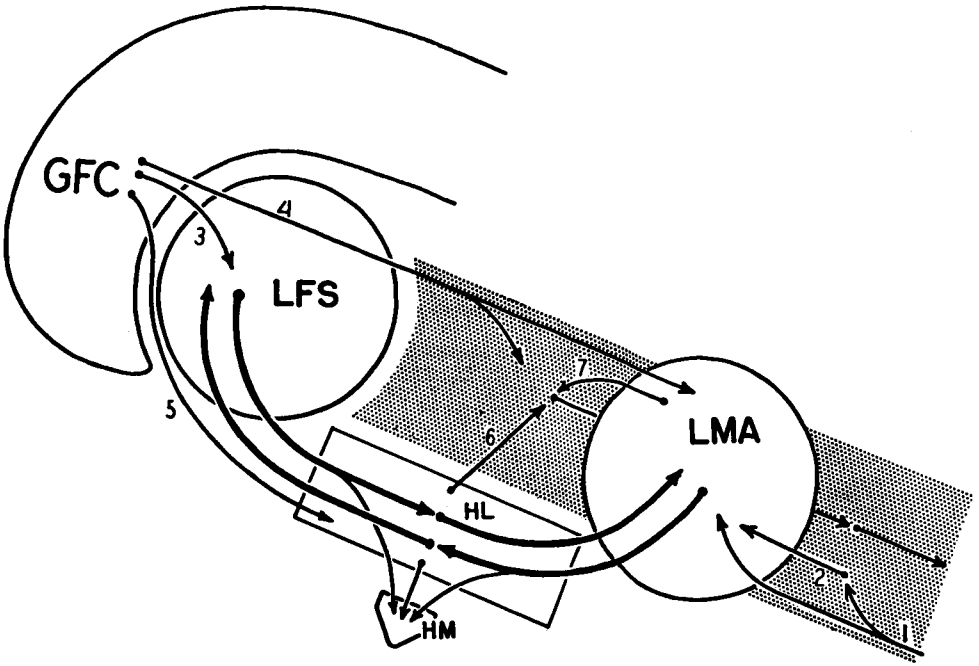

Figure 12. Extreme schematization of neural mechanisms related to the hypothalamus. (Slightly modified from Nauta [1963].) HL: lateral preoptico-hypothalmic region; HM: medial and periventricular zones of the hypothalamus; LFS: limbic forebrain structures as enumerated in the text; LMA: "limbic midbrain area," composed of the ventral tegmental area, interpeduncular nucleus, nuclei tegmenti of Gudden, nucleus centralis tegmenti superior of Bechterew, and central grey substance; GFC: prefrontal cortex. The stippled area represents the brain stem reticular formation (actually, LMA forms a paramedian subdivision of the midbrain reticular formation). The heavy arrows outline the limbic system - midbrain circuit in which the lateral preoptico-hypothalamic region appears as a nodal way station. Arrow 1 indicates the afferent connections of the circuit with the primordial spinobulbar lemniscus (e.g. spinothalamic tract); arrow 2, further ascending afferents of the circuit, relayed through the bulbar reticular formation. Probable additional trans-reticular afferents, in part directly to the hypothalamus, have not been indicated. Arrows 3, 4, and 5 represent afferents of the circuit from the frontal cortex to both poles of the circuit and hypothalamus respectively. The diagram does not indicate the probable afferent connection from the olfactory cortex via the medial forebrain bundle. Arrows 6 and 7 represent pathways connecting both the lateral hypothalamus and the limbic midbrain area with largely multisynaptic fiber systems descending through the reticular formation [Nauta].

Morgan found the intimate reciprocal connections between granular frontal cortex and the limbic system very interesting, saying that behavioral investigations of this granular frontal area indicate that it has to do with attention. These attention mechanisms evidently enable an organism to store, on a short-term memory basis, information it should hold in mind so that, as in a delayed response test at a slightly later time, it can make a correct response. These functions relate closely to learning and to the orienting response mechanisms of the hippocampus.

Output

Where does neural activity spread from this limbic-hypothalamic configuration? A main hypothalamic outflow system was identified by physiological methods by Magoun (1940) as an extremely diffuse conduction system descending through the midbrain tegmentum. The first link of this pathway, as identified by anatomical studies, spreads to midbrain RF throughout almost the entire width of the tegmentum. From here on down the anatomical picture of this descending conduction pathway is virtually a blank, with the exception of a periventricular fiber system which has been moved caudalward to the vicinity of the dorsal motor nucleus of the vagus.

Input

Nauta thinks that this entire telo-di-mesencephalic system can be aroused from two different directions: One is by direct ascending pathways for exteroceptive and viscero-ceptive stimuli, probably largely of a nociceptive nature, delivering impulses into the paramedian "limbic" midbrain zone. In this zone the central grey substance, especially, appears as a main entrance portal into the circuit for impulses signaling events that require unconditional activation of physiological defense mechanisms, such as the stress response elicited by pain, cold, and certain visceral functional changes. Adequate inputs along these channels will elicit functional changes in the circuit manifesting themselves in both autonomic and endocrine responses as well as in subjective changes in mood. Delgado et al. (1956), and Zanchetti (personal communication) found that stimulation of the central grey substance in the cat evokes a dramatic panic behavior suggestive of intolerable distress. The stimulated regions lie very close to the midline in areas where many spinothalamic tract fibers enter. A very slight distance farther lateral or ventral, in the midbrain tegmentum proper, stimulation yields alerting but no comparable states of distress.

The frontal lobe neocortex, according to Nauta, must act like a "pontifical analyzer system," which signals to the hypothalamic switchboard, which in turn modifies behavior. Nauta believes that impulses enter the lower part of the circuit and thence find their way to the hippocampus. He is confident that the hippocampus derives much of its input through ascending subcortical pathways which relay through the septum. The hippocampus, however, also receives input from the neocortex.

The second main category of afferents to the limbic forebrain-midbrain circuit is derived from the neocortical hemisphere. The prefrontal and inferior temporal cortical fields, reciprocally connected by massive fiber systems, appear to be major sources of such connections. The question remaining is: Whence does the prefronto-temporal cortex obtain its input? Input channels to this large cortical field are still poorly understood. The prefronto-temporal cortex seems to be maximally remote from primary sensory analyzers such as auditory and visual cortex. According to strychnine-neurophysiological findings (McCulloch, 1948), it receives most of its input from areas such as the parietal area 39 and temporal 22 of Brodmann, which are difficult to characterize functionally in terms of sensory modality. It appears likely that both areas 39 and 22 represent a type of "association" cortex in which confluence of information from various sources may take place. These areas could be regarded as engaged in multimodal synthesis to a larger extent than is the case for the modality-specific cortical analyzers. The prefronto-temporal fields are several steps away from the latter, and it is tempting to suggest that the frontal lobe may be that brain region farthest removed from sensory inputs, and thus, in a figure of speech, the area of cortex which is "most serene" and equipped to engage in some form of epi-analysis of the organism's environments or its own program of environmental activity.

The frontal lobe is a specific cortical area, cytologically speaking, and the mediodorsal thalamic nucleus projects to it in apparently the same "point-for-point" fashion that is found to exist in the visual geniculo-calcarine connections and other functionally specific thalamo-cortical systems. However, instead of the homogeneous modality-specific pathways leading into these thalamo-cortical systems, one finds a diversity of functionally ill-defined afferent pathways converging upon the mediodorsal nucleus. Among the sources of this heterogeneous composite of afferent inputs are olfactory cortex, amygdala, midbrain tegmentum, and cingulate cortex. In all likelihood, at least part of the information conveyed by these afferent systems is derived from the internal

milieu. If this is true, the thalamo-prefrontal connection could be in part interpreted as supplying the frontal cortex with information concerning the organisms's internal environment.

Other thalamocortical projections to the prefrontal lobe may arrive directly or indirectly from nonspecific or diffusely projecting thalamic nuclei. Nauta here mentioned experiments involving stimulation of the nonspecific thalamic nuclei, having an effect on an animal's ability to learn in a pattern discrimination situation. Jasper and Hunter (1949) obtained arrest of ongoing behavior when stimulation was applied to these areas. Mahut (1962,1964) obtained the same effects when using similar current intensities, but found that weaker stimulation of certain nonspecific thalamic nuclei applied while a cat was scanning alternatives in a choice situation, accelerated the rate of learning. When applied immediately following the choice, the same stimulation had the opposite effect of impairing the learning process. Stimulation in the mesencephalic RF was found to cause facilitation of learning, but never appeared to have an interfering effect.

Konorski talked about results of ablation of various parts of prefrontal areas in dogs and monkeys. If, in monkey, the dorsolateral part is removed, the symptom is impairment of delayed responses; lesions in the caudate nucleus produce the same effect but dorsomedial lesions do not affect delayed response (Peters, Rosvold, and Mirsky, 1956; Mishkin, 1957; Battig, Rosvold, and Mishkin, 1960). The second symptom is disinhibition, which involves impairment of Pavlovian internal inhibition observed during differentiation, extinction, etc. This syndrome is obtained in monkeys when the orbital surface of the frontal lobe is removed (Brutkowski, Mishkin, and Rosvold, 1963), and in dogs when the medial orbital surface is removed (Stepién et al., 1963; Szwejkowska, Kreiner, and Sychowa, 1963; Brutkowski, 1964).

Judging from the physiological results, Konorski finds it difficult to understand how the medial part of the orbital surface in dogs can correspond to the lateral part of the orbital surface in monkeys. Livingston considers this correspondence to be likely on the basis of his comparative analysis of differences in location of the eye motor fields of cats (and presumably dogs) as compared with monkeys. Cat frontal eye motor fields lie on the medial surface of the frontal lobe, yielding responses that correspond to those elicited

from the lateral surface of the monkey frontal lobe (Adey, Segundo, and Livingston (1957).

Nauta said that the mosaic of frontal lobe efferents in the monkey suggests a split between the orbital surface (caudal half) and the convexity. From the dorsal part of the convexity, association fibers pass in the direction of the cingulate gyrus and the presubiculum; thus, the dorsal half of the convexity is more especially related by outflow to hippocampal mechanisms. He is tempted to think that the ventral half of the frontal lobe is directly related to the amygdala. Of course, both hippocampus and amygdala are components of the limbic hemisphere, and both are closely related to the hypothalamus.

Konorski finds it interesting that although destruction of connections between hippocampus and prefrontal cortex gives results similar to removal of the prefrontal dorsal areas, everyone wonders why removal of the mediodorsal thalamic nucleus does not have a similar effect. Brutkowski and Dabrowska, according to Konorski, have recently found that extensive lesions in the mediodorsal nucleus produce a disinhibitory syndrome. Nauta suggested that the kind of information coming in over the dorsomedial cortical circuit may bear on another parameter of ongoing behavior not adequately approached by present-day testing methods.

VIII. STRUCTURAL CHANGES ASSOCIATED WITH LEARNING

Rosenzweig described work done with his associates at Berkeley to determine whether or not measurable structural changes occur in the nervous system during prolonged periods of learning (Fig. 13) (Bennett, Diamond, Krech, and Rosenzweig, 1964). It was found that rats kept in "enriched environments" show an increase of about 5% in weight of cortex. Total activity of acetylcholine esterase (AChE) and of cholinesterase (ChE) is also increased in this group. All areas of cortex show rather similar changes, but occipital cortex shows relatively more and somesthetic cortex relatively less. An increase in the thickness of cortex is also found. Handling, differential locomotion, and general stimulation do not produce these changes. Learning is thought to be the crucial variable in the enriched environment. Lindsley suggested that, in keeping with Sokolov's idea that there is peripheral vasoconstriction and brain vasodilitation during the orienting reflex, these animals may reflect long-term effects of cerebral vasodilation. Rosenzweig said that in one experiment, which is being repeated, cortical capillaries of enriched-environment animals were found to have larger diameters than those of their litter-mate controls.

A detailed study of a sample of visual cortex in the brains of experimental animals (Diamond, Law, Rhodes, Lindner, Rosenzweig, Krech, and Bennett, 1966) reveals a 14% ($P<.02$) increase in glia; those identified as to specific glial types showed 5% increase in astrocytes and 20% in oligodendrocytes. Neurons decreased by 3% but this is presumed to be the result of neurons' becoming spread farther apart in the area studied due to swelling of cortex and increase in the number of glia. The enriched-environment animals show a glial-neuronal ratio that is about 16% higher than controls ($P<.02$). Nauta suggested that there nevertheless might be a total increase in number of neurons. Rosenzweig said that some of the brains are being studied by Schadé in the Netherlands with this question in mind as well as in regard to dendritic branching. Some also are being studied by Coleman at the University of Maryland, who is working on dendritic branching. Recently Coleman studied the brains of paired cats raised by Riesen in darkness and in light. Coleman's results indicate that littermates raised in light have somewhat more complex dendritic branching, especially among second- and third- order branchings (Riesen, 1964). Changes in the cholinesterase to acetylcholine esterase ratio seem to go along with the change in numbers and ratios of cells, ChE being higher in glia than AChE, and the reverse holding in neurons.

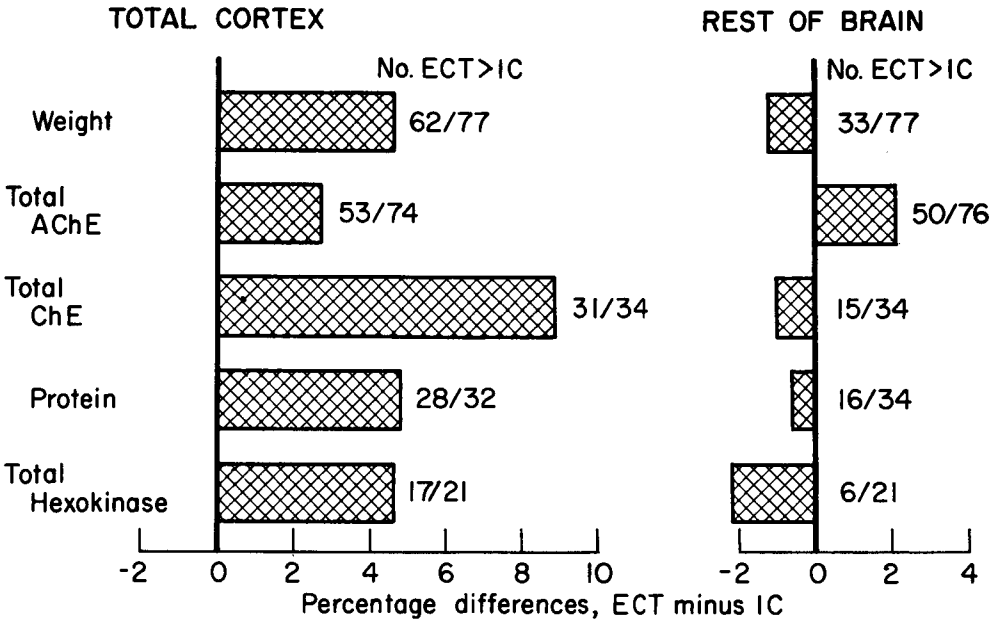

Figure 13. Relative differences between enriched-experience (ECT) and restricted (IC) groups on several cerebral measures. Each difference is expressed as a percentage of the IC value. For each measure, the number of littermate pairs in which the ECT value exceeded the IC value is also given. In the cortex, the ECT-IC difference in AChE is less than that for tissue weight, the difference in ChE is greater, and the differences in protein and hexokinase are almost identical to the weight difference. In the rest of the brain, only AChE is greater for the enriched-experience than for the restricted animals; all other measures show the ECT animals lower than the IC animals, and by roughly equal percentages. The figure is based entirely upon male rats of the Berkeley S_1 line [Bennett el al., 1964].

Konorski suggested an experiment in which one group of rats would be required to respond correctly to visual cues in order to get food, with a frequent change of problems in order to maintain a high level of learning dependent on visual experience. There may be a distinction between utilization, that is, perception for a purpose, and sensory stimulation. Galambos suggested that this could be done with a yoked control wherein both groups would get the same amount of visual stimulation but one group would have to discriminate in order to get food while the other group would just be fed. Rosenzweig said that such experiments have been planned in the Berkeley program but not yet carried out. (Experiments to the end of 1966, based on 20 pairs of rats, have not yielded positive results.) He added that he and people in Hebb's laboratory and elsewhere have shown that animals raised in a complex environment can learn better than in a simple one (Bingham and Griffiths, 1952; Forgays and Forgays, 1952); the harder the test devised, the better the contrast revealed. Konorski added another suggestion for an experiment with a built-in control à la Sperry -- using a cat with a split corpus callosum and other midline crossings and a split optic chiasm. The animal would be taught with one eye only while the other eye would be unengaged. Comparisons of the two hemispheres would reduce ambiguity by having the control in the same brain.

IX. SOME COMMENTS RELATING TO HUMAN LEARNING

Rowland spoke briefly on the relationship between learning in man and in animals. It is usually assumed that extrapolations from animals to man are not far-fetched; but the question arises whether or not some behaviors are distinctly and peculiarly human. When we think of human behavior, we generally think of reasoning power, insight, and language. When we try to reduce these terms to experimentally measurable dimensions, we find it difficult to specify exactly what does characterize human behavior. Erect posture, opposable thumb, use of tools, and vocalization do not seem to give us any particular advantages in understanding how human behavior differs from non-human behavior.

It may be possible, using an order-disorder frame of reference, to conclude that human behavior is characteristically capable of reducing disorder to a greater extent than can be done by other species. This approach has two advantages: First, it provides a single discriminant to scale. Second, it may be particularly useful because the Second Law of Thermodynamics and entropy have been related to information theory through contributions by Szilard, Shannon, and Wiener. There may be particular advantage in this approach for the purpose of communicating across disciplines. It may have special value in relating human with non-human behavior and in securing comparisons useful for understanding higher brain functions. V. R. Potter (1964) has emphasized this notion and experimental work based on these ideas is presented by Berlyne (1966) and others.

There was some discussion and disagreement over the use of the term "order-disorder"; but Rowland said that his real point is that the capacity to handle and to order information is greater (at least in some categories and undoubtedly in the aggregate) in man as compared with other animals. The reason for taking this position is that little else appears to be distinctly human. It could be said that humans tend to disorder the environment, but they really only disorder it in the short term; in the long term, and especially in intellectual activity, humans are consistently seeking to increase order. Too much order is not tolerated either, and deliberate disordering for the pleasure of subsequent ordering (mastery) is the basis of much sport, games, aesthetics, and other avoidances of monotony. When man solves a problem he reduces disorder; when Einstein gave us $E = mc^2$ he took many ambiguities and simplified them. The original phenomena contained more potential information, although disordered; when

Einstein tied them together, he invoked a principle which, for those data, reduced the disorder.

Miller indicated that Broadbent (1958) has made much the same point as Rowland, emphasizing the uniqueness of man's ability to handle large amounts of information rapidly. At least one point seems reasonably certain: human superiorities are not obvious in the formation of the simplest kinds of associations. Man does not learn eyelid conditioning or simple avoidance reflexes any more rapidly or more enduringly than many lower animals. In simple situations we are impressed by the consistency of learning phenomena in various mammals. The big differences appear in more complex situations which put greater demands on information processing and short-term memory.

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A NOTE ON THE FIRST N.R.P. INTENSIVE STUDY PROGRAM

In the summer of 1966, from July 18 to August 12, the Associates and staff of the NRP convened more than 100 other scientists on the campus of the University of Colorado in Boulder for the first NRP Intensive Study Program (ISP) in the Neurosciences.

Eight years previously, on the same site, an N.I.H.-sponsored Intensive Study Program of comparable size had helped to cohere and advance the burgeoning field of biophysics. The 1966 program was intended to play a similar catalytic role in furthering unification of the disparate neurosciences and in drawing attention to the wide range of emerging opportunities for pioneer research to advance scientific understanding of human brain function.

In keeping with the multidisciplinary scope of the NRP, its first ISP surveyed conclusions drawn from many levels, approaches, and disciplines (see the lecture schedule given below). The participants represented many different professional backgrounds, including the fields of psychiatry, pharmacological psychology, physiological psychology, neurology, neuroanatomy, experimental embryology, physiology, neurophysiology, cell biology, neurochemistry, immunochemistry, biochemistry, molecular biology, biophysics, physical chemistry, physics, and mathematics.

A major part of the four-week program was the series of 60 morning lectures, each of which was a survey of the major findings, concepts, and implications of an important field of research as seen by an expert in the subject. These morning lectures were supplemented by several special afternoon lectures, evening addresses, and film programs; but most afternoons were devoted to intra- and interdisciplinary discussions of the morning lectures, to a series of seminars, or to the four sessions of the tutorial in brain structure given by Professors Nauta, Palay, Angevine, and Bodian.

As with the biophysical ISP, it was always intended that the lectures of this neuroscientific ISP be published in a year, even allowing for revision after delivery in the light

of the authors' experiences at multidisciplinary discussions of their own and other lectures. Manuscripts thus based on the morning, afternoon, and evening lectures are in hand and will be published later in 1967 by The Rockefeller University Press in a volume tentatively entitled The Neurosciences -- A Study Program. Advance book-order information will be available in a few months.

In the following program of lectures as scheduled, names of chairmen of individual mornings are listed in capital letters. Names of liaison chairmen, also in capital letters, precede the blocks of mornings they coordinated. The overall chairman was Professor Francis O. Schmitt and the program director was Dr. Gardner C. Quarton. -- T.M.

I. MORNING LECTURES

A. MAJOR CONCEPTUAL ISSUES IN THE NEUROSCIENCES	**F.O. SCHMITT**
1. Molecular biology	A.L. Lehninger
2. Molecular biology of brain cells	F.O. Schmitt
3. Neuronal physiology	T.H. Bullock
4. Brain correlates of functional behavioral states	R.B. Livingston
5. Brain correlates of learning	R. Galambos
B. STRUCTURE OF THE NERVOUS SYSTEM	**S.L. PALAY**
1. Neurons, glia, and circuits	D. Bodian
2. Intercellular relations	S.L. Palay

(Block I - A.L. LEHNINGER, Liaison Chairman)

C. CONFORMATION OF MACROMOLECULES	**M. EIGEN**
1. Forces stabilizing macromolecular conformation	N.R. Davidson
2. Conformation of proteins	E.R. Blout
3. Conformation of nucleic acids and conformation changes	D.M. Crothers

D. SUPRAMOLECULAR ORGANIZATION	A.L. LEHNINGER
1. Enzyme complexes	L.J. Reed
2. Organelles	A.L. Lehninger
3. Ribosomes	A.J. Rich
E. CONTROL MECHANISMS AT THE LEVEL OF ENZYME ACTION	M. CALVIN
1. Control networks in enzyme systems	B.D. Davis
2. Conformational change and modulation of enzyme activity	D.E. Atkinson
3. Kinetics of conformational changes in proteins and enzymes	M. Eigen
F. CONTROL MECHANISMS: GENETIC INFORMATION TRANSFER	L.C.M. DE MAEYER
1. Genetic information processing	M. Nirenberg
2. Induction and repression; regulation of enzyme synthesis	G.S. Stent
3. Mutation; genetic recombination	C.A. Thomas
G. IMMUNE RESPONSE AND INFORMATION TRANSFER	G.M. EDELMAN
1. Biology of immune response	G.J.V. Nossal
2. Antibody structure and activity: implication for theories of antibody formation	G.M. Edelman
3. Possible means of information transfer in the immune response	N.K. Jerne

(Block II - F.O. SCHMITT, Liaison Chairman)

H. MOLECULAR SPECIFICITY AND RECOGNITION IN THE CNS	F.O. SCHMITT
1. Neuronal specificity	M.V. Edds, Jr.
2. Chemical specificity in the nervous system	J.D. Ebert
3. Molecular recognition in CNS by antibodies	L. Levine

I. NEUROCHEMICAL CORRELATES	P.F. DAVISON
1. Biosynthesis and control in brain cells	H.V. Hyden
2. Proteins of nervous tissue: specificity, turnover, and function	P.F. Davison
3. Lipids and membranes	E.P. Kennedy
J. BIOELECTRIC DYNAMICS: AXON	A. KATCHALSKY
1. Nerve cell membrane potentials and ion permeability	R.E. Taylor
2. Molecular basis for the active transport of cations	R. Whittam
3. Thermodynamic analysis of the axonal membranes	A. Katchalsky

(Block III - T.H. Bullock, Liaison Chairman)

K. BIOELECTRIC DYNAMICS: SYNAPSE, DENDRITES, CELL ASSEMBLIES	T.H. BULLOCK
1. Synapses and transmission of the nerve impulse	H. Grundfest
2. Dendrites	D.P. Purpura
3. Internal analysis and coding in axons	V.B. Mountcastle
L. CHEMICAL TRANSMISSION AND MODULATION	S.S. KETY
1. Catecholamines	I.J. Kopin
2. Acetylcholine and other possible transmitters	E.A. Kravitz
3. Central physiological, pharmacological, and behavioral effects of biogenic amines	S.S. Kety
M. ELECTRICAL ACTIVITY OF BRAIN	F. MORRELL
1. The nature of the EEG	F. Morrell
2. Evoked potentials	W.M. Landau
3. Slow-potential phenomena	V. Rowland

(Block IV - R.B. LIVINGSTON, Liaison Chairman)

N. SLEEP AND WAKEFULNESS	W.J.H. NAUTA
1. Biological rhythms	F. Strumwasser
2. Mechanisms of sleep states	M. Jouvet
3. Unit activity in sleep and wakefulness	E.V. Evarts
O. DRIVES, REINFORCEMENT, AND CONTROL OF VISCERAL FUNCTION	W.R. ADEY
1. Biology of drive	P. Teitelbaum
2. Reinforcement	R.B. Livingston
3. Biology of visceral endocrine adaptation	W.J.H. Nauta
P. PROGRAM SELECTION: ALERTING, ORIENTING, DISCRIMINATION	R.B. LIVINGSTON
1. Anatomical bases of attention mechanisms in vertebrate brains	A.B. Scheibel
2. Subcortical and cortical mechanisms in arousal and emotional behavior	A. Zanchetti
3. Intrinsic organization of cerebral tissue in arousal, orienting and discriminatory behavior	W.R. Adey

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(Block V - R. GALAMBOS, Liaison Chairman)

Q. ELECTRICAL CORRELATES OF LEARNING	T.H. BULLOCK
1. The use of invertebrate preparations in studies of learning	E.M. Eisenstein
2. Electrical changes: single cells	E.R. Kandel
3. Electrical changes: EEG and evoked responses	E.R. John
R. ANATOMICAL CORRELATES OF LEARNING	R. GALAMBOS
1. Effects of ablation	K.L. Chow
2. Split brain	R.W. Sperry
3. Postnatal growth of the brain and its implications for a morphological theory of memory	J. Altman

S. BIOCHEMICAL CORRELATES OF LEARNING — H.V. HYDEN

1. Enhancement of memory and learning by drugs and transfer of learning by macromolecules — G.C. Quarton
2. Impairment of learning and memory by drugs — B.W. Agranoff
3. Biochemical changes accompanying learning — H.V. Hydén

T. PERSPECTIVES — F.O. SCHMITT

II. SPECIAL LECTURES AND ADDRESSES

A. AFTERNOON LECTURES

1. Thermodynamics and molecular aspects of information — L. Onsager
2. Membrane ultrastructure in nerve cells — H. Fernandez-Moran
3. Inhibition in the central nervous system — J.C. Eccles

B. EVENING ADDRESSES

1. Neurological determinants of our environment — D. Bronk
2. Chemical evolution of life and sensibility — M. Calvin
3. $1 + 1 \neq 2$ — P.A. Weiss
4. Men, machines, and molecules — S. Toulmin

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